PSA MAGLUMI

Medical Systems: oltre 30 anni di diagnostica del PSA

Il primo test

PSA RIA

è stato prodotto da DPC

(Diagnostic Products Corp, USA)

e rilasciato alle vendite nel 1984

Hybritech Tandem-R PSA:

rilasciato nel 1986

406 RADIOIMMUNOASSAY FOR PROSTATE SPECIFIC ANTIGEN (PSA): PERFORMANCE AND CLINICAL CORRELATION, A.Said El Shami (Diagnostic Products Corporation, Los Angeles, CA 90045), and C.S. Killian Roswell Park Memorial Inst., Buffalo, NY 14263.) (Spon:J.DAlvise)

The double-antibody I^{125} radioimmunoassay was developed for the quantitative measurement of prostate specific antigen (PSA) in serum or plasma. Its sensitive, 16 hour procedure detects approximately 0.7 ng/ml of PSA. Highly specific antiserum for PSA did not crossreact with other tumor markers.

The performance characteristics for the PSA-RIA were documented. Precision studies evaluated the reproducibility of PSA measurements on five serum samples, intra-assay and inter-assay reproducibility included CV's which ranged from 3.0-7.0% and 3.8-11.0%,respectively. Spiking recovery, curve displacement and parallelism studies revealed recoveries of PSA ranging from 92-108%. The double-antibody PSA procedure maintains good linearity upon dilution.

Serial measurements of PSA were compared with the clinical disease status of two prostatic cancer patients. Both patients were surgically staged with D1 disease. After receiving an initial definitive therapy, patients were evaluated as having no clinical evidence of disease. During a three year follow-up, the disease in one patient recurred after 18 months, while the other patient remained clinically disease free. All serial levels of PSA were found to be consistently elevated before recurrence in the former patient, in contrast to the almost non-detectable levels of PSA in the latter. Results of this longitudinal study, although brief, suggest that PSA as measured by this method may be useful for therapeutic monitoring in patients with prostate cancer.

Medical Systems: >20 anni di **PSA 3G**

Int J Biol Markers. 1995 Oct-Dec;10(4):229-33.
Third-generation PSA:
ultrasensitive or ultraprecise assay ?

Mione R, Barichello M, Sartorello P, Leon A, Barioli P, Gion M

The ultrasensitive PSA assay has been recently acknowledged as a useful tool for the monitoring of patients prostatectomized for prostatic cancer. We have evaluated a commercially available ultrasensitive PSA assay (**Immulite Third Generation PSA**, DPC Los Angeles CA) in comparison with the routinely used PSA (Immulite PSA, DPC). When evaluated with different approaches, the analytical sensitivity of ultrasensitive PSA ranged between 0.0029 and 0.0038 ng/ml. The biological detection limit was 0.0098 ng/ml. Dilution of samples with low PSA levels showed a good recovery (from 88 to 113%) up to 1:128 dilution factor (final PSA levels ranging from 0.004 to 0.016 ng/ml in different samples). The assay precision was excellent in the low dose range, the highest interassay interadjustment CV among replicates being 5.84% when assaying serum samples with PSA lower than 1.0 ng/ml. Besides its role in the follow-up of prostatectomized patients, the evaluated ultrasensitive PSA could be reliably used for the detection of clinically meaningful PSA variations in the low dose range, and it could therefore be a candidate for the assessment of PSA velocity.

Test PSA 3° Generazione vs test PSA convenzionali

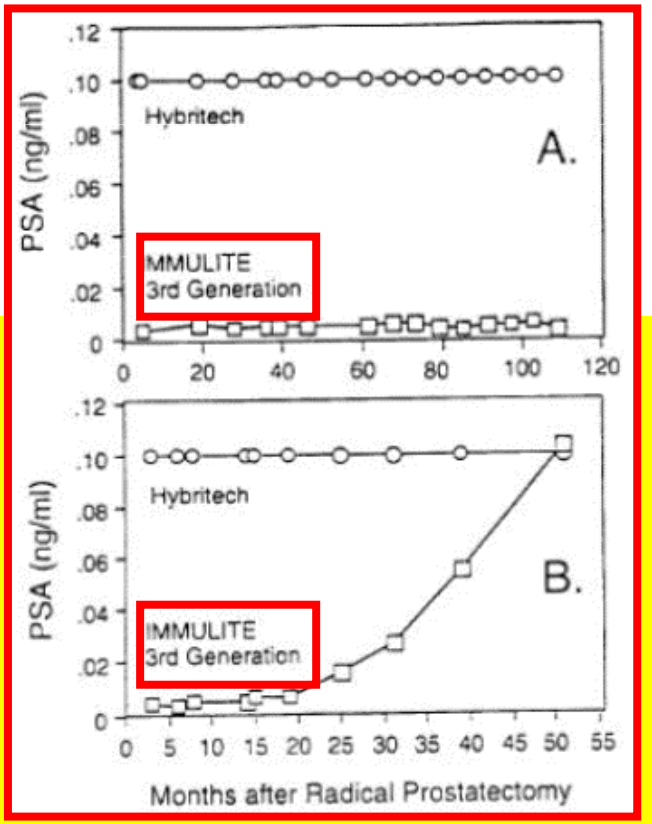
J Urol. 1997 Apr;157(4):1322-8.
Sensitive prostate specific antigen measurements identify men with long disease-free intervals and differentiate aggressive from indolent cancer recurrences within 2 years after radical prostatectomy.

Witherspoon LR, Lapeyrolerie T.

… We measured PSA in 1,037 serum samples obtained serially from 127 men after radical prostatectomy using the IMMULITE Third Generation PSA assay. …

The IMMULITE Third Gen. PSA assay has an analytical sensitivity of less than 0.002 ng/ml and a clinically useful decision threshold of 0.01 ng/ml ….

… The IMMULITE Third Gen. PSA assay provides clinically useful information not previously available from PSA assays with conventional sensitivity, which is highly predictive of cancer activity in patients within 2 years after radical prostatectomy.



Test PSA 3° Generazione vs test PSA convenzionali

Br J Urol. 1997 Mar;79 Suppl 1:82-6.
Early detection of cancer relapse after prostatectomy using very sensitive prostate-specific antigen measurements.

Witherspoon LR.

… The improved clinical detection limit provided by the Immulite 3rd Gen assay (0.01 ng/mL) provided clinically useful information not previously available using assays of conventional sensitivity (Fig.4). … All of the patients destined after prostatectomy to have biochemical and clinical cancer recurrence were correctly identified using the Immulite 3rd Gen assay by about 2 years after surgery. Conversely, patients at minimal or no risk of early cancer recurrence were also correctly identified. …

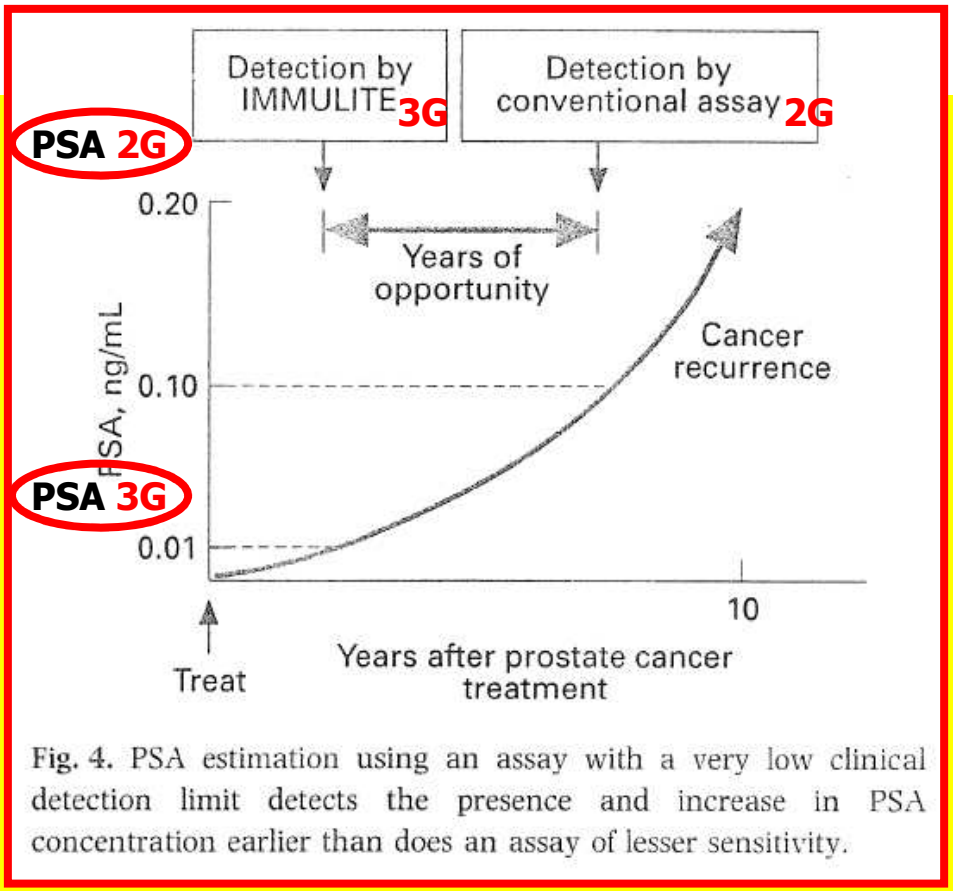
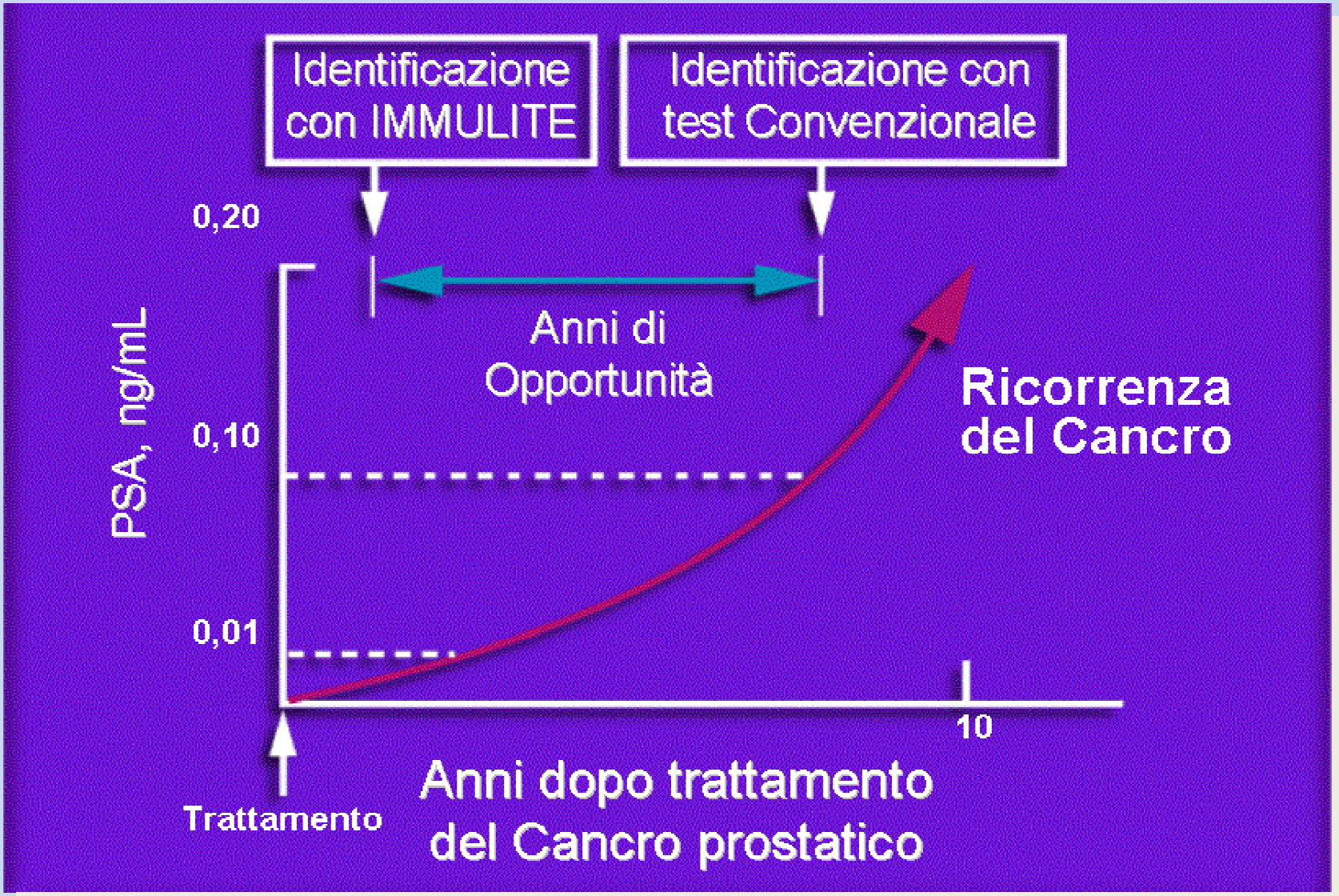


Fig. 4. PSA estimation using an assay with a very low clinical detection limit detects the presence and increase in PSA concentration earlier than does an assay of lesser sensitivity.

Test PSA 3° Generazione vs test PSA convenzionali



Medical Systems: >20 anni di **PSA 3G**

Br J Cancer. 2000 Dec;83(11):1432-6.
Undetectable ultrasensitive PSA after radical prostatectomy for prostate cancer predicts relapse-free survival.
Doherty A, Bower M, Smith GL, Miano R, Mannion E, Mitchell H, Christmas T.

…Serum PSA levels were measured with the Roche COBAS CORE assay in the first 80 patients (lower detecting limit = 0.1 ng ml–1). From 1997 onwards, 120 patients had measurements using **the IMMULITE 'Third Generation' sPSA assay** (Diagnostic Products Corporation, DPC, Gwynedd, UK). This assay detects PSA down to below levels of 0.01 ng ml–1. Interassay variation is negligible at ≥ 0.01 ng ml–1. This low detection level is a consequence of the efficient centrifugal wash, which results in a low non-specific signal accompanied by a large specific signal afforded by the chemiluminescent label (Babson et al, 1991).
…CONCLUSIONS. The role of RRP has been controversial in the UK partly because of the scepticism regarding the effectiveness of the procedure. Undoubtedly, not all patients undergoing RRP are cured of prostate cancer and patient selection is an important factor. Patients are keen to know if they have been cured of cancer after RRP. Until recently, to predict this we have been reliant upon histology alone. However, ultrasensitive PSA assays now enable us more accurately to advise patients of their chance of PSA relapse within 2 months of surgery and appears to be a reliable predictor of cure of prostate cancer.

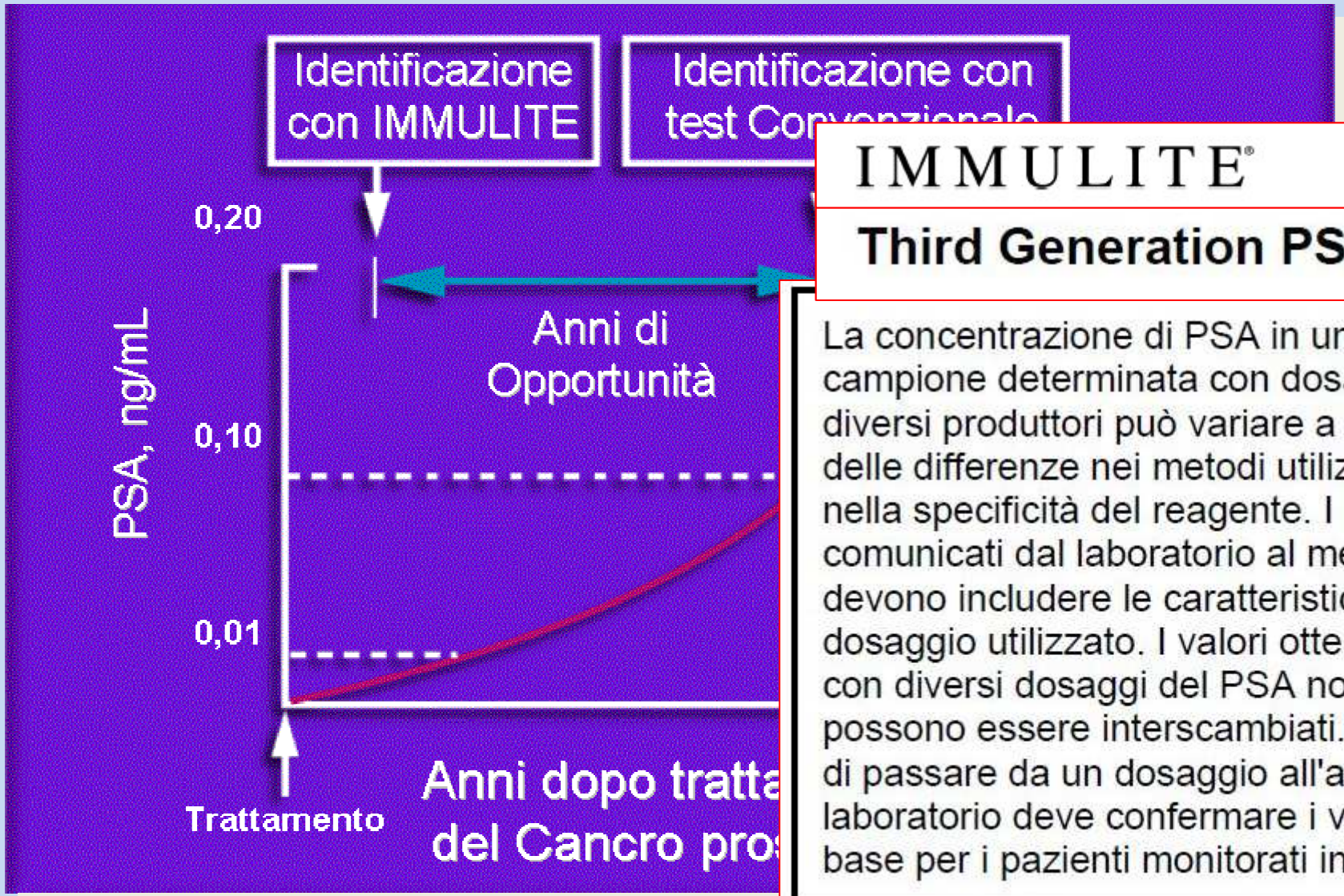
Medical Systems: >20 anni di **PSA 3G**

BMC Urol. 2014 Oct 2;14:79.
The use of early postoperative prostate-specific antigen to stratify risk in patients with positive surgical margins after radical prostatectomy.
Vesely S1, Jarolim L, Duskova K, Schmidt M, Dusek P, Babjuk M.

