Società Medico Chirurgica di Ferrara

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Il PSA: quando richiedere un approfondimento e la biopsia

IL TUMORE della PROSTATA a FERRARA

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ESPLORAZIONE RETTALE (ER)

- CaP ER^{+}: 18% [1]
- ER *by* MMG: sens/spec. < 60% (non indicata)
- ER^{+} ; PSA ≤2: PPV 30% [2]
- ER^{+} + ↑PSA: Rischio Bx^{POS} x 2 (48% vs 22%) [3]
- ER $^{+}$: indicazione a RM e Bx [3-4]

1. *Urology, 1993. 42: 365*
2. *J Urol, 1999. 161: 835*
3. *Eur Urol, 2008.54: 581*
4. *Urology, 2007. 70: 1117*

Prostate Specific Antigen (PSA)

- organo ma non cancro-specifico
- può ↑ in BPH, prostatite et aa condizioni non maligne
- come variabile indipendente è un fattore predittivo di CaP MIGLIORE di ER e TRUS [1]

Table 5.3: Risk of PCa identified by systemic PCa biopsy in relation to low PSA values [160] [2]

PSA level (ng/mL)	Risk of PCa (%)	Risk of ISUP grade ≥ 2 PCa (%)
0.0–0.5	6.6	0.8
0.6–1.0	10.1	1.0
1.1–2.0	17.0	2.0
2.1–3.0	23.9	4.6
3.1–4.0	26.9	6.7

1. *Okotie, O.T., et al. - Urology, 2007. 70: 1117*
2. *EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer, 2022*

SCREENING

Obiettivi:

- Individuare individui «a rischio»
- ↓ mortalità da Cap
- ↔ la QoL

principale endpoint in tutti i trials

Cochrane review (2013[1]-2015[2]):

- Screening: ↑ diagnosis of PCa (RR: 1.3, 95% CI: 1.02–1.65)
- Screening: ↑ detection of more localised disease (RR: 1.79, 95% CI: 1.19–2.70) and less advanced PCa (T3–4, N1, M1) (RR: 0.80, 95% CI: 0.73–0.87)
- No PCa-specific survival benefit observed (RR: 1.00, 95% CI: 0.86–1.17)
- No overall survival (OS) benefit was observed (RR: 1.00, 95% CI: 0.96–1.03)

1. Ilic, D., et al. Screening for prostate cancer. Cochrane Database Syst Rev, 2013: CD004720. https://pubmed.ncbi.nlm.nih.gov/23440794/

2. Hayes, J.H., et al. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. JAMA, 2014. 311: 1143.

SCREENING

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Table 1 Selected summary of evidence-based guideline recommendations

Organization	Year	Country	Recommendation
Canadian Task Force on Preventive Health Care	2014	Canada	<55 or ≥70: Recommended against screening (strong recommendation, low-quality evidence) 55 to 69: Recommended against screening (weak recommendation; moderate quality evidence)
American College of Physicians	2015	USA	<50 or ≥70: Recommended against screening 50 to 69: Recommended shared decision making
Members of the rapid recommendation panel	2018	International	Recommended against systematic PSA-based screening (weak recommendation). Shared decision making is needed for men considering screening.
U.S. Preventive Services Task Force	2018	USA	55 to 69: Recommended shared decision making ≥70: Recommended against screening
American Academy of Family Physicians	2019	USA	Recommended against screening. For individuals aged 55 to 69 and considering periodic screening: Recommended shared decision making
UK National Screening Committee	2020	UK	Recommended against systematic population screening

A. Bennett et al, Systematic Reviews 2022;11:230

EARLY DETECTION (shared decision)

- PSA
- ER
- FATTORI DI RISCHIO
  - età (life expectancy)
  - comorbidità
  - familiarità per CaP
  - mutazioni genetiche

FATTORI DI RISCHIO

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- ETA’ > 50 aa (>45 aa se familiarità)
- MUTAZIONI GENETICHE (BRCA1 –BRCA2)

BASSO RISCHIO

- PSA <1 a 40 aa
- PSA <2 a 60 aa
- NO FAMILIARITA’

→ ↓ R di CaP anche decadi dopo! [1,2]

1. *BMJ, 2013. 346: f2023*
2. *BMJ, 2014. 348: g2296*

GENETIC TESTING

Germline BRCA1 and BRCA2 mutations occur in approximately **0.2%** to **0.3%** of the general population [1]

2

5.1.4 ***Guidelines for germline testing****

Recommendations	Strength rating
Consider germline testing in men with metastatic PCa.	Weak
Consider germline testing in men with high-risk PCa who have a family member diagnosed with PCa at age < 60 years.	Weak
Consider germline testing in men with multiple family members diagnosed with PCa at age < 60 years or a family member who died from PCa.	Weak
Consider germline testing in men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.	Weak

**Genetic counseling is required prior to germline testing.*

1. John, E.M., et al. Jama, 2007. 298: 2869
2. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer, 2022

VALUTAZIONE INIZIALE (PSA + ER)

- A RISCHIO: ogni 2 anni
- NON A RISCHIO: fino a 8 anni

Studio ERSPC[1]: PSA <1 → Detection Rate a 8 anni ≃ 1%

1. *Urology, 2005.65: 343*

SCREENING and EARLY DETECTION

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Recommendations	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man and a life-expectancy of at least 10 to 15 years.	Weak
Offer early PSA testing to well-informed men at elevated risk of having PCa: • men from 50 years of age; • men from 45 years of age and a family history of PCa; • men of African descent from 45 years of age; • men carrying *BRCA2* mutations from 40 years of age.	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk: • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up to 8 years in those not at risk.	Weak
Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < 15 years are unlikely to benefit.	Strong

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RISK-ASSESSMENT: determinare l' indicazione a Bx

- Risk Calculators
- mpMRI
- (PSA-density)

RISK-ASSESSMENT - COMORBIDITA' - ASPETTATIVA DI VITA

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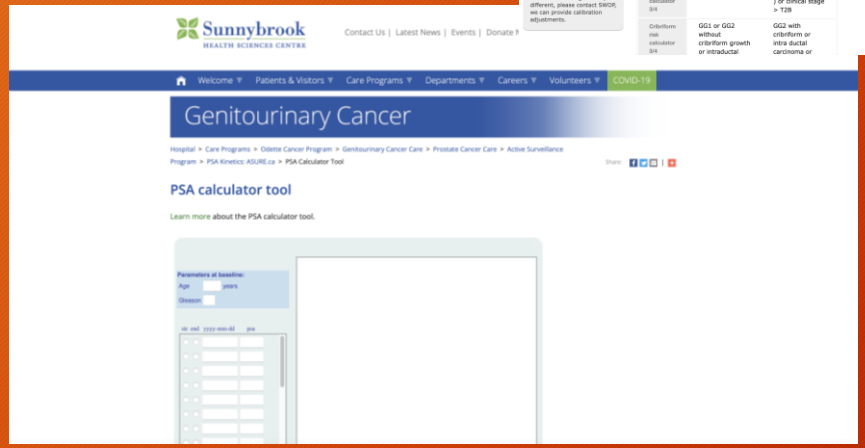
Studi PIVOT ed ERSPC[1]

Life expectancy <15 anni: → NO beneficio da DIAGNOSI PRECOCE

1. *Eur J Cancer, 2019. 116:116*

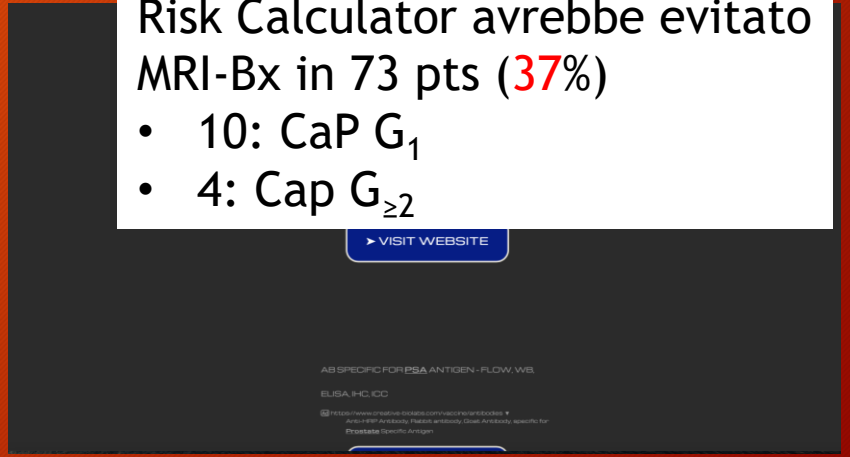
RISK-ASSESSMENT: Risk Calculators

- Età
- PSA
- ER
- comorbidità



200 pts[1]
Risk Calculator avrebbe evitato MRI-Bx in 73 pts (37%)