…All the PSA tests were performed in a single hospital laboratory under standardized settings using the **Immulite third-generation PSA assay** (Diagnostic Products Corp, Los Angeles, California; lower detection limit 0.003 ng/ml). Biochemical recurrence was defined as a single post-nadir PSA level of 0.2 ng/ml or greater.

…Conclusions: The level of ultrasensitive PSA yields valuable information about the prostatectomy outcome already at the first month after the surgery and should aid risk stratification in patients with PSM. Patients not likely to experience subsequent disease progression may be spared the toxicity of immediate adjuvant radiotherapy.

Test PSA 3° Generazione vs test PSA convenzionali



IMMULITE®

Third Generation PSA

La concentrazione di PSA in un dato campione determinata con dosaggi di diversi produttori può variare a causa delle differenze nei metodi utilizzati e nella specificità del reagente. I risultati comunicati dal laboratorio al medico devono includere le caratteristiche del dosaggio utilizzato. I valori ottenuti con diversi dosaggi del PSA non possono essere interscambiati. Prima di passare da un dosaggio all'altro, il laboratorio deve confermare i valori di base per i pazienti monitorati in serie.

Definizione di Generazioni dei test PSA totale

Limite di Sensibilità Funzionale (anche detta: LoQ, Limit of Quantitation) con CV inter-assay <20%	Generazione test PSA
1 – 3 ng/mL	Prima Generazione
0,1 – 0,3 ng/mL	Seconda Generazione
0,01 – 0,03 ng/mL	Terza Generazione

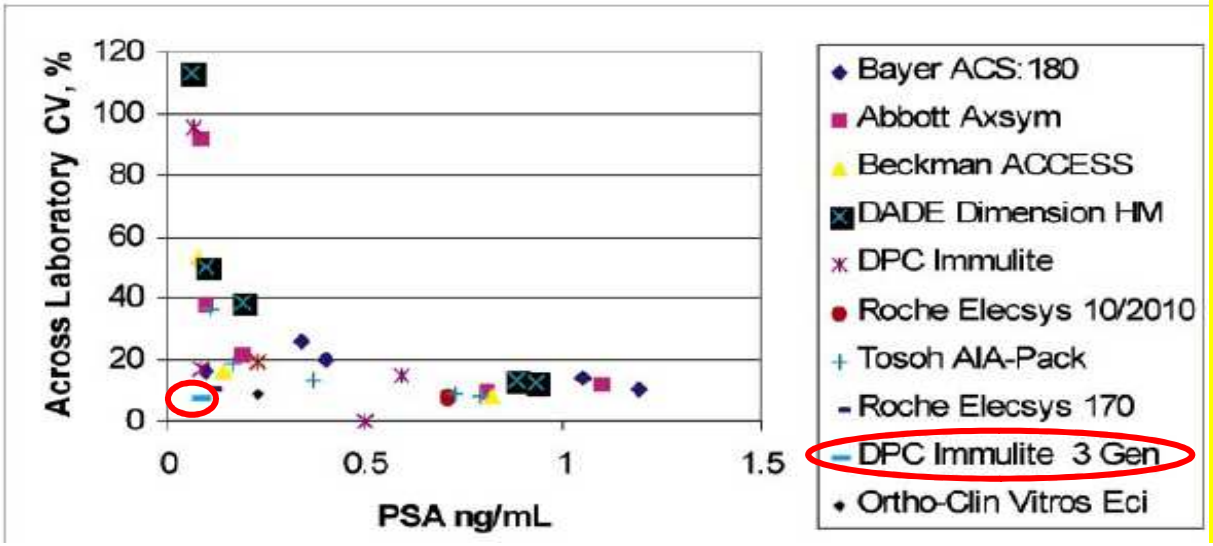
Test PSA 3° Generazione vs test PSA convenzionali

Arch Pathol Lab Med. 2004 Mar;128(3):341-3.
How sensitive is a prostate-specific antigen measurement? How sensitive does it need to be?

Bock JL, Klee GG.

… many of the currently used assays have intralaboratory coefficients of variation greater than 20% for PSA concentrations less than 0.4 ng/mL.
Also, there are major differences in the level of PSA reported by various assays in these low concentration samples. These level differences (if they are also seen in clinical samples) may cause clinical problems when fixed serum PSA thresholds (eg, 0.2 ng/mL) are used to make clinical decisions related to prostate tumor recurrence.

Cross plot of the interassay coefficient of variation (CV) of College of American Pathologists prostate-specific antigen (PSA) proficiency test results against the average value for various peer groups. In general, the CVs increase as the level of PSA decreases. Across-laboratory CVs are not consistently less than 20% until the concentration is 0.4 ng/mL or greater.



Autunno 2013:
Dismissione PSA 3° Generazione IMMULITE 2000

SIEMENS

A91DX-CAI-130655-XC1-4A00

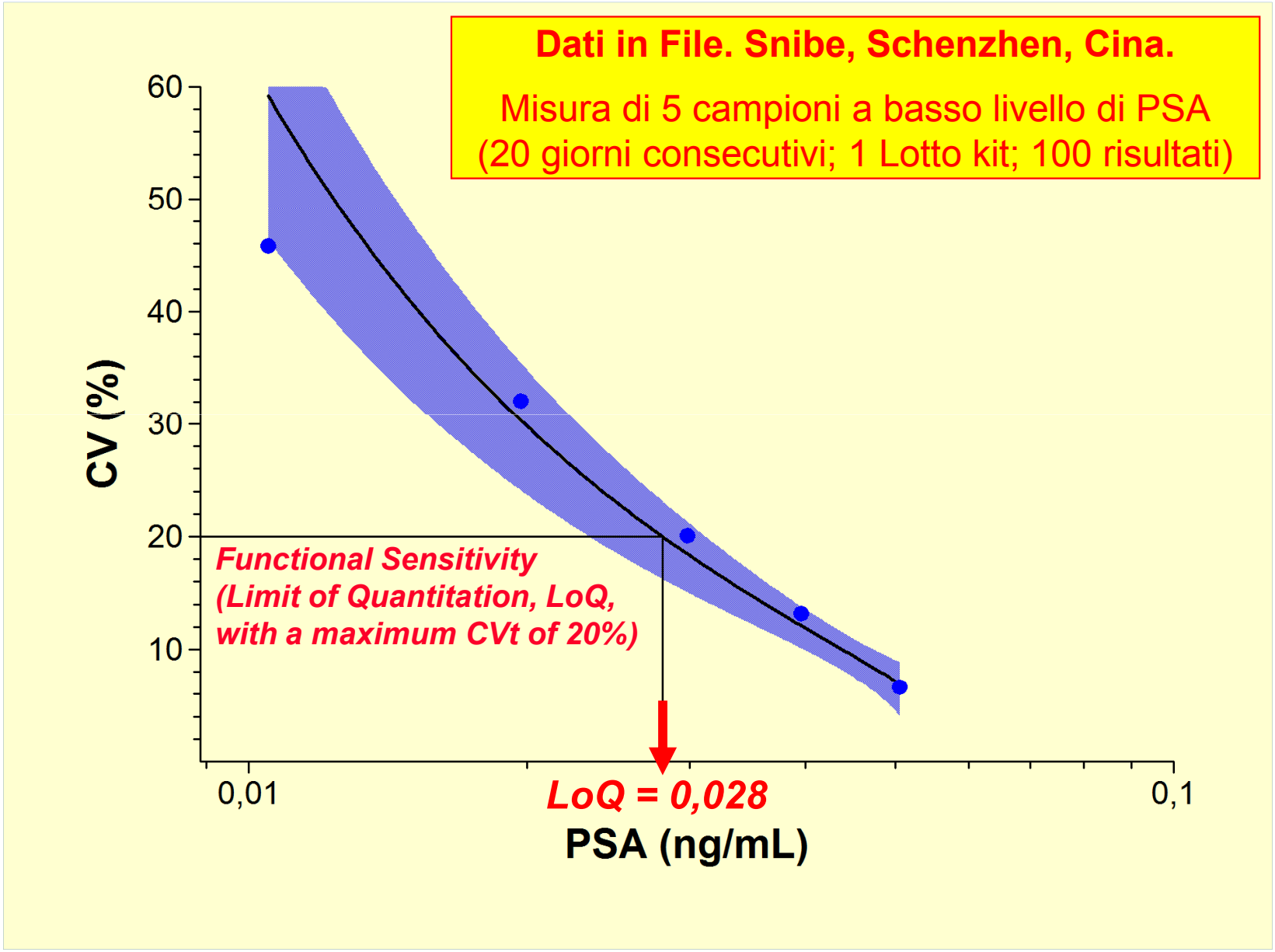
Importante Comunicazione relativa a prodotti

Annuncio di dismissione dal commercio dei kit

PSA di terza generazione per i sistemi IMMULITE 2000/2000 XPi

Soluzione:
PSA Maglumi !!!

Sensibilità Funzionale PSA Maglumi



Sensibilità Funzionale: NECESSITÀ DI VERIFICA TRA LOTTI KIT

Clin Biochem. 2012 Oct;45(15):1260-2.
Should functional sensitivity of a new thyroid stimulating hormone immunoassay be monitored routinely?
The ADVIA Centaur TSH3-UL assay experience.

Reix N, Massart C, Gasser F, Heurtault B, Agin A.

DESIGN AND METHODS:

The functional sensitivity (FS) of the ADVIA Centaur system TSH assay was assessed. We report the values yielded for QC materials in two clinical laboratories.

RESULTS:

The FS was <0.02 mIU/L. **The low-TSH QC (a serum pool) showed unacceptable between-lot imprecision (mean 0.0252 mIU/L, CV 22%).**

CONCLUSION:

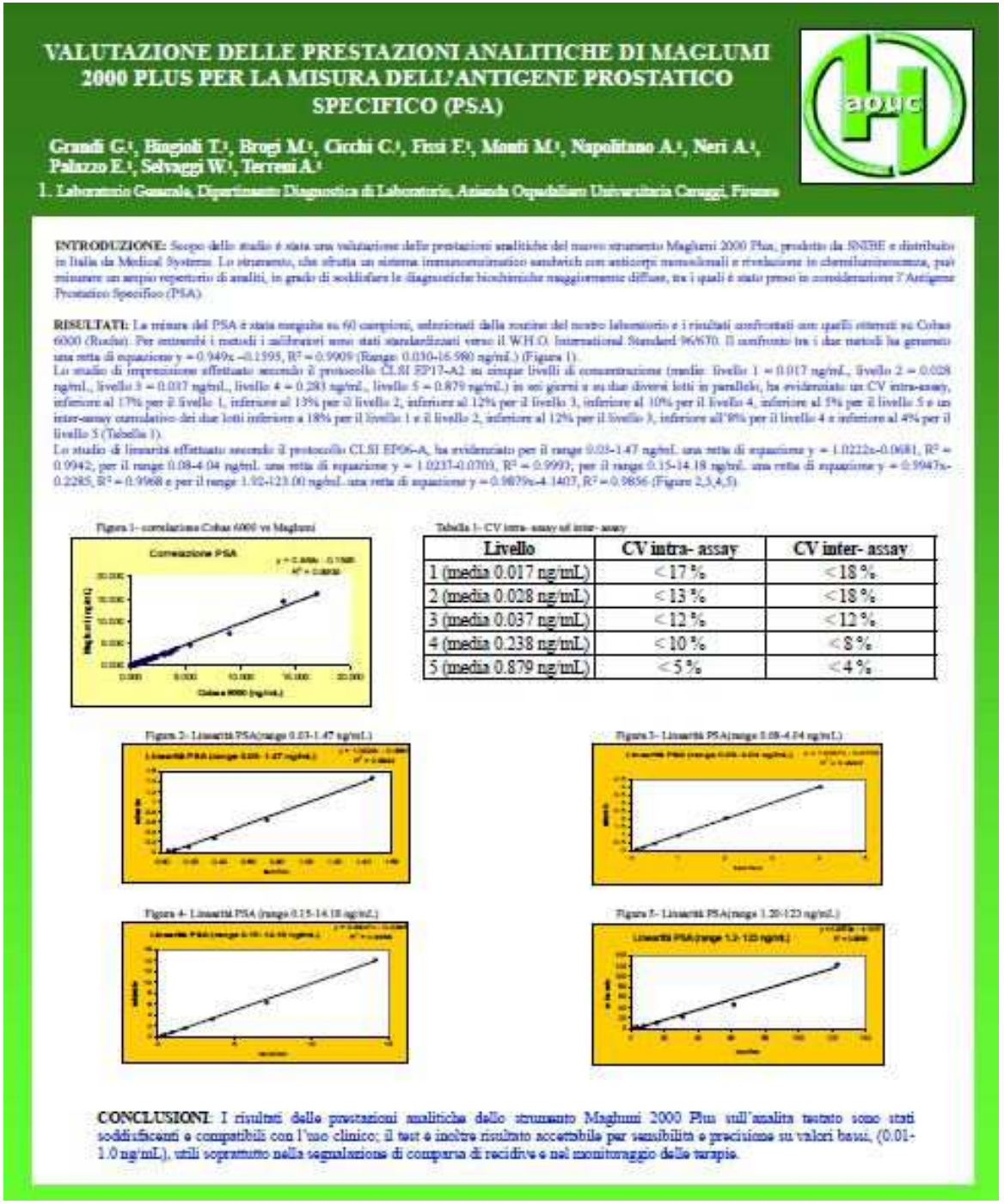
We do encourage healthcare laboratories to constitute low-TSH serum pools to ensure that the results they report meet 3rd-generation criteria.

Validazione
PSA Maglumi

ELAS 2013

VALUTAZIONE DELLE PRESTAZIONI ANALITICHE DI MAGLUMI 2000 PLUS PER LA MISURA DELL'ANTIGENE PROSTATICO SPECIFICO (PSA)

Laboratorio Generale, Dipartimento Diagnostica di Laboratorio, Azienda Ospedaliero Universitaria Careggi, Firenze



VALUTAZIONE DELLE PRESTAZIONI ANALITICHE DI MAGLUMI 2000 PLUS PER LA MISURA DELL'ANTIGENE PROSTATICO SPECIFICO (PSA)

Grandi G.[1], Bingioli T.[1], Brogi M.[1], Cicchi C.[1], Fizzi F.[1], Monti M.[1], Napolitano A.[1], Neri A.[1], Palazzo E.[1], Selvaggi W.[1], Terreni A.[1]

1. Laboratorio Generale, Dipartimento Diagnostica di Laboratorio, Azienda Ospedaliero Universitaria Careggi, Firenze

INTRODUZIONE: Scopo dello studio è stata una valutazione delle prestazioni analitiche del nuovo strumento Maglumi 2000 Plus, prodotto da SNIBE e distribuito in Italia da Medical Systems. Lo strumento, che sfrutta un sistema immunoenzimatico sandwich con anticorpi monoclonali e rivelazione in chemiluminescenza, può misurare un ampio repertorio di analiti, in grado di soddisfare le diagnostiche biochimiche maggiormente diffuse, tra i quali è stato preso in considerazione l'Antigene Prostatico Specifico (PSA).