- 10: CaP G_1
- 4: Cap $G_{\geq 2}$



1.Mannaerts, C.K., et al. Eur Urol Oncol, 2018. 1: 109

RISK-ASSESSMENT: PSA-density

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PSA / P vol

- CUT OFF:
  - <0,10 low risk
  - 0,10-0,15 intermediate-low
  - 0,15-0,2 intermediate-high
  - ≥ 0,2 high
- Più importante fattore predittivo nei RISK CALCULATORS!
- Incostantemente utilizzato
- Utile MAX per PSA > 4 ng/ml

PSA Velocity e Doubling Time

- **PSA velocity** (PSA-V): ↑ assoluto annuale del PSA (ng/mL/anno)
- **PSA doubling time** (PSA-DT): misura l' ↑ esponenziale del PSA nel tempo

REGOLE:

PSA-V

- $PSA_2 - PSA_1$

PSA-DT

- almeno 3 PSA misurazioni
- tempo minimo tra due misurazioni (4 sett.)
- PSA totale > 0.20 ng/mL (trend in ↑)
- valori di PSA valutabili: entro gli ultimi 12 mesi

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f/t PSA

Risente di fattori pre-analitici e clinici

- instabile a 4°
- diversi assays
- BPH

Risultati

- <10%: PPV 56%
- >25%: PPV 8%
- tPSA 4-10: sensibilità 70%
- tPSA >10: nessuna utilità

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RISONANZA MAGNETICA multiparametrica

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DETECTION RATES (significant cancer):

- Pi-Rads 2: 9%
- Pi-Rads 3: 16%
- Pi-Rads 4: 59%
- Pi-Rads 5: 85%

Oerther, B., et al. Prostate Cancer Prostatic Dis, 2021 - https://pubmed.ncbi.nlm.nih.gov/34230616/

RISK-ASSESSMENT

Recommendations	Strength rating
In asymptomatic men with a prostate-specific antigen (PSA) level between 3–10 ng/mL and a normal digital rectal examination (DRE), repeat the PSA test prior to further investigations.	Weak

In asymptomatic men with a PSA level between 2–10 ng/mL and a normal DRE, use one of the following tools for biopsy indication: • risk-calculator; • Magnetic resonance imaging of the prostate	Strong
• an additional serum, urine or tissue-based biomarker test.	Weak

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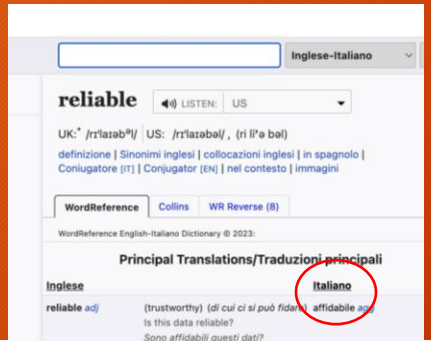
IMAGING: TRUS



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»Standard TRUS is <u>not reliable</u> at detecting PCa and the diagnostic yield of additional biopsies performed on hypoechoic lesions is negligible«

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IMAGING: MRI

PERFORMANCE DIAGNOSTICA (metanalisi 17 studi[1])

- Medio PPV per ISUP grade >2 cancers di lesioni PI-RADSv2.1 score:
  - **3**: 16% (7–27%)
  - **4**: 59% (39–78%)
  - **5**: 85% (73–94%)

NB: marcata eterogeneità tra i vari studi

1. Barkovich, E.J., et al. AJR Am J Roentgenol, 2019. 212: 847

IMAGING: MRI + PSAD

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Detection of clinically significant prostate cancer (ISUP grade 2 and higher)					
		PSA-density risk groups			
PI-RADS risk categories	Prevalence ISUP ≥ 2 PCa	Low < 0.10	Intermediate-low 0.10–015	Intermediate-high 0.15–0.20	High ≥ 0.20
		31% (678/2199)	28% (612/2199)	16% (360/2199)	25% (553/2199)
Compiled totals of csPCa risk					
PI-RADS 1–2	6% (48/839)	3% (11/411)	7% (17/256)	8% (8/104)	18% (12/68)
PI-RADS 3	16% (41/254)	4% (3/74)	13% (11/88)	29% (12/41)	29% (15/51)
PI-RADS 4–5	62% (687/1106)	31% (59/189)	54% (144/286)	69% (148/215)	77% (336/434)
All PI-RADS	35% (776/2199)	11% (73/674)	28% (172/612)	47% (168/360)	66% (363/553)
Risk-adapted matrix table for biopsy decision management					
PI-RADS 1–2		No biopsy	No biopsy	No biopsy	Consider biopsy
PI-RADS 3		No biopsy	Consider biopsy	Highly consider biopsy	Perform biopsy
PI-RADS 4–5		Perform biopsy	Perform biopsy	Perform biopsy	Perform biopsy

very low	0–5% csPCa (below population risk) #
low	5–10% csPCa (acceptable risk) ##
Intermediate-low	10–20% csPCa
Intermediate-high	20–30% csPCa
High	30–40% csPCa
Very high	> 40% csPCa