RISULTATI: La misura del PSA è stata eseguita su 60 campioni, selezionati dalla routine del nostro laboratorio e i risultati confrontati con quelli ottenuti su Cobas 6000 (Roche). Per entrambi i metodi i calibratori sono stati standardizzati verso il W.H.O. International Standard 96/670. Il confronto tra i due metodi ha generato una retta di equazione y = 0.949x –0.1595, R^2 = 0.9909 (Range: 0.030-16.980 ng/mL) (Figura 1).
Lo studio di imprecisione effettuato secondo il protocollo CLSI EP17-A2 su cinque livelli di concentrazione (medie: livello 1 = 0.017 ng/mL, livello 2 = 0.028 ng/mL, livello 3 = 0.037 ng/mL, livello 4 = 0.283 ng/mL, livello 5 = 0.879 ng/mL) in sei giorni e su due diversi lotti in parallelo, ha evidenziato un CV intra-assay, inferiore al 17% per il livello 1, inferiore al 13% per il livello 2, inferiore al 12% per il livello 3, inferiore al 10% per il livello 4, inferiore al 5% per il livello 5 e un inter-assay cumulativo dei due lotti inferiore a 18% per il livello 1 e il livello 2, inferiore al 12% per il livello 3, inferiore all'8% per il livello 4 e inferiore al 4% per il livello 5 (Tabella 1).
Lo studio di linearità effettuato secondo il protocollo CLSI EP06-A, ha evidenziato per il range 0.03-1.47 ng/mL una retta di equazione y = 1.0222x-0.0681, R^2 = 0.9942, per il range 0.08-4.04 ng/mL una retta di equazione y = 1.0237-0.0703, R^2 = 0.9993, per il range 0.15-14.18 ng/mL una retta di equazione y = 0.9947x-0.2285, R^2 = 0.9968 e per il range 1.92-123.00 ng/mL una retta di equazione y = 0.9879x-4.1407, R^2 = 0.9856 (Figure 2,3,4,5).

Figura 1- correlazione Cobas 6000 vs Maglumi

Tabella 1- CV intra- assay ed inter- assay

Livello	CV intra- assay	CV inter- assay
1 (media 0.017 ng/mL)	< 17 %	< 18 %
2 (media 0.028 ng/mL)	< 13 %	< 18 %
3 (media 0.037 ng/mL)	< 12 %	< 12 %
4 (media 0.238 ng/mL)	< 10 %	< 8 %
5 (media 0.879 ng/mL)	< 5 %	< 4 %

Figura 2- Linearità PSA(range 0.03-1.47 ng/mL)

Figura 3- Linearità PSA(range 0.08-4.04 ng/mL)

Figura 4- Linearità PSA (range 0.15-14.18 ng/mL)

Figura 5- Linearità PSA(range 1.20-123 ng/mL)

CONCLUSIONI: I risultati delle prestazioni analitiche dello strumento Maglumi 2000 Plus sull'analita testato sono stati soddisfacenti e compatibili con l'uso clinico; il test è inoltre risultato accettabile per sensibilità e precisione su valori bassi, (0.01-1.0 ng/mL), utili soprattutto nella segnalazione di comparsa di recidive e nel monitoraggio delle terapie.

Validazione PSA Maglumi

VALUTAZIONE DELLE PRESTAZIONI ANALITICHE DI MAGLUMI 2000 PLUS PER LA MISURA DELL'ANTIGENE PROSTATICO SPECIFICO (PSA)

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ELAS 2013

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Lo studio di imprecisione effettuato secondo il protocollo CLSI EP17-A2 su cinque livelli di concentrazione **(medie: livello 1 = 0.017 ng/mL, livello 2 = 0.028 ng/mL, livello 3 = 0.037 ng/mL, livello 4 = 0.283 ng/mL, livello 5 = 0.879 ng/mL) in sei giorni e su due diversi lotti in parallelo, ha evidenziato un CV intra-assay, inferiore al 17% per il livello 1**, inferiore al 13% per il livello 2, inferiore al 12% per il livello 3, inferiore al 10% per il livello 4, inferiore al 5% per il livello 5 **e un inter-assay cumulativo dei due lotti inferiore a 18% per il livello 1** e il livello 2, inferiore al 12% per il livello 3, inferiore all'8% per il livello 4 e inferiore al 4% per il livello 5 (Tabella 1).

PSA Terza Gen.

Tabella 1- CV intra- assay ed inter- assay

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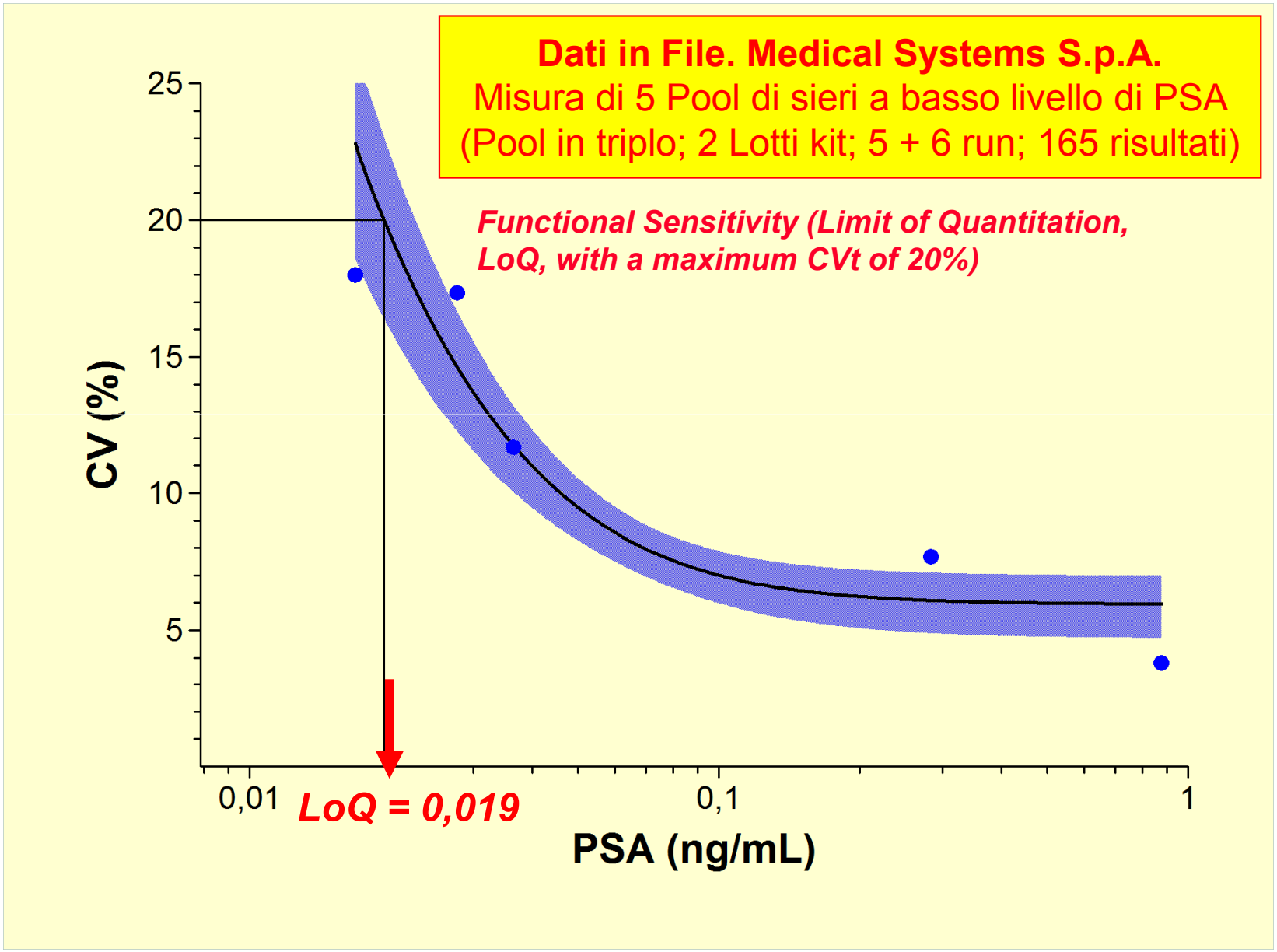
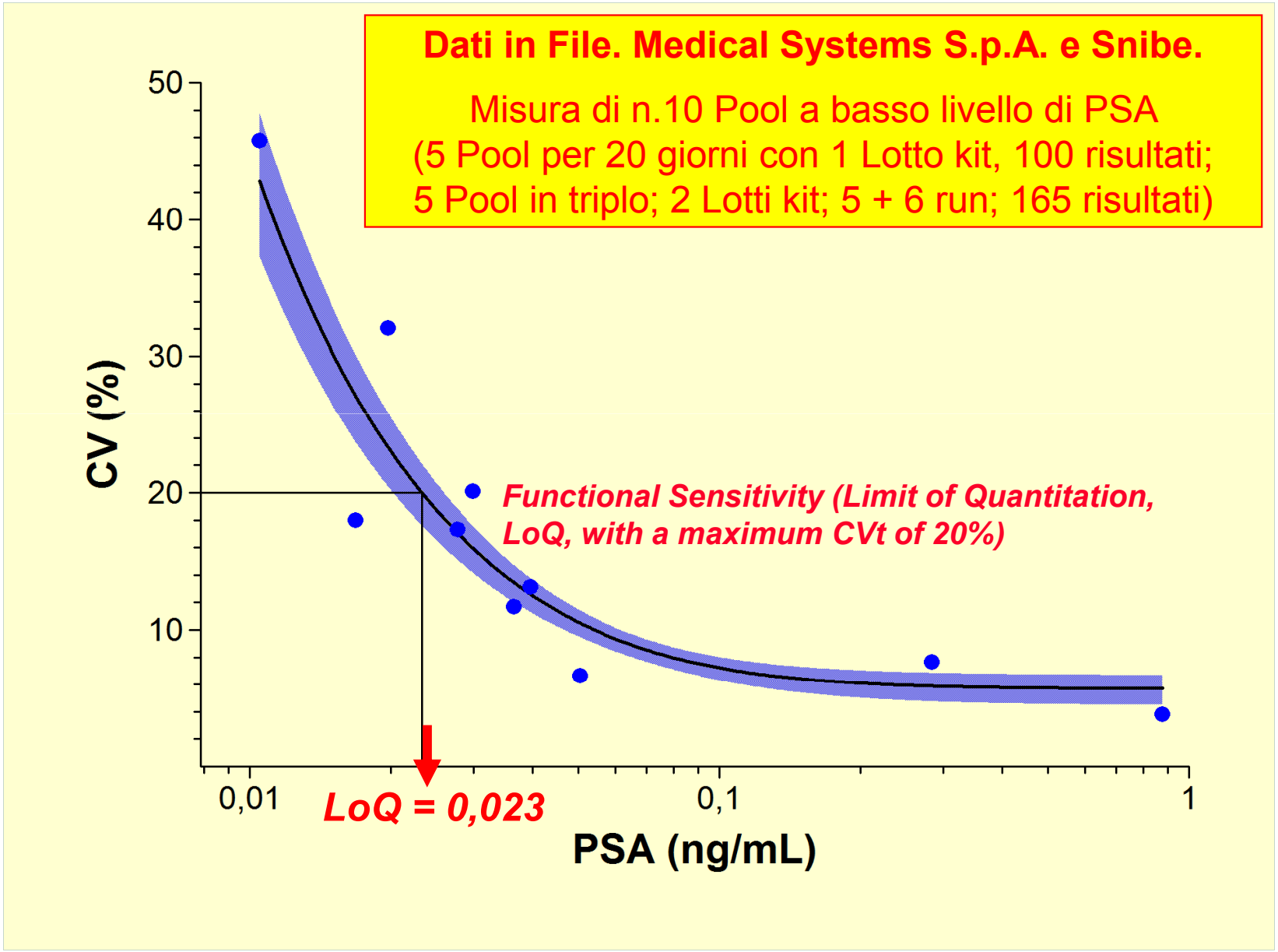
Sensibilità Funzionale PSA Maglumi: verifica su 2 lotti kit



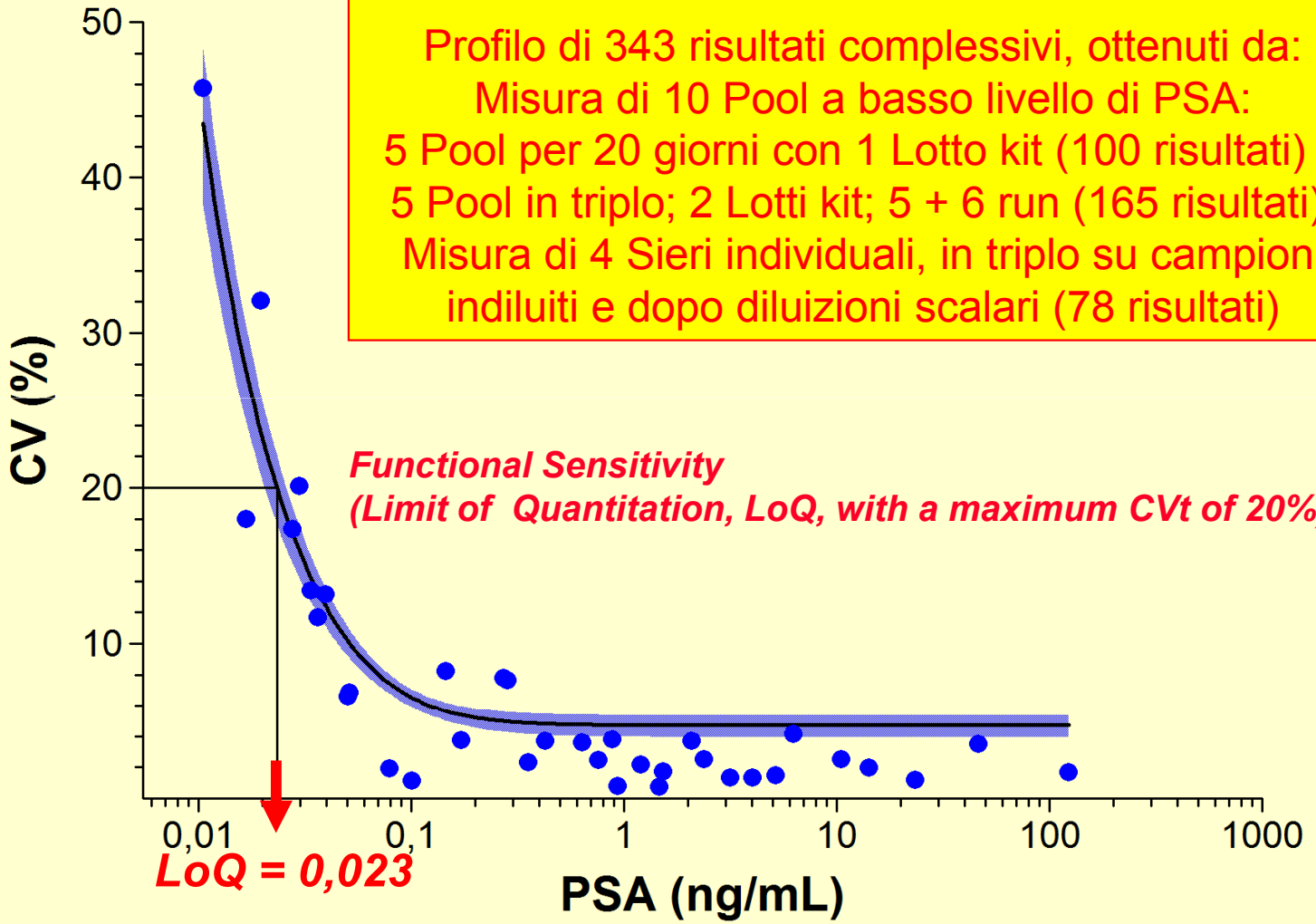
Sensibilità Funzionale PSA Maglumi: verifica su 3 lotti kit



Profilo di Precisione PSA Maglumi: verifica su 3 lotti kit (range campioni dosati: 0,010 – 123 ng/mL)

Dati in File. Medical Systems S.p.A. e Snibe.