Thompson IM *et al.* N Engl J Med. 2004 May 27;350(22):2239-46. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng/ml.
2019 EAU guidelines: csPCa 9% (95%CI: 6–14%).

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IMAGING: MRI

Recommendations for all patients	Strength rating
Do not use magnetic resonance imaging (MRI) as an initial screening tool.	Strong
Adhere to PI-RADS guidelines for MRI acquisition and interpretation and evaluate MRI results in multidisciplinary meetings with pathological feedback.	Strong

Recommendations for biopsy-naïve patients	Strength rating
Perform MRI before prostate biopsy.	Strong
When MRI is positive (i.e. PI-RADS ≥ 3), combine targeted and systematic biopsy.	Strong
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is low (e.g. PSA density < 0.15 ng/mL), omit biopsy based on shared decision-making with the patient.	Weak

Recommendations for patients with prior negative biopsy	Strength rating
Perform MRI before prostate biopsy.	Strong
When MRI is positive (i.e. PI-RADS ≥ 3), perform targeted biopsy only.	Weak
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is high, perform systematic biopsy based on shared decision-making with the patient.	Strong

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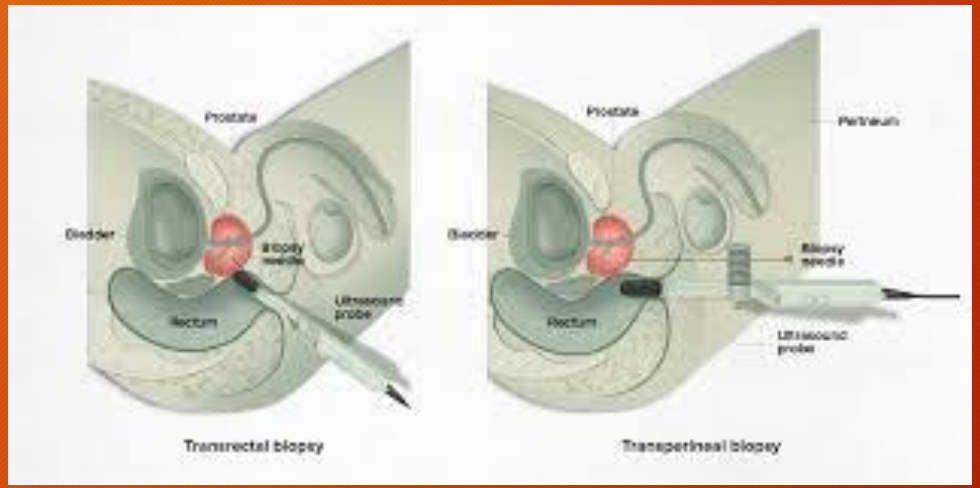
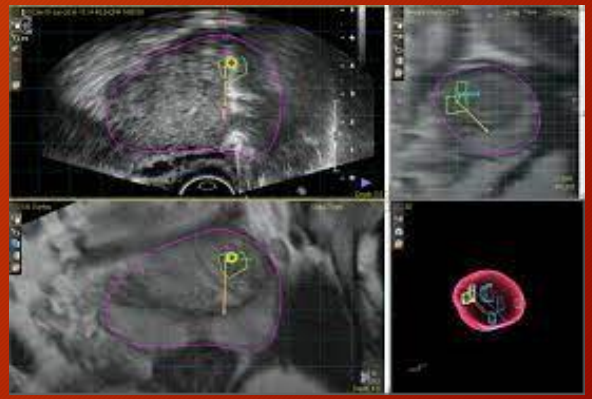
DIAGNOSTICA: BIOPSIA FUSION





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DIAGNOSTICA: BIOPSIA FUSION

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Table 5.4: Absolute added values of targeted and systematic biopsies for ISUP grade ≥ 2 and ≥ 3 cancer detection