Profilo di 343 risultati complessivi, ottenuti da:
Misura di 10 Pool a basso livello di PSA:
5 Pool per 20 giorni con 1 Lotto kit (100 risultati) e
5 Pool in triplo; 2 Lotti kit; 5 + 6 run (165 risultati);
Misura di 4 Sieri individuali, in triplo su campioni indiluiti e dopo diluizioni scalari (78 risultati)



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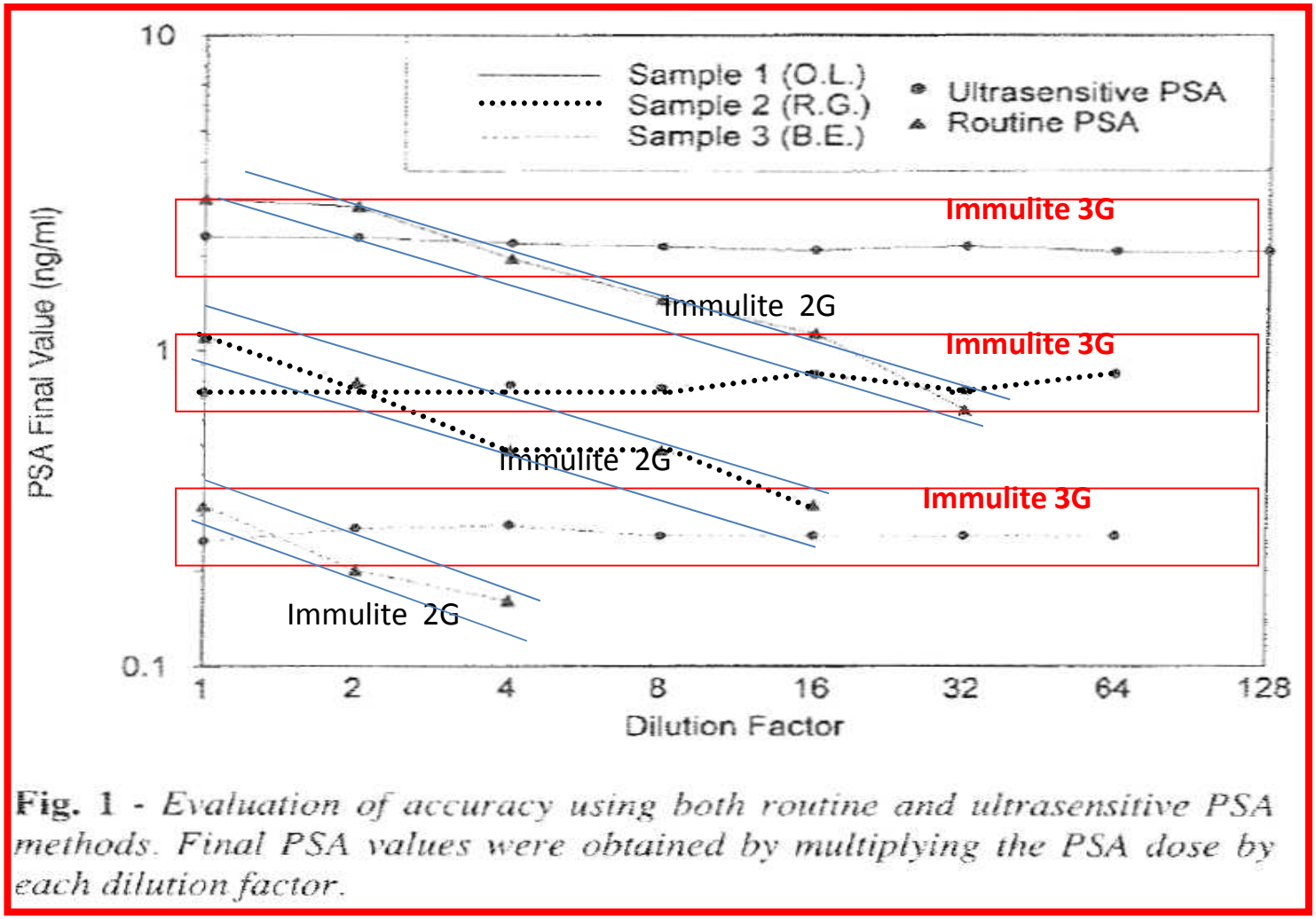
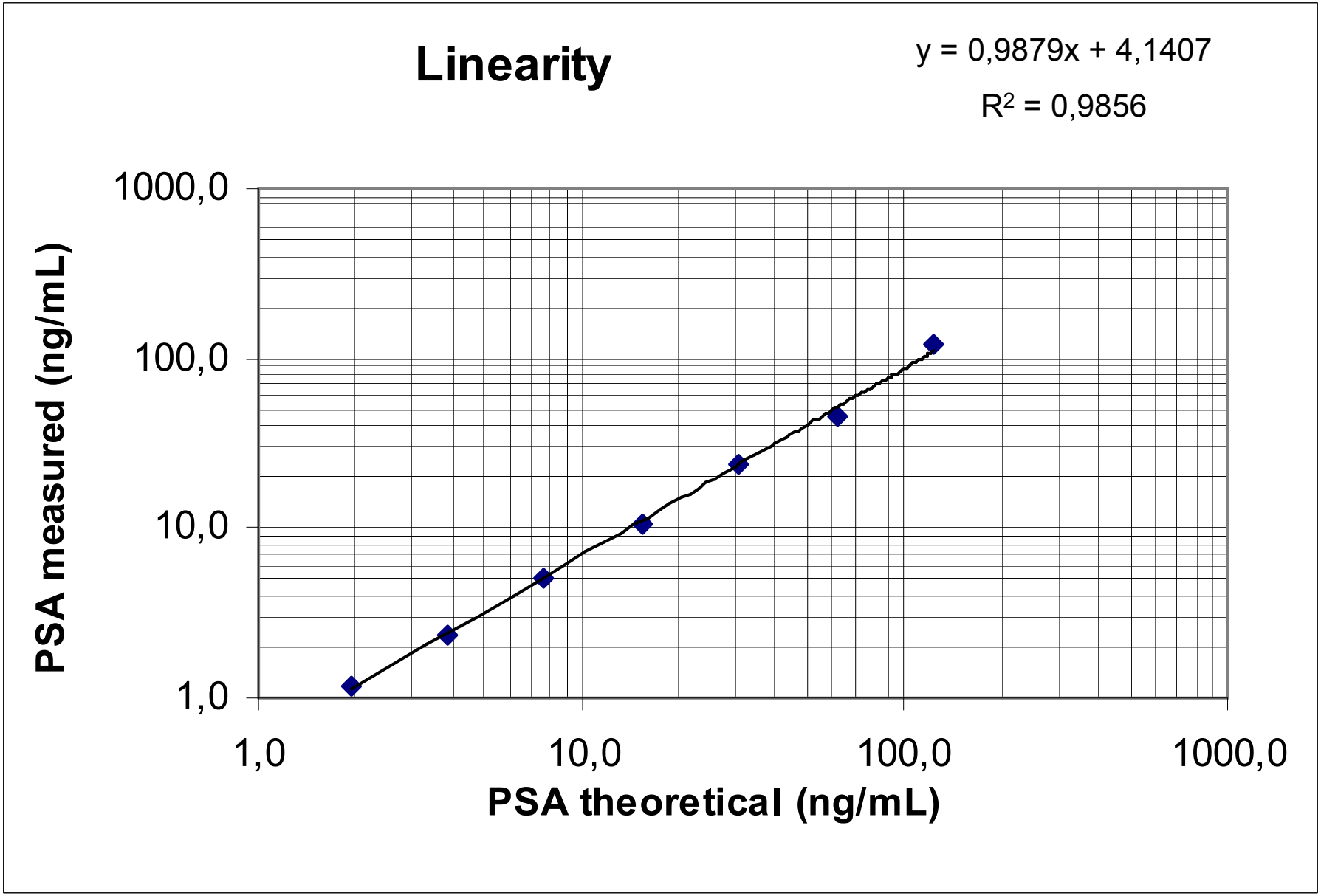
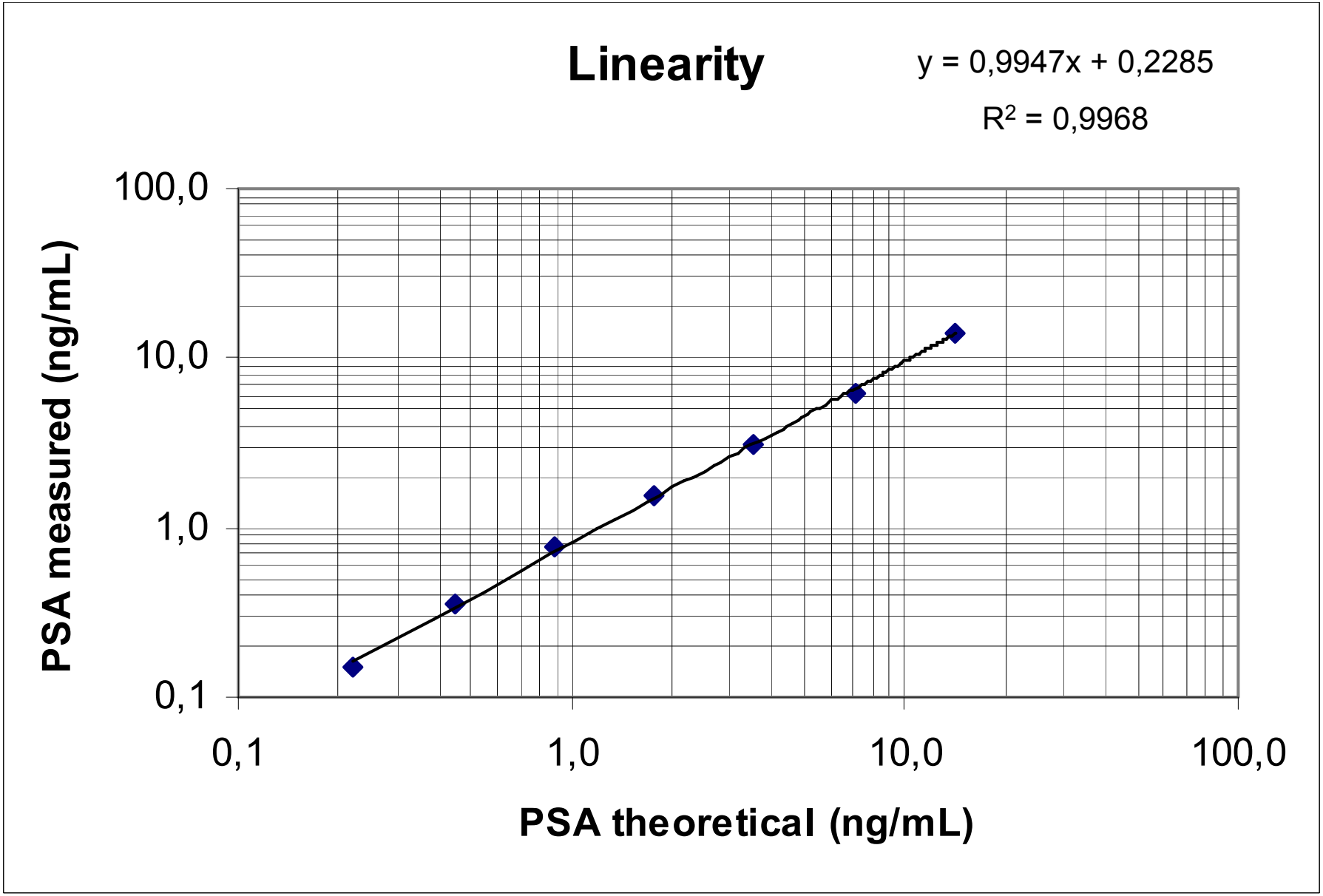


Fig. 1 - *Evaluation of accuracy using both routine and ultrasensitive PSA methods. Final PSA values were obtained by multiplying the PSA dose by each dilution factor.*

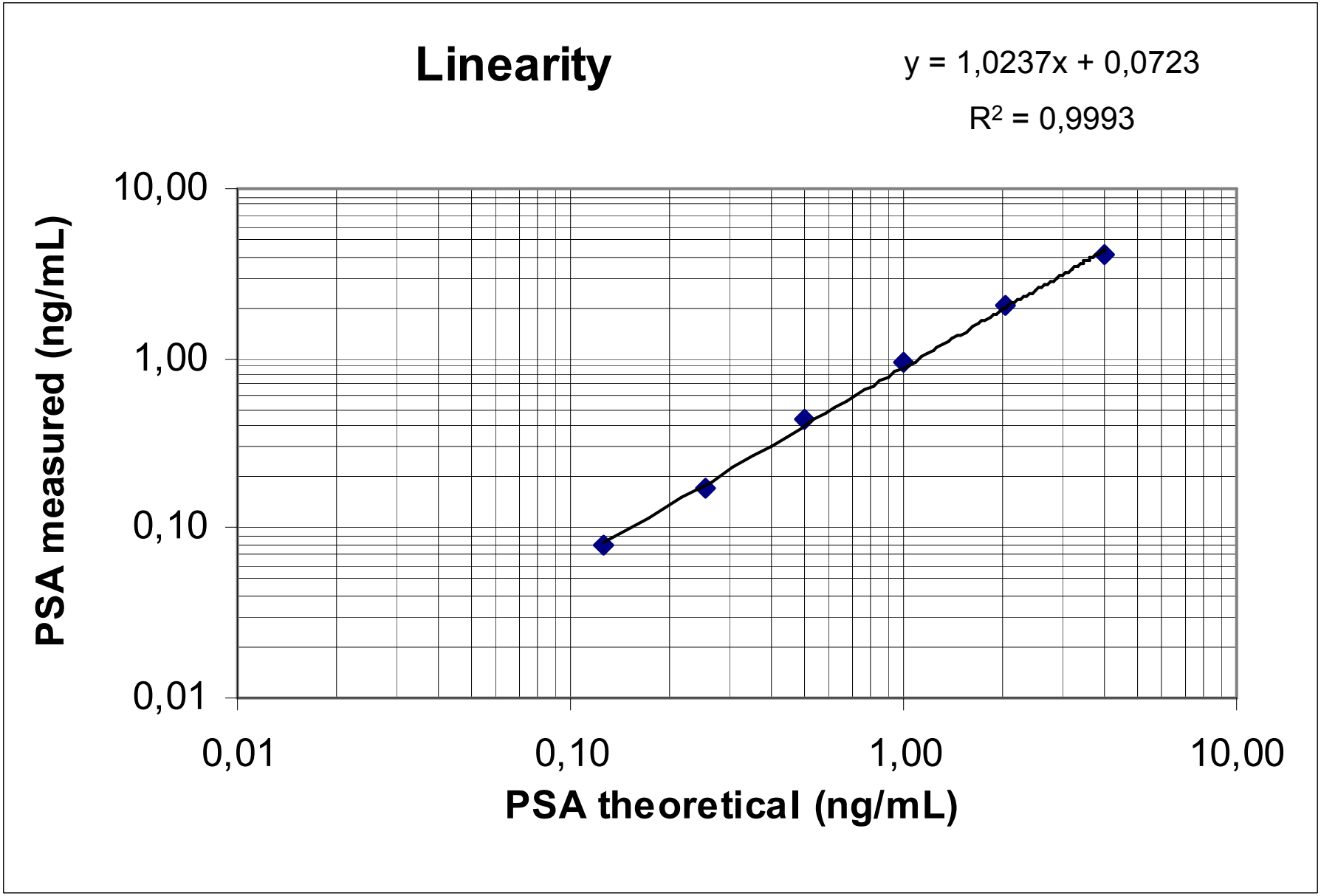
Diluizione PSA Maglumi (siero tal quale = 123 ng/mL)
Dati in File, Medical Systems S.p.A.



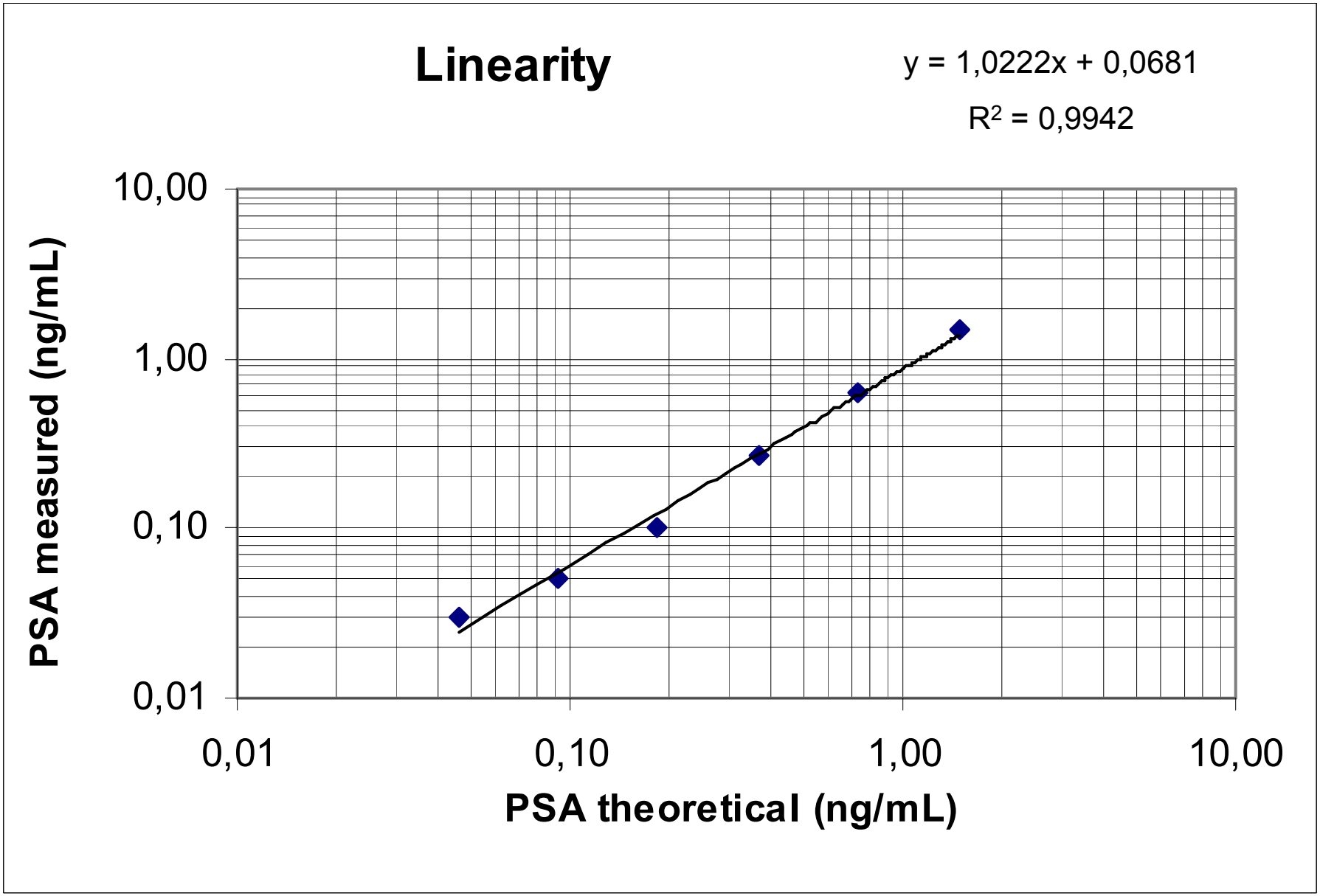
Diluizione PSA Maglumi (siero tal quale = 14,18 ng/mL)
Dati in File, Medical Systems S.p.A.



Diluizione PSA Maglumi (siero tal quale = 4,04 ng/mL)
Dati in File, Medical Systems S.p.A.



Diluizione PSA Maglumi (siero tal quale = 1,47 ng/mL)
Dati in File, Medical Systems S.p.A.



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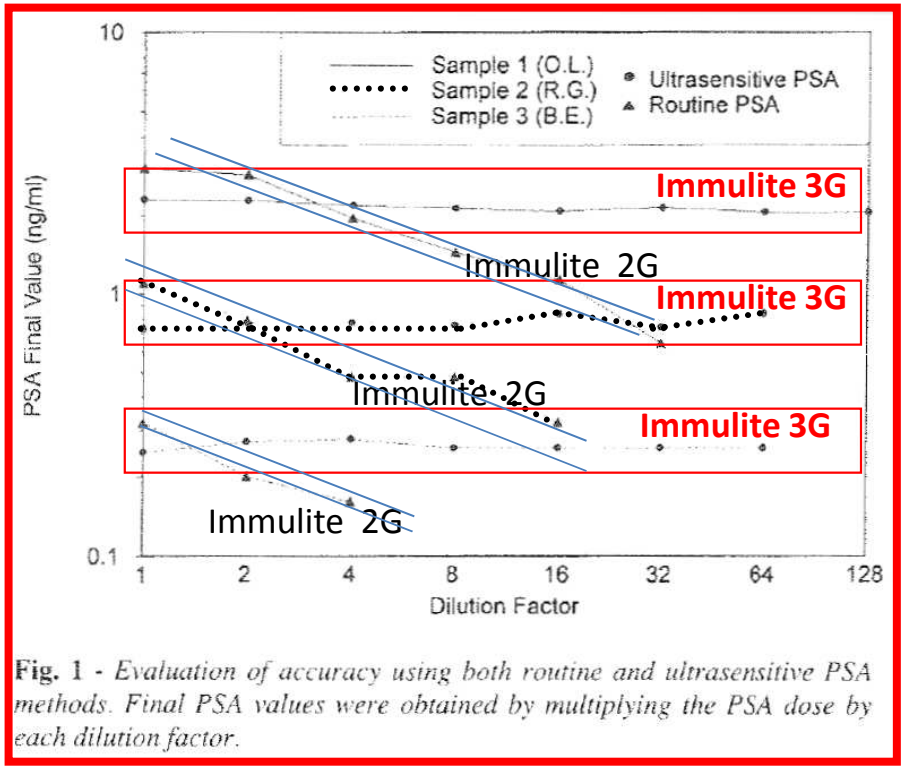

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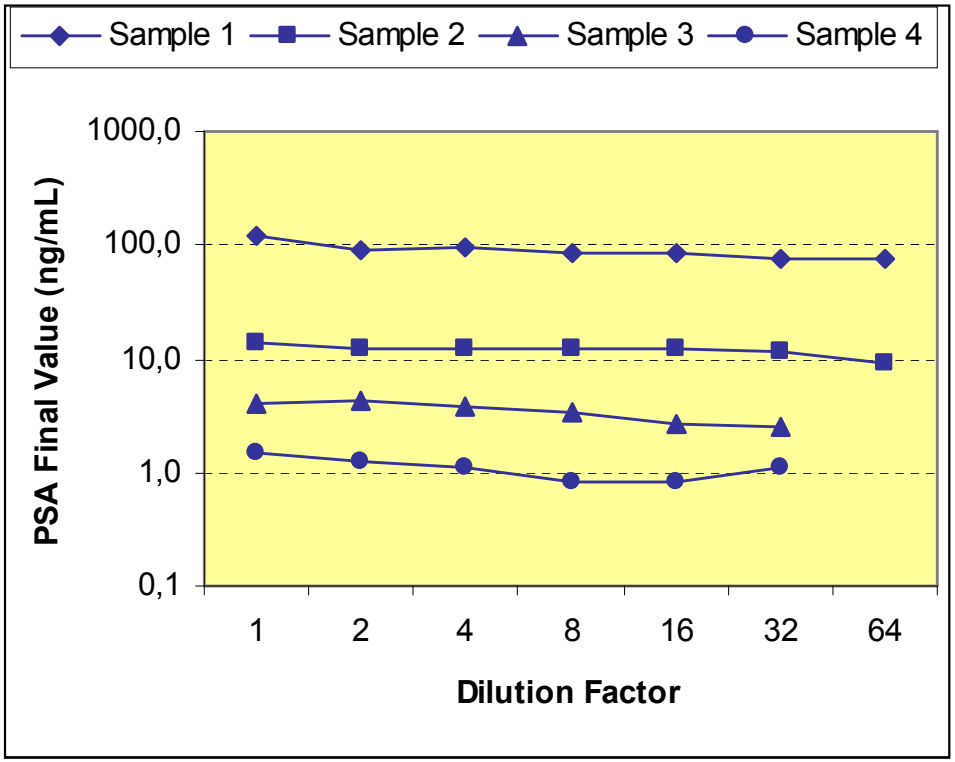
Diluizione PSA Maglumi

Dati in File.
Medical Systems S.p.A.



Calibrazione PSA Access:
Hybritech non intercambiabile con WHO

Clin Chem Lab Med 2008;46(5):623–629 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2008.129

Toward metrological traceability in the determination of prostate-specific antigen (PSA): calibrating Beckman Coulter Hybritech Access PSA assays to WHO standards compared with the traditional Hybritech standards

Carsten Stephan[1], Anna-Maria Kahrs[1], Silke Klotzek[1], Janett Reiche[3], Christian Müller[3], Michael Lein[1,2], Serdar Deger[1], Kurt Miller[1] and Klaus Jung[1,2,*]

[1] Department of Urology, Charité-Universitätsmedizin Berlin, Berlin, Germany
[2] Berlin Institute for Urologic Research, Berlin, Germany
[3] Institute of Laboratory Medicine and Pathobiochemistry, Charité-Universitätsmedizin Berlin, Berlin, Germany

Abstract

Background: The metrological traceability of prostate-specific antigen (PSA) assay calibration to WHO standards is desirable to potentially improve the comparability between PSA assays. A method comparison was performed between the traditionally standardized Beckman Coulter Hybritech Access PSA and free PSA (fPSA) assays and a new alternate calibration of assays aligned to the WHO standards 96/670 and 96/668, respectively.

Methods: Sera from 641 men with and without prostate cancer, various control materials and mixtures of different proportions of the WHO standards were measured with both assay calibrations.

Results: Excellent comparability between the corresponding assay calibrations was observed, with correlation coefficients of at least 0.996. The Passing-Bablok slopes were 0.747 for total PSA (tPSA), 0.776 for fPSA and 1.02 for the percentage ratio of fPSA to tPSA (%fPSA), while the corresponding percentages of the new WHO-aligned assay results related to the traditional assays were 76.2%, 77% and 102.2%. Receiver operating characteristics revealed no differences between the two PSA assay calibrations.

Conclusions: The WHO calibration yields results approximately 25% lower for tPSA and fPSA values when compared with the conventional Hybritech calibration. Using the WHO-aligned PSA assay, a tPSA cut-off of 3 µg/L should be considered in clinical practice, while %fPSA cut-offs could be retained.

Clin Chem Lab Med 2008;46:623–9.

Calibrazione PSA Access:
Hybritech non intercambiabile con WHO

Access®
Immunoassay Systems

Hybritech® PSA
REF 37200

BECKMAN COULTER®

Warning PSA concentrations are dependent on the standard used to calibrate the assay. PSA concentrations based on calibration to the WHO 96/670 Reference Preparation will differ significantly from PSA concentrations based on calibration to the original Hybritech Tandem™-R assay. The concentrations are not interchangeable. If the calibration is changed, accepted laboratory practice is to establish a new baseline for patient monitoring.[1]

Calibrazione PSA Access:
Hybritech non intercambiabile con WHO

Access®
Immunoassay Systems

Hybritech® PSA
REF 37200

BECKMAN COULTER®

Materials Provided	R1 Access Hybritech PSA Reagent Packs
Materials Required But Not Provided	1. Access Hybritech PSA Calibrators Cat. No. 37205 Two options for calibration are provided with the Access Hybritech PSA Calibrators, Hybritech calibration or WHO calibration. **Hybritech calibration:** concentrations are zero and approximately 0.5, 2.0, 10, 75 and 150 ng/mL **WHO calibration:** concentrations are zero and approximately 0.4, 1.7, 8, 58 and 121 ng/mL
Limitations of the Procedure	1. Samples can be accurately measured within the analytic range of the lower limit of detection and the highest calibrator value (approximately 0.008–150 ng/mL Hybritech calibration or 0.008 – 121 ng/mL WHO calibration).

Sensibilità Funzionale PSA Immulite 2000 3G

Third Generation PSA

Analytical Sensitivity: 0.003 ng/mL

Functional Sensitivity: 0.01 ng/mL, as demonstrated by the studies summarized in the Precision section. (Functional sensitivity is defined as the lowest concentration that can be measured with an interassay CV of 20%.)

Sensibilità Funzionale PSA Immulite 2000

IMMULITE 2000

PSA *(Range Esteso)*

Analytical Sensitivity: 0.04 ng/mL

? **Functional Sensitivity:** ***?***

(Functional sensitivity is defined as the lowest concentration that can be measured with an interassay CV of 20%.)

Sensibilità Funzionale PSA Roche Cobas

total PSA

total (free + complexed) PSA - Prostate-specific antigen (tPSA)

Elecsys® Systems 1010/2010/MODULAR ANALYTICS E170

Functional sensitivity:

0.03 ng/ml

The functional sensitivity is the tPSA concentration that can be reproducibly measured with an interassay coefficient of variation of ≤ 20%.

Sensibilità Funzionale PSA Abbott Architect

ARCHITECT SYSTEM

CE 0843 E

Total PSA

IVD REF 7K70

B7K700

77-4138/R2

Total PSA

Sensitivity[a]

Functional

Functional sensitivity is defined as the lowest concentration that can be measured with an inter-assay coefficient of variation (CV) less than or equal to 20%. The calculated %CV for one reagent lot from all sites was plotted against the mean concentration of each panel. A parametric curve was fitted through the data, and the functional sensitivity was determined to be less than 0.05 ng/mL, which corresponded to less than 20% CV on the fitted curve.

Sensibilità Funzionale PSA Tosoh AIA

EU rev. PSA-020312

Attention: **This IFU complies with IVD directive 98/79/EC and is intended for use by customers operating in a member state of the European Union**

ST AIA-PACK PSAII

INTENDED USE

ST AIA-PACK PSAII is designed for in vitro diagnostic use only for the quantitative measurement of prostate specific antigen (PSA) in human serum or heparinised plasma on Tosoh AIA System Analysers.

SENSITIVITY

Sensibilità Analitica

The minimum detectable concentration (MDC) of prostate specific antigen is estimated to be 0.01 ng/ml. The MDC is defined as the concentration of PSA that corresponds to the rate of fluorescence which is two standard deviations from the mean rate of fluorescence of 5 repeat determinations by ST AIA-PACK PSAII CALIBRATOR (1).

Sensibilità Funzionale ?

Sensibilità Funzionale PSA Tosoh AIA

LIPPINCOTT WILLIAMS & WILKINS
A Wolters Kluwer Company

The Journal of Urology

Volume 155(5) May 1996 pages 1658-1660

The Periurethral Glands do not Significantly Influence the Serum Prostate Specific Antigen Concentration

[Clinical Urology: Original Article, Accepted for publication November 17, 1995.]

Oesterling, Joseph E.*; Tekchandani, Anita H.; Martin, Sandra K.; Bergstralh, Erik J.; Reichstein, Esther; Diamandis, Eleftherios P.; Yemoto, Cheryl; Stamey, Thomas A.

…The analytical sensitivity of the Tosoh PSA assay is 0.02 ng/mL, which was determined by running the 0 calibrator 20 times in the ultra-sensitive format and represents the addition of 2 standard deviations above the mean…The inter-assay coefficient of variation is 26.3% at a PSA of 0.11 ng/mL…

Sensibilità Funzionale: ~ 0,14 ng/mL

(lowest concentration that can be measured with an inter-assay CV of 20%)

Sensibilità Funzionale PSA DiaSorin Liaison

DiaSorin Deutschland GmbH
Von-Hevesy-Str. 3, 63128 Dietzenbach - GERMANY
www.diasorin.com

CE 0197

Changes: § 4, 11, 12, 15.10
Deletions: §

LIAISON® PSA (REF 314381)

15.10. Analytical and functional sensitivity

Analytical sensitivity:
Analytical sensitivity is defined as the minimum detectable dose distinguishable from zero by 2 standard deviations.

Functional sensitivity:
The functional sensitivity (defined as the lowest analyte concentration that can be determined with an inter-assay CV < 20%)

	Analytical sensitivity	Functional sensitivity
LIAISON® Analyzer family	0.09 ng/mL	0.15 ng/mL

Sensibilità Funzionale PSA Brahms Kryptor

B·R·A·H·M·S

Total PSA

KRYPTOR

Instruction for Use

B·R·A·H·M·S Total PSA KRYPTOR

IVD

for professional use only

CE 0483

Sensitivity

The functional assay sensitivity (20 % CV) has been assessed as being 0.16 ng/mL.

Sensibilità Funzionale PSA Snibe Maglumi

深圳市新产业生物医学工程股份有限公司
Shenzhen New Industries Biomedical Engineering Co., Ltd (SNIBE Co., Ltd)

MAGLUMI Total PSA (CLIA)

1) Traceability

To perform an accurate calibration, we have provided the test calibrators standardized against the WHO 1st Reference Reagent 96/670.

3) Functional Sensitivity

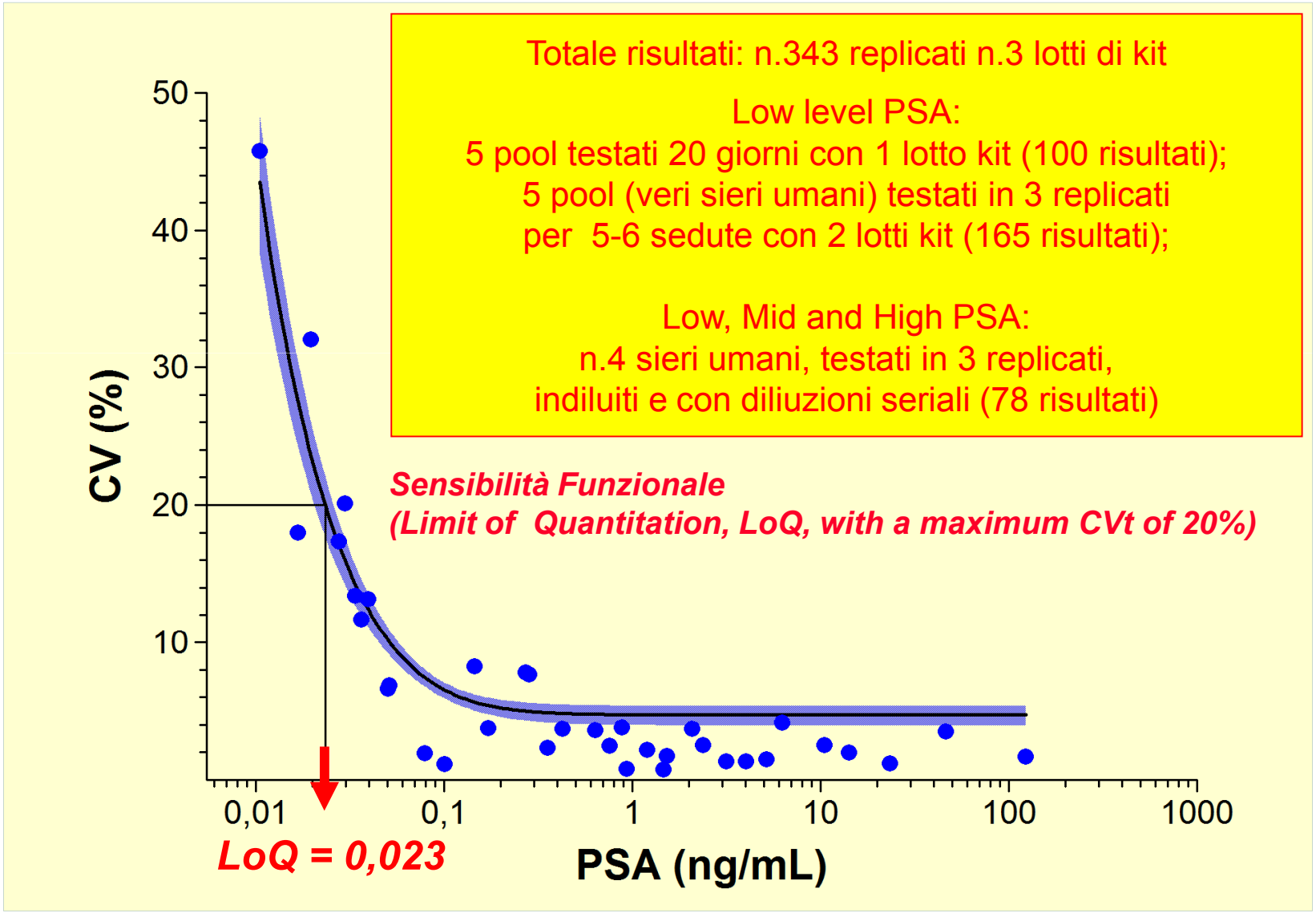
The functional sensitivity is defined as the concentration of total PSA at a total %CV exceeds 20%. The functional sensitivity of total PSA is less than 0.03ng/ml.