		ISUP ≥ 2			ISUP ≥ 3		
ISUP grade		**Cochrane meta-analysis*** [155]	**MRI-FIRST trial*** [100]	**4M trial** [101]	**Cochrane meta-analysis*** [155]	**MRI-FIRST trial*** [100]	**4M trial** [101]
Biopsy-naïve	Added value of MRI-TBx	6.3% (4.8–8.2)	7.6% (4.6–11.6)	7.0% (ND)	4.7% (3.5–6.3)	6.0% (3.4–9.7)	3.2% (ND)
	Added value of systematic biopsy	4.3% (2.6–6.9)	5.2% (2.8–8.7)	5.0% (ND)	2.8% (1.7–4.8)	1.2% (0.2–3.5)	4.1% (ND)
	Overall prevalence	27.7% (23.7–32.6)	37.5% (31.4–43.8)	30% (ND)	15.5% (12.6–19.5)	21.1% (16.2–26.7)	15% (ND)
Prior negative biopsy	Added value of MRI-TBx	9.6% (7.7–11.8)	-	-	6.3% (5.2–7.7)	-	-
	Added value of systematic biopsy	2.3% (1.2–4.5)	-	-	1.1% (0.5–2.6)	-	-
	Overall prevalence	22.8% (20.0–26.2)	-	-	12.6% (10.5–15.6)	-	-

Intervals in parenthesis are 95% CI.

The absolute added value of a given biopsy technique is defined by the percentage of patients of the entire cohort diagnosed only by this biopsy technique.

ISUP = International Society for Urological Pathology (grade); MRI-TBx = magnetic resonance imaging-targeted biopsies; ND = not defined.

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DIAGNOSTICA: re-BIOPSIA

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INDICAZIONI

- Pregressa Bx negativa e MRI Pirads >3
- PSA persist.te elevato o in ↑
- ER^{pos}
- Carcinoma intraduttale
  (solitary finding: > 90% rischio di associato CaP alto grado)

Probabilità di csCaP DOPO Re-BX per ASAP e/o HG-PIN: **6-8%**
(simile alle re-Bx per altri motivi)

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DIAGNOSTICA: SATURATION (repeat) BIOPSY

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> 20 prelievi

- Detection Rate: 30-43% (per via perineale: + 38%)
- Complicanze: RITENZIONE URINARIA (1.2 – 10%)

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DIAGNOSTICA: BIOPSIA PROSTATICA

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Summary of evidence	LE
Literature review including multiple biopsy schemes suggests that a 10 to 12-core scheme is optimal in the majority of initial and repeat biopsy patients, dependent on prostate size. These biopsy schemes should be heavily weighted towards the lateral aspect and the apex of the prostate to maximize peripheral zone sampling [3].	3
A systematic review and meta-analysis comparing MRI-targeted transrectal biopsy to MRI-targeted transperineal biopsy, analysing 8 studies, showed a higher sensitivity for detection of csPCa when the transperineal approach was used (86% vs. 73%).	2
Current literature, including systematic reviews and meta-analyses, does not show a clear superiority of one image-guided technique (cognitive guidance, US/MR fusion software or direct in-bore guidance) over the other.	2

Recommendations	Strength rating*
At least 8 systematic biopsies are recommended in prostates with a size of about 30 cc and 10 to 12 core biopsies are recommended in larger prostates, with > 12 cores not being significantly more conclusive.	Strong
Transperineal biopsies are preferred over transrectal biopsies.	Strong
Where MRI has shown a suspicious lesion MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance.	Weak

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CONCLUSIONI

- Nel Ca Prostata lo screening di massa è controindicato; è invece incoraggiata la **DECISIONE CONDIVISA** (adattata al rischio) nell' uomo >50 <75 aa
- Il **PZ A RISCHIO** dovrebbe controllare il PSA al massimo ogni 2 anni; gli altri anche ogni 8 anni
- La **DIAGNOSI PRECOCE** non riveste utilità clinica nel soggetto con L.E. < 15 anni
- **RISK CALCULATORS** e **RISONANZA MAGNETICA** sono i migliori strumenti per definire l' indicazione alla biopsia
- L' **ECOGRAFIA PROSTATICA TRANSRETTALE** mantiene oggi un ruolo fondamentale SOLO nella biopsia: non deve essere considerata nella diagnostica
- La **RISONANZA MAGNETICA** è il vero GAME CHANGER dei primi decenni degli anni duemila
- La **BIOPSIA FUSION** garantisce un netto ↑ della performance diagnostica e rappresenta oggi lo standard nel sospetto di Ca Prostata potenzialmente organo-confinato