Sensibilità Funzionale (S.F.) e Range di Misura dei test PSA (ng/mL)

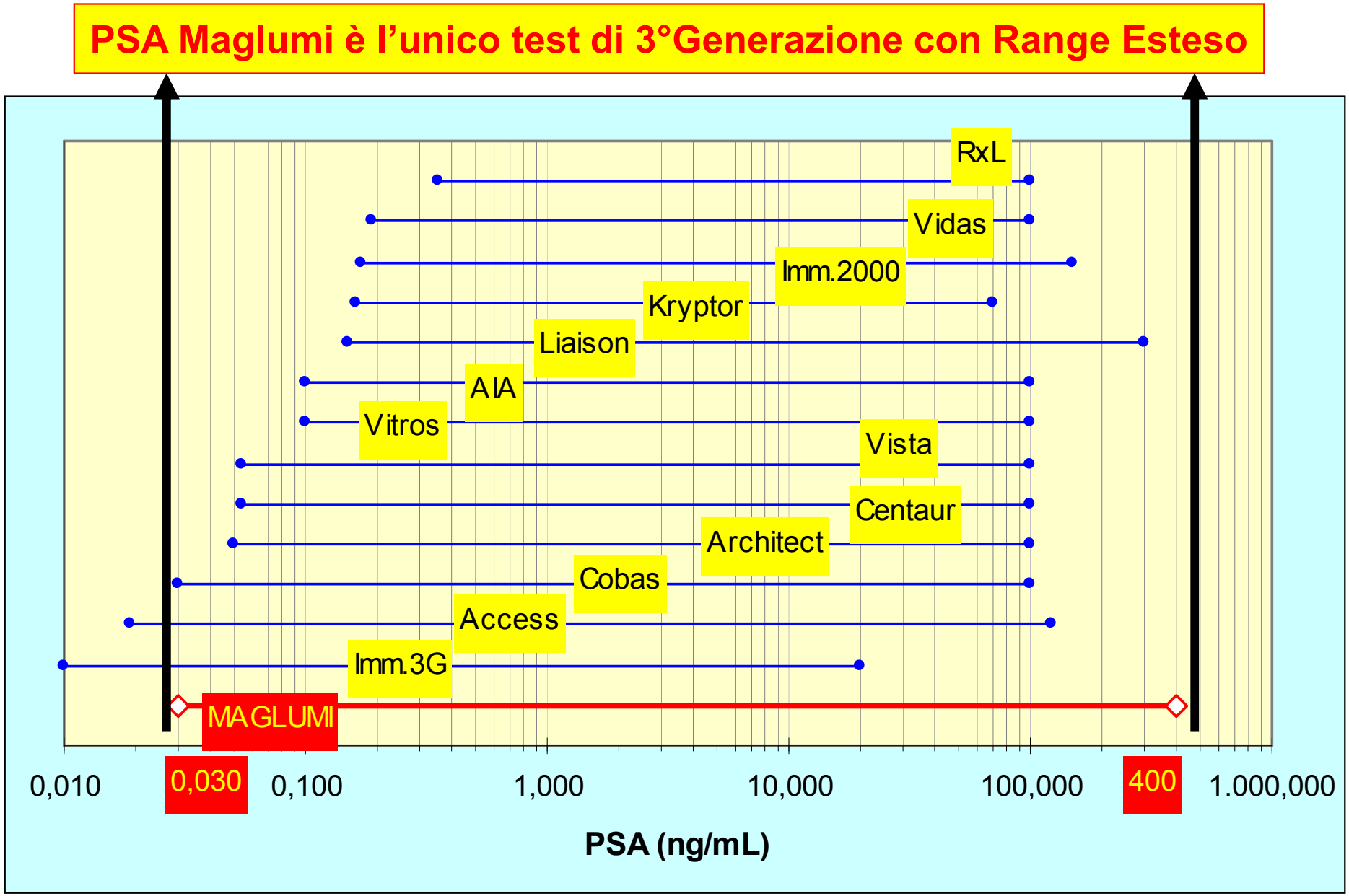
	S.F.	Range
~~PSA 3G Immulite 2000~~ *(cessata disponibilità)*	0,01	20
PSA Immulite 2000	~0,20	150
PSA Roche Cobas	0,03	100
PSA Snibe Maglumi	0,03	400
PSA Abbott Architect	0,05	100
PSA DiaSorin Liaison	0,15	300

MAGLUMI Total PSA

Profilo di Precisione (range: 0,010 – 123 ng/mL)
Dati in File: Medical Systems



Test PSA: Sensibilità Funzionale e Intervallo di Misura



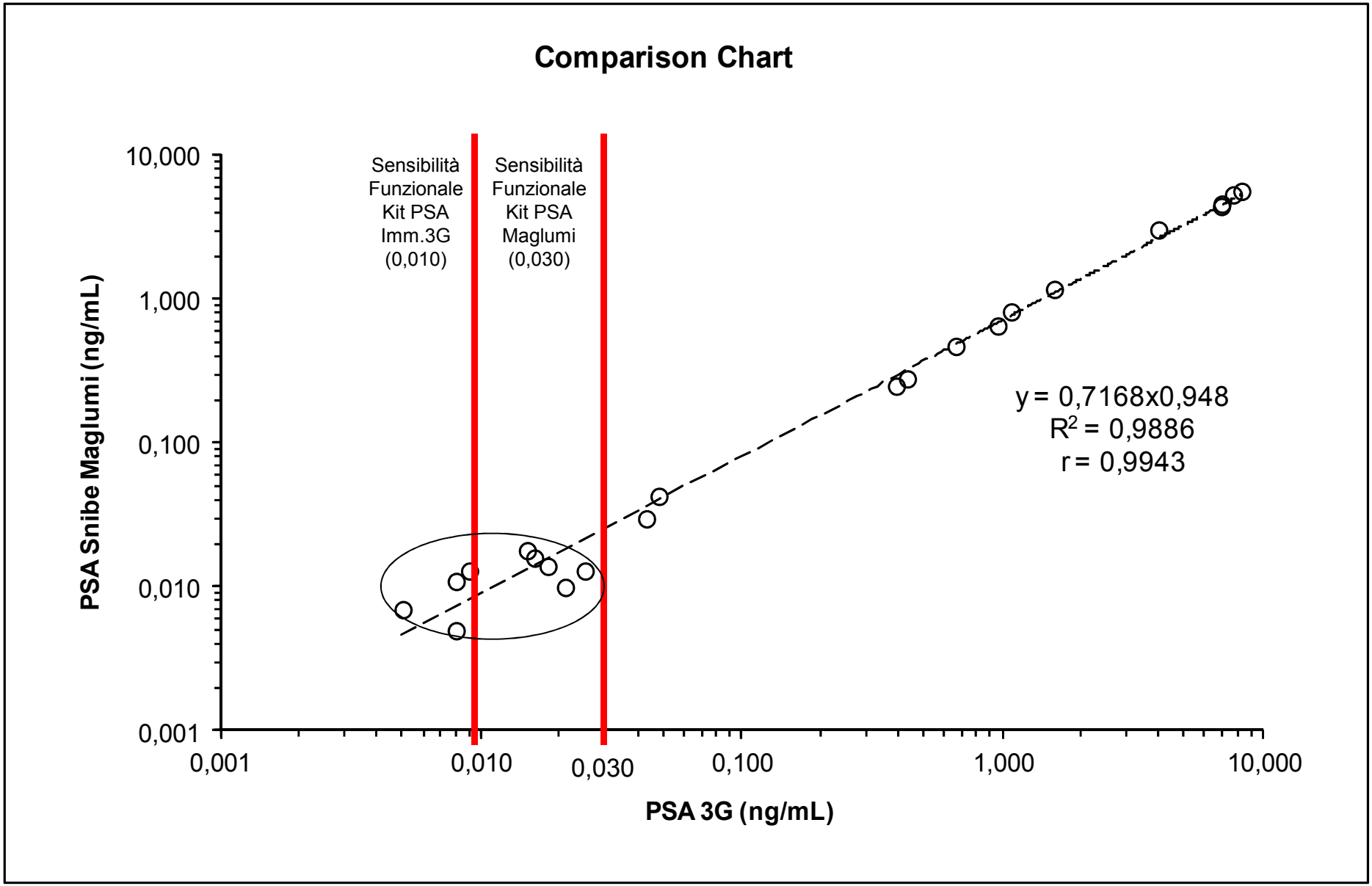
Sensibilità Funzionale PSA Immulite 2000 3G

Third Generation PSA

Analytical Sensitivity: 0.003 ng/mL

Functional Sensitivity: 0.01 ng/mL, as demonstrated by the studies summarized in the Precision section. (Functional sensitivity is defined as the lowest concentration that can be measured with an interassay CV of 20%.)

Correlazione kit PSA Maglumi vs test PSA Immulite 3G
Dati in File. Medical Systems S.p.A.



Sensibilità Funzionale PSA Abbott Architect

ARCHITECT SYSTEM

CE 0843 E

Total PSA

IVD REF 7K70

B7K700

77-4138/R2

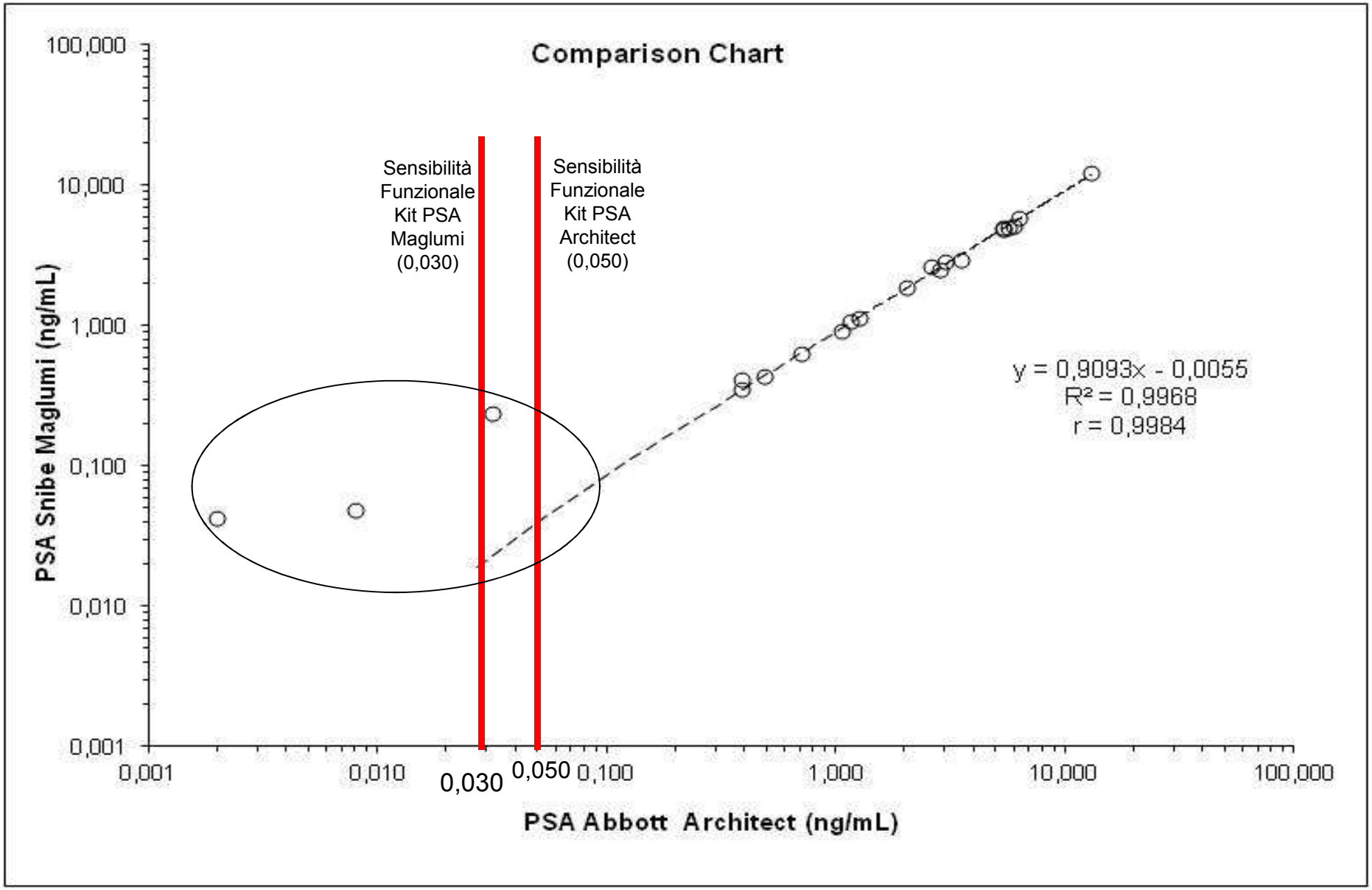
Total PSA

Sensitivity[a]

Functional

Functional sensitivity is defined as the lowest concentration that can be measured with an inter-assay coefficient of variation (CV) less than or equal to 20%. The calculated %CV for one reagent lot from all sites was plotted against the mean concentration of each panel. A parametric curve was fitted through the data, and the functional sensitivity was determined to be less than 0.05 ng/mL, which corresponded to less than 20% CV on the fitted curve.

Correlazione kit PSA Maglumi vs test PSA Architect
Dati in File. Medical Systems S.p.A.



Variabilità tra metodi PSA e Ratio F/T PSA %

Tumor Biol. (2014) 35:1867–1873
DOI 10.1007/s13277-013-1249-2

RESEARCH ARTICLE

Variability of assay methods for total and free PSA after WHO standardization

(pag. 1 di 3)

Tumour Biol. 2014 Mar;35(3):1867-73.
Variability of assay methods for total and free PSA after WHO standardization.
Foj L, Filella X, Alcover J, Augé JM, Escudero JM, Molina R.

The variability of total PSA (tPSA) and free PSA (fPSA) results among commercial assays has been suggested to be decreased by calibration to World Health Organization (WHO) reference materials. To characterize the current situation, it is necessary to know its impact in the critical cutoffs used in clinical practice. In the present study, we tested 167 samples with tPSA concentrations of 0 to 20 µg/L using seven PSA and six fPSA commercial assays, including Access, ARCHITECT i2000, ADVIA Centaur XP, IMMULITE 2000, Elecsys, and Lumipulse G1200, in which we only measured tPSA. tPSA and fPSA were measured in Access using the Hybritech and WHO calibrators. Passing–Bablok analysis was performed for PSA, and percentage of fPSA with the Hybritech-calibrated access comparison assay. ***For tPSA, relative differences were more than 10% at 0.2 µg/L for ARCHITECT i2000, and at a critical concentration of 3, 4, and 10 µg/L, the relative difference was exceeded by ADVIA Centaur XP and WHO-calibrated Access. For percent fPSA, at a critical concentration of 10%, the 10% relative difference limit was exceeded by IMMULITE 2000 assay. At a critical concentration of 20 and 25%, ADVIA Centaur XP, ARCHITECT i2000, and IMMULITE 2000 assays exceeded the 10% relative difference limit.*** *We have shown significant discordances between assays included in this study despite advances in standardization conducted in the last years. Further harmonization efforts are required in order to obtain a complete clinical concordance.*

… The Access PSA assay using the Hybritech calibrators was selected as the reference assay because it was the original assay developed for the measurement of tPSA, and it was the first FDA-approved assay for prostate cancer detection …

Variabilità tra metodi PSA e Ratio F/T PSA %

Tumor Biol. (2014) 35:1867–1873
DOI 10.1007/s13277-013-1249-2

RESEARCH ARTICLE

Variability of assay methods for total and free PSA after WHO standardization

L. Foj · X Filella · J. Alcover · J. M. Augé · J. M. Escudero · R. Molina

(pag. 2 di 3)

… For patients with tPSA of <2 µg/L, the slopes ranged from 0.882 to 1.098 for ADVIA Centaur XP and IMMULITE 2000 assays, respectively. The y-intercepts ranged from −0.0088 to 0.0030 µg/L for ARCHITECT i2000 and Lumipulse G1200 assays, respectively. The correlation coefficients ranged from0.969 to 0.995. At the critical concentration of 0.2 µg/L, a relative difference of 10% was exceeded by ARCHITECT i2000.

… Results for percent fPSA for patients with tPSA between 2 and 20 µg/L and the Hybritech-calibrated Access comparison assay are shown in Fig. 4. The slopes ranged from 0.936 to 1.245 for IMMULITE 2000 and ARCHITECT i2000 assays, respectively. The y-intercepts ranged from −2.862 to 0.172 µg/L for ARCHITECT i2000 and Elecsys assays, respectively. The correlation coefficients ranged from 0.947 to 0.976. For the percentage of fPSA, at a critical concentration of 10%, the 10% relative difference limit was exceeded only by IMMULITE 2000 assay. At a critical concentration of 20 and 25%, ADVIA Centaur XP, ARCHITECT i2000, and IMMULITE 2000 assays exceeded the 10% relative difference limit (Table 4).

… The reference range of 4 µg/L was originally determined for the Hybritech Tandem-R assay [15] and later ratified, using the same test, by Catalona et al. [16] in a large multicenter study. This cutoff has been used to select patients for biopsy in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial [17] and in the European Randomized Study of Screening for Prostate Cancer until 1997, when all the centers involved in this study recommended biopsy in men with PSA of ≥3 µg/L [18]. Both studies used the Hybritech PSA test, currently manufactured by Beckman Coulter.

These critical points have been used also for other tests, even when there are differences between assays.

Variabilità tra metodi PSA e Ratio F/T PSA %

Tumor Biol. (2014) 35:1867–1873
DOI 10.1007/s13277-013-1249-2

RESEARCH ARTICLE

Variability of assay methods for total and free PSA after WHO standardization

(pag. 3 di 3)

According to our data, differences higher than the limit bias of 10% at the critical points of 3 and 4 µg/L were observed for ADVIA Centaur and WHO-calibrated Access. On the other hand, differences between 5 and 10% at these critical points were observed for ARCHITECT 2000.

Differences in tPSA values were lower for patients with PSA between 0 and 2 µg/L. This is a decisive range of results with usefulness in following patients treated with radical prostatectomy. Nevertheless, there is a high degree of variability in the definition of biochemical recurrence after radical prostatectomy, and the PSA cutoffs of 0.2 and 0.4 µg/L are the most commonly points used [20]. We have chosen these critical points to evaluate differences between assays. Relative differences higher than 10% were observed only for ARCHITECT at the critical point of 0.2 µg/L. However, differences between 5 and 10% were observed for three and five assays at the cutoffs of 0.2 and 0.4 µg/L, respectively (Table 2).

… We studied the variability of percent fPSA using six different assays, especially considering the cut points of 10, 20, and 25%. Relative differences higher than 10% in reference to the Hybritech-calibrated Access were observed for the majority of assays, especially at the cutoffs of 20 and 25%. Differences lower than 5% were observed only for Elecsys at the three critical points evaluated in our study. Initial results comparing Access PSA test using WHO and Hybritech calibrators showed that results of tPSA are 20–25% lower when WHO standard is adopted [21]. This trend is also observed for other assays using the reference material from WHO, but for other assays, differences with the Hybritech PSA test are minimal despite the use the WHO standard. Discordant PSA and percent fPSA results between assays are maintained despite the introduction of WHO standards for the measurement of both biomarkers. Differences between PSA assays using WHO standards may be due to other factors, including matrix effects and affinity antibodies.

… We have shown in our study that differences between assays could be considerable. We obtained that the maximum differences for tPSA could be over 20% in 74% of patients and over 40% in 41% of patients.

Variabilità tra metodi PSA e Ratio F/T PSA %

Clin. Lab. 2012;58:XXX-XXX

ORIGINAL ARTICLE

Method Comparison for Determination of the Tumor Markers AFP, CEA, PSA and Free PSA Between Immulite 2000 XPI and Dimension Vista 1500

(pag. 1 di 1)

Clin Lab. 2012;58(1-2):97-105.

Method comparison for determination of the tumor markers AFP, CEA, PSA and free PSA between Immulite 2000 XPI and Dimension Vista 1500.

Zur B, Holdenrieder S, Walgenbach-Brünagel G, Albers E, Stoffel-Wagner B.

… The assays for tPSA and fPSA, as developed with the LOCI technology for the Dimension Vista, show good comparability with results obtained from the IMMULITE 2000 XPI. However, lower measurement ranges for fPSA as well as individual divergences must be taken into consideration in the event of method changeover.

… For the entire measuring range, correlation of Vista PSA and IMMULITE 2000 PSA (N = 711) was at r = 0.971, slope 1.006 (1.000 - 1.013, 95% CI), intercept 0 (-0.003 – 0.95% CI) (Figure 4). In the measuring range relevant for clinical diagnosis, <20 ng/mL, correlation of both tests was very good (r = 0.994) … A changeover from IMMULITE 2000 PSA to Vista PSA would not necessarily result in misinterpretations since we found no significant differences in the method comparison, not even in the generally defined cut-off value of 4 ng/mL [27].

… For the entire measuring range, correlation of Vista free PSA and IMMULITE 2000 free PSA (N = 95) was at r = 0.988, slope 0.910 (0.886 - 0.949, 95% CI), intercept 0.007 (-0.005 - 0.018, 95% CI) (Figure 5) … Correlation between Vista free PSA and IMMULITE 2000 free PSA was very good. However, values were slightly lower across the entire measurement range (Figure 5).

… Our method comparison with IMMULITE 2000 delivered convincing results. However, in individual cases, markedly different values were obtained. Therefore, parallel measurements, as required in all tumor marker changeovers, are essential in the event of instrument changeover.

Variabilità tra metodi PSA


Clinical Biochemistry 47 (2014) 897–900

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

(pag. 1 di 3)

Assessing the necessity of including a crossover period with dual reporting when changing total prostate-specific antigen methods

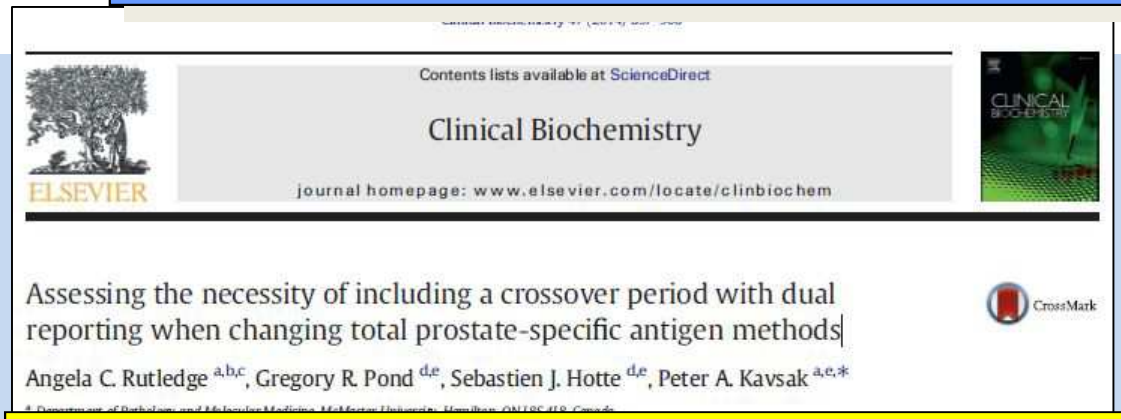
Clin Biochem. 2014 Jul;47(10-11):897-900.
Assessing the necessity of including a crossover period with dual reporting when changing total prostate-specific antigen methods.
Rutledge AC, Pond GR, Hotte SJ, Kavsak PA.

… Protein tumor marker results do not agree well across platforms from different manufacturers when immunoassays are not standardized. Accordingly, it is recommended that laboratories have a specific protocol in place when changing tumor marker platforms [1]. One strategy is to run the current and the new methods in parallel for a period of time and to report results from both tests (i.e., dual reporting). This permits new baseline values to be established.

… Options are limited for the laboratory when changing analytical methods for tumor markers. Standardization between methods should alleviate this burden. Our objective was to assess the necessity of dual reporting for total prostate-specific antigen (tPSA) when changing methods that have been calibrated against the World Health Organization PSA reference material.

… Despite the WHO primary reference material for PSA, a reference measurement procedure is still lacking for tPSA [7]. This deficiency has prevented tPSA results from different platforms from being used interchangeably, with differences of up to 15% being observed [2,3]. The lack of interassay agreement in tPSA results has also been noted to affect clinical interpretation [8].

Variabilità tra metodi PSA



Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Assessing the necessity of including a crossover period with dual reporting when changing total prostate-specific antigen methods

Angela C. Rutledge [a,b,c], Gregory R. Pond [d,e], Sebastien J. Hotte [d,e], Peter A. Kavsak [a,e,*]

(pag. 2 di 3)

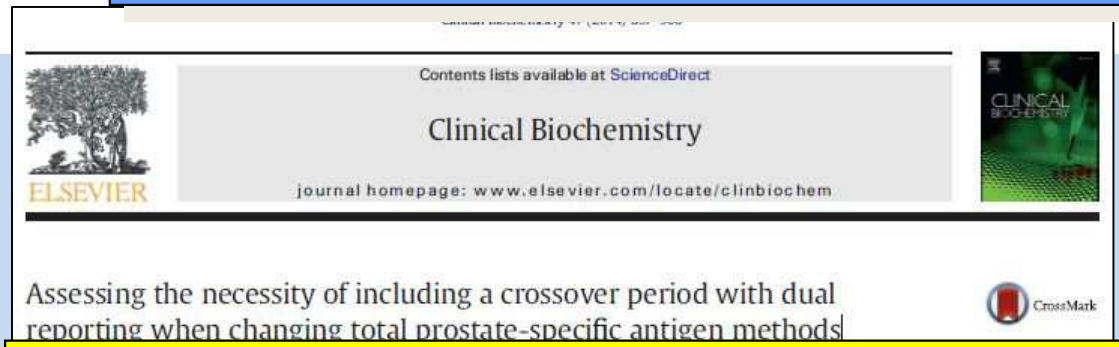
… Based on the Passing & Bablok regression and Pearson correlation, the data from the initial validation and the crossover period appear to agree and correlate very well between the Roche E-Modular and Abbott ARCHITECT tPSA assays.

However, when assessing comparability of tPSA results using the CLSI guideline [5] (Method#1), only half of the results are in agreement. Using this criterion of comparability based on CVi, it would be prudent to perform dual reporting when changing tPSA methods. The dual reporting would ensure that the total PSA results from the new method could be placed in context by the results from the current method, thereby avoiding confusion and possible misinterpretation by clinicians.

Using an alternative approach (Method#2), based on analytical imprecision, a metric the laboratory is accustomed to assessing and discussing, a concentration range of optimal agreement between the two tPSA assays may be empirically determined. With as few as 40 samples covering a sufficient span of tPSA results, a concentration range where agreement is most acceptable may be observed. In our validation study, the range of concentrations where the most consecutive Roche results fell within the allowable imprecision of the Abbott tPSA assay was 3.3 to 19 µg/L. Importantly, testing this range in the crossover period confirmed that 3.3 to 19 µg/L yielded an optimal agreement range where 95% of the 331 paired results in this region were in agreement.

If only samples falling outside of the range of optimal agreement were tested on the current platform as well as the new platform, in this case only 70% of the samples would have required dual reporting.

Variabilità tra metodi PSA



Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Assessing the necessity of including a crossover period with dual reporting when changing total prostate-specific antigen methods

(pag. 3 di 3)

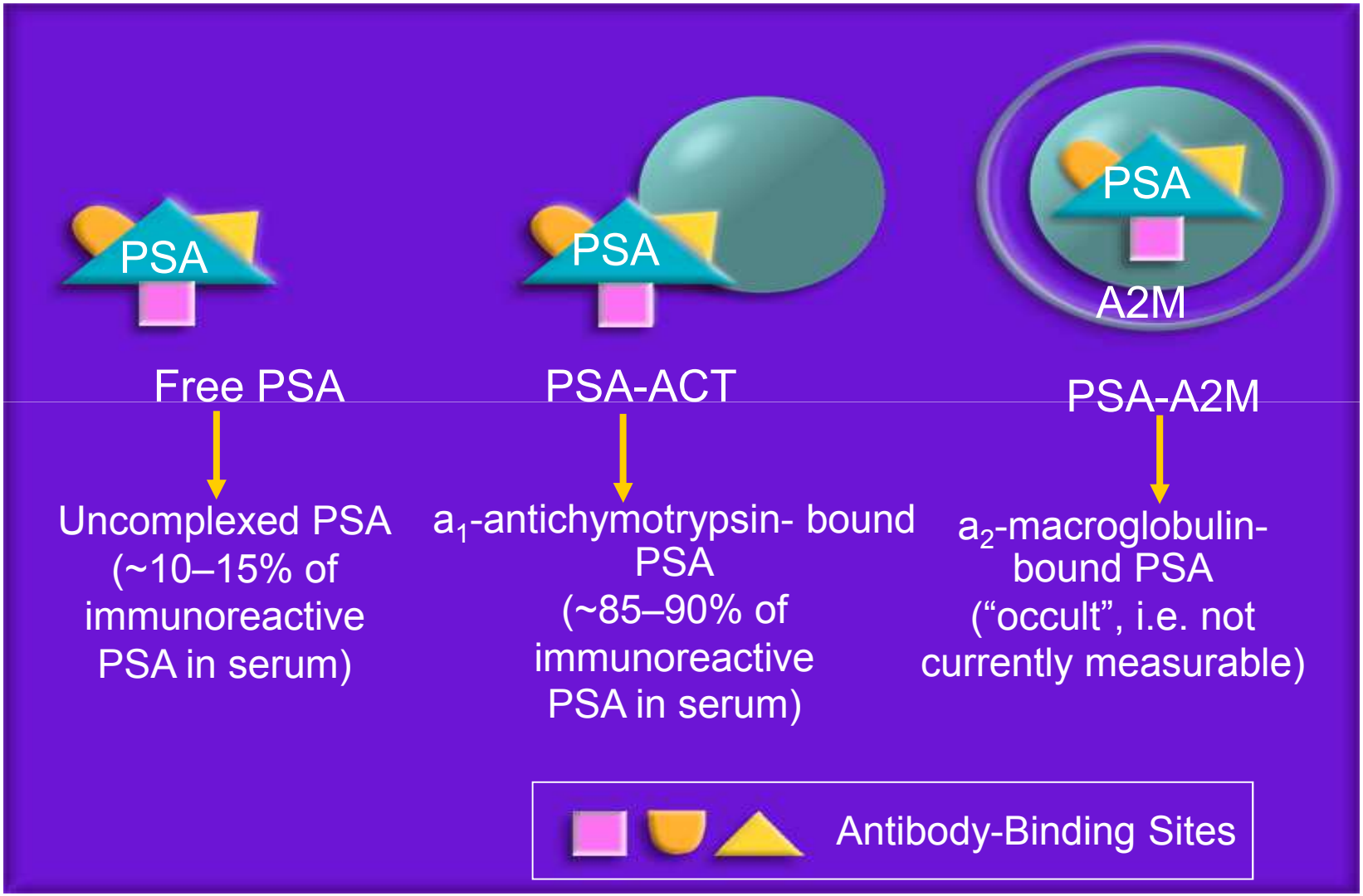
It is important to emphasize that although the differences observed between the Roche and Abbott tPSA assays are most often not clinically relevant, there a number of instances where the variations alone may affect clinical decision making.

… For example, many would argue that the difference between a value of 2.9 and 4.2 µg/L (an identified discordant result in our crossover study) is minimal and unlikely to be clinically relevant. However, if a patient had monthly tPSA concentrations of 2.1, 2.3, 2.6, and then 4.2 µg/L, it would likely become clinically actionable given the rapid rise and doubling time, whereas concentrations of 2.1, 2.3, 2.6, then 2.9 µg/L might still warrant a wait and see approach. As if often the case, the laboratory is unaware of the clinical rationale on ordering a tPSA, as it may be used for monitoring therapy, detecting recurrence and possibly for screening [9], as such it is difficult to truly assess what impact an inaccurate tPSA result would have on patient care.

… Recommendations on how to best change tumor marker assays are limited; however, methods that have undergone some form of standardization, such as tPSA, should agree much better between platforms than the other tumor markers. Therefore, for tPSA, it may be possible to restrict dual reporting to concentrations outside an optimal agreement range. The approaches outlined here are unlikely to be useful for other tumor markers, which have not undergone standardization efforts and are likely to need complete dual reporting. It is important to note that while partial dual reporting would help both budgetary and workload issues, until a study assessing the impact of such an approach on clinical care is conducted, laboratories should still consider performing dual reporting of tPSA when changing methods so that clinicians can re-establish baseline values.

… These findings suggest that dual reporting of tPSA is required when changing methods. However, the extent of dual reporting may be limited to specific concentration ranges with future studies required to validate selective dual reporting when changing tPSA assays.

Forme molecolari di PSA



Medical Systems: oltre 20 anni di automazione di PSA & Free PSA per il Ratio F/T PSA %

Il primo test al mondo

Free PSA in AUTOMAZIONE

prodotto da DPC

(Diagnostic Products Corp, USA)

è stato rilasciato alle vendite

nel 1994

IMMULITE®
Magazine

IMMULITE® *Magazine* n.2, febbraio 1995

Free PSA: NOVITA' MONDIALE !!!

La recente disponibilità di due nuovi test DPC IMMULITE, entrambi in relazione alle determinazioni dell'Antigene Prostatico Specifico (PSA), conferma la leadership mondiale raggiunta dalla DPC nello studio delle patologie prostatiche, ed offre l'opportunità di un breve aggiornamento sugli sviluppi diagnostici in questo settore.

PSA

Il PSA è una singola glicoproteina presente nel siero in forma libera ed in diversi complessi, il principale dei quali è quello con l'alfa1-anti-chimotripsina (ACT). La proporzione di PSA libero (Free PSA) e complessato (PSA-ACT) è del 15% e, rispettivamente, 85% (Rif.8, 24). Entrambe le forme costituiscono il PSA "totale" immunoreattivo, ed entrambe sono egualmente dosate con il kit IMMULITE PSA (extended range) e con il nuovissimo kit IMMULITE Third Generation PSA.

PSA: CARATTERISTICHE BIOCHIMICHE

Glicoproteina:	93% aminoacidi; 7% glucidi
Peso molecolare:	~ 32-35 kD (catena singola)
Att.enzimatica:	proteasi sierica (famiglia kallicreine)
Forme:	* non complessata (Free PSA); * complessate a proteine con attività inibitrice delle proteasi sieriche: -Alfa1-AntiChimoTripsina (PSA-ACT); -Alfa2-MacroGlobulina (PSA-AMG)
Produzione:	espresso tipicamente dalla prostata, sia nel tessuto normale che tumorale

NOTA:
la nozione che il PSA sia esclusivamente tessuto-specifico e genere-specifico è stata rettificata da recenti conferme che minimi livelli di PSA sono rilevabili anche nelle ghiandole peri-uretrali femminili, nei citosol di tumori mammari positivi per i recettori progestinici e nel latte materno (Rif. 22). E' stato quindi ipotizzato che il PSA sia un utile indice endocrino di risposta d'organo a steroidi circolanti, principalmente androgeni e progesterone.

MEDICAL SYSTEMS & DPC PER IL PSA:
SIAMO DA 11 ANNI SEMPRE IL N° 1 !

ESPERIENZA E QUALITA' NON SI IMPROVVISANO... SOPRATTUTTO NELLA DIAGNOSTICA !

INFATTI, DPC VANTA OLTRE 11 ANNI DI STUDI SUL DOSAGGIO DEL PSA & OLTRE 23 ANNI NELLA PRODUZIONE DI DOSAGGI RIA E IMMUNOCHIMICI

STATO-DELL'ARTE NEI DOSAGGI PSA DPC:

-Dosaggio Ultra-Sensibile del PSA-Totale (ACT-PSA + FREE PSA):
IMMULITE® Third Generation PSA

-Dosaggio Ultra-Sensibile del solo PSA-Libero (non complessato):
IMMULITE® Free PSA

Tutti i test PSA DPC sono calibrati in riferimento agli Standard PSA dell'Università di Stanford - USA, adottati quali Standards Internazionali per le differenti forme molecolari del PSA (Cancer. 1995. 75: 122-128)

Edito da MEDICAL SYSTEMS S.p.A.
Via Rio Torbido. 40. Genova. Tel: 010/83401 - Fax: 010/803363

Free PSA e Ratio F/T PSA % - Melone et al, 1996

FREE TO TOTAL PSA (F/T) RATIO FOR DISTINGUISHING BENIGN PROSTATIC HYPERPLASIA FROM PROSTATE CANCER.

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The discovery that the concentrations and the ratio of the different molecular forms of the PSA circulating in the bloodstream vary according to the presence of benign prostatic hyperplasia or prostatic carcinoma has improved the clinical utility of PSA testing.
OBJECTIVES. The objectives of this study were 1) to compare the ability of the Free/Total PSA ratio with the ability of PSA alone to differentiate between BPH and CaP in men with all values of total PSA and between 4 and 20 ng/mL (the diagnostic grey zone); 2) to evaluate if the measurement of Free PSA could influence the decision-making process of performing biopsies and 3) to calculate the cost-effectiveness, processing all results with the "ProSTAT™" software (Medical Systems S.p.A., Genoa, Italy), which generates a real-time interactive statistics.
MATERIALS AND METHODS. In a retrospective study we evaluated 90 patients with proven biopsy results or surgery of BPH (66 pts) and CaP (24 pts). Total PSA and Free PSA were assayed with DPC Immulite assay on deep frozen sera sample, before any physical manipulation. The F/T ratio was calculated for all patients.
A Wilcoxon non parametric analysis was used to test the statistical significance of differences in the median values of Total PSA and F/T PSA between BPH and CaP patients. Sensitivity and specificity were calculated. Receiver-Operating Characteristic (ROC) curves were generated to evaluate the assay performances for Total PSA and F/T PSA.
RESULTS. Calculation of F/T ratio revealed a significant difference between patients with CaP (median 6.1% ± 3.8 SD) versus patients with BPH (17.8 ± 17.6 SD; $p < 0.0001$). Considering only patients with PSA values between 4,1 and 20 ng/mL, the difference between patients with CaP versus patients with BPH remained significant only for F/T ratio ($p < 0.0008$). The combined evaluation of F/T ratio and Total PSA was assessed. In patients with all values of serum PSA, at a 15% cut-off for F/T ratio, at the same sensitivity of 92%, specificity increased from 48% with TPSA alone to 76%. It could avoid performing biopsies in 32% of patients and reduce costs of 19%. When evaluating patients with serum PSA between 4.1 and 20 ng/mL, the 15% cut-off, while retaining high sensitivity for detecting cancer, increased specificity to 55%. The number of biopsies reduced from 41 to 24 (- 42%) and diagnostic costs decreased of 33%.
CONCLUSION. Measurement of Free PSA and calculation of F/T ratio enhances the ability to distinguish benign prostatic conditions from cancer and may markedly reduce the number of unnecessary biopsies and the diagnostic costs.

Biomed & Pharmacother 1996; 50: 416-417

Melone F, Muraro G, Maggio A.

Free to total PSA (F/T) ratio for distinguishing benign prostatic hyperplasia from prostate cancer.

Biomedecine & Pharmacotherapy Vol.50, 8, 1996, 416

Metodi utilizzati:

IMMULITE Free PSA
IMMULITE 3G PSA
Sw ProSTAT Medical Systems

Free PSA IMMULITE - Aimo et al, 1996

11 Use of the Free/Total PSA Ratio in the Management of Prostatic Disease

G. Aimo,[1] C. Terrone,[2] A. Maggio,[3] L. Bellei,[2] G. Pelucelli,[2] T. Zaccaria,[1] L. Lucatello,[1] F. Turmolini,[3] G. C. Mazzocchi;[3] [1]Central Laboratory "Baldi e Riberi", "Molinette" Hospital, Turin; [2]Urology Division, University of Turin; [3]Scientific Department, Medical Systems S.p.A., Genoa, Italy.

It is well known that PSA is the best biochemical indicator for prostate cancer, but also well known are the specificity and sensitivity limitations of this marker—especially in the 4 to 20 ng/mL "gray zone," where there is a significant overlap between benign prostatic hyperplasia (BPH) and prostate cancer. Many attempts have been made in recent years to increase the clinical significance of PSA testing: PSA density, PSA velocity, age-related PSA, and association of PSA determinations with other clinical interventions such as digital rectal examination (DRE) and transrectal ultrasound (TRUS).

A recent and most promising development is the employment of the F/T PSA ratio, that is, the free form of circulating PSA expressed as a fraction, or percent, of total immunoreactive PSA (PSA-ACT + free PSA).

The aim of this study was to evaluate the clinical utility of the F/T PSA ratio, in association with total PSA, for distinguishing BPH from prostate cancer in a wide selection of symptomatic patients.

Materials and Methods

Patients

313 patients at first visit to the Ambulatory of Turin University, Urology Division, in the period from July 1995 to February 1996. Age 39-85, average 67 years. All patients were symptomatic for urinary/prostatic disorders.

259 out of the 313 had untreated BPH at first diagnosis, confirmed by biopsy or histology. Age 39-85, average 66 years.

The remaining 54 out of 313 had untreated prostate cancer at first diagnosis, confirmed by biopsy or histology. Age 59-84, average 68 years.

Sampling Procedure

Blood samples were collected in the morning from fasting patients in vacuum tubes without additives. The tubes were sent to the laboratory within two hours, where they were centrifuged as soon as possible, and the serum kept at –20°C until assayed.

Analytical Methods

Total PSA: IMMULITE Third Generation PSA (DPC, Los Angeles, US).
Free PSA: IMMULITE Free PSA (DPC, Los Angeles, US).

Data Processing

All results were processed using the "ProSTAT" software recently developed by Medical Systems S.p.A. (Genoa, Italy) for calculating diagnostic efficiency and cost-effectiveness in prostate disease studies. ProSTAT is an automated Microsoft Excel (version 5.0 or higher) for Windows template, which can generate real-time interactive statistics.

Results and Discussion

The following table summarizes the statistical evaluation of the data for all 313 patients.

	BPH		Prostate Cancer	
	TPSA	F/T PSA	TPSA	F/T PSA
N	259	259	54	54
Mean Value	3.9	20.8	33.2	7.1
Median	1.6	18.7	14.6	6.6
SD	4.2	10.9	77.8	3.9
SE	0.3	0.68	10.6	0.54
25th Percentile	0.63	13.9	9.6	4.5
75th Percentile	5.7	24.8	9.6	8.7

ROC curve analysis showed that the F/T PSA ratio cutoff value giving the best compromise between sensitivity and specificity is 11%. So we used this as the cutoff for the F/T PSA ratio and 4.0 ng/mL as the cutoff for total PSA in the ProSTAT analysis, which allows for evaluating the clinical significance of the two tests either separately or combined.

The four pathological criteria we introduced were:

Criterion 1: malignant disease for PSA > 4.0 ng/mL
Criterion 2: malignant disease for F/T PSA < 11%
Criterion 3: malignant disease for PSA > 4.0 ng/mL or F/T PSA < 11%
Criterion 4: malignant disease for PSA > 4.0 ng/mL and F/T PSA < 11%

The evaluation results are described in the following table.

Criterion:	1	2	3	4
True Positives	50	47	54	43
True Negatives	176	228	160	244
False Positives	83	31	99	15
False Negatives	4	7	0	11
Total	313	313	313	313
Sensitivity	93%	87%	100%	80%
Specificity	68%	88%	62%	94%
Positive Predictive Value	38%	60%	35%	74%
Negative Predictive Value	98%	97%	100%	96%
Diagnostic Efficiency	72%	88%	68%	92%

The data analysis shows that the F/T PSA ratio represents an improvement in the diagnosis of prostate disease when compared to total PSA. The F/T PSA ratio by itself (criterion 2) yields an increase in diagnostic efficiency (88% compared to 72%); but the best results are obtained by combining the F/T PSA ratio with total PSA (criterion 4). In this way, we achieved a diagnostic efficiency of 92% and very good sensitivity, specificity, positive predictive value and negative predictive value scores. Criterion 3 has a sensitivity of 100%, but of course it causes a loss in specificity.

The ProSTAT software allows us to calculate that, using the fourth criterion, we could avoid performing 75 biopsies, thus reducing the number of biopsies to 58, in contrast to the 133 biopsies indicated by the first criterion (50 true positives + 83 false negatives). Starting from average cost estimates for TRUS, biopsy and assays for free and total PSA, we can have a monetary saving of 35% in the diagnosis of prostatic patients, and also make the process less traumatic for the patient.

Aimo G, Terrone C, Maggio A, Bellei L, Pelucelli G, Zaccaria T, Lucatello L, Turmolini F, Mazzocchi G.

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International Conf. PSA & Prostatic Disease.
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ZB143-B 1996, A11, 45

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Sw ProSTAT Medical Systems SpA

Free PSA IMMULITE - Aimo et al, 1996

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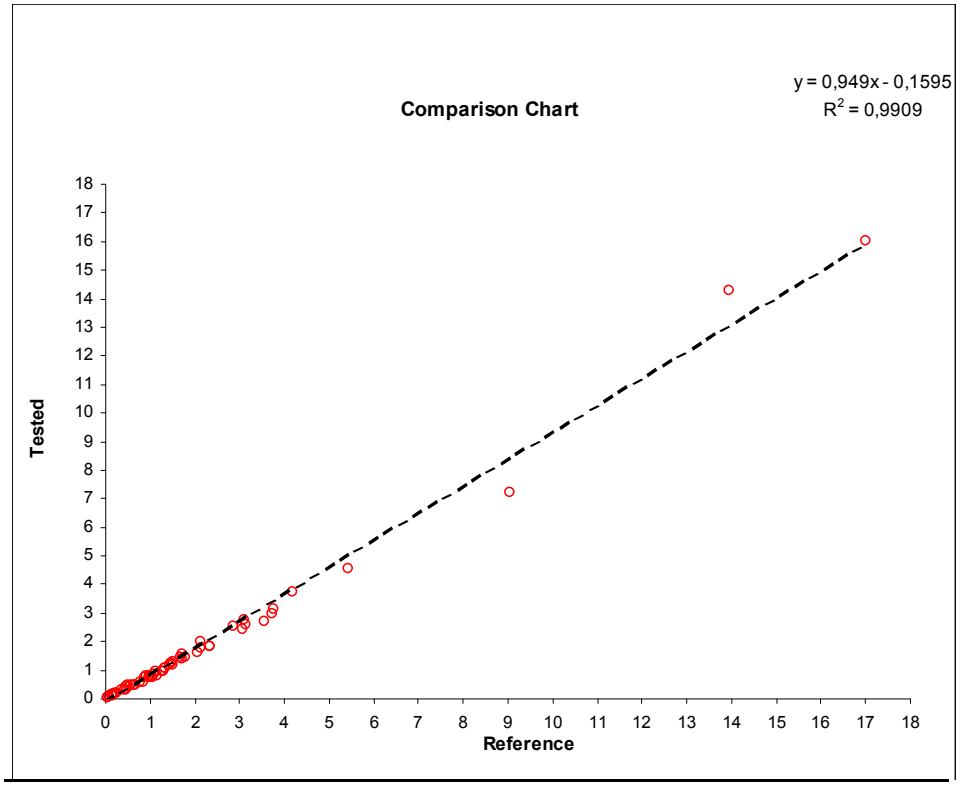
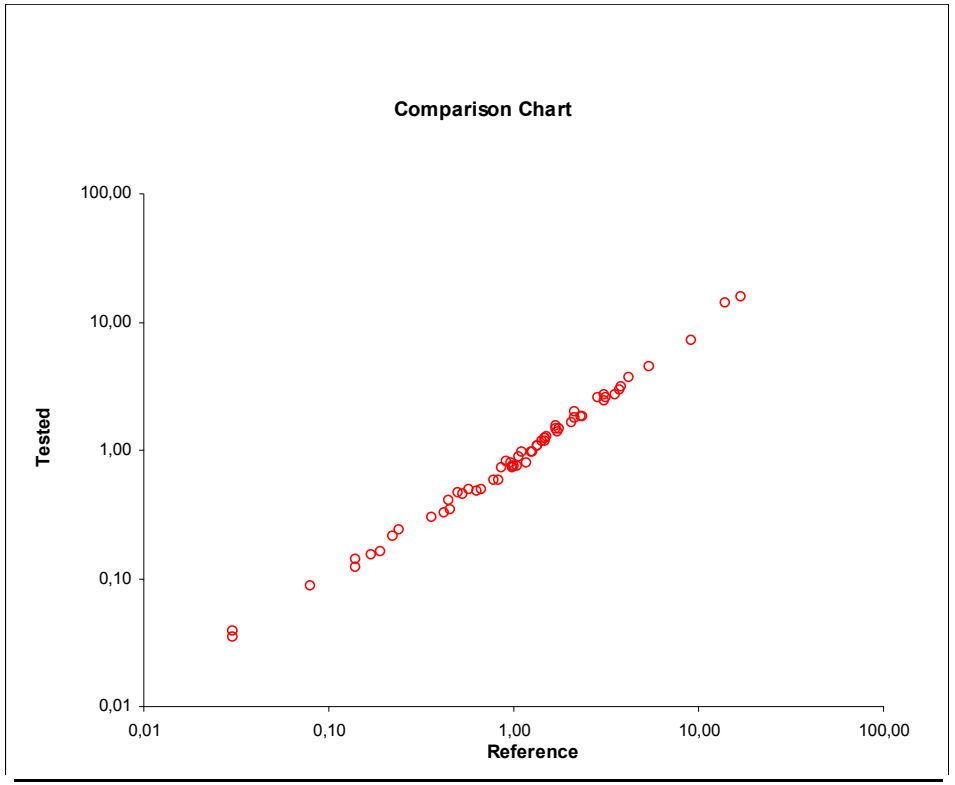
Sw ProSTAT Medical Systems SpA

Correlazione PSA Maglumi vs test Roche Elecsys
Dati in File, Medical Systems S.p.A.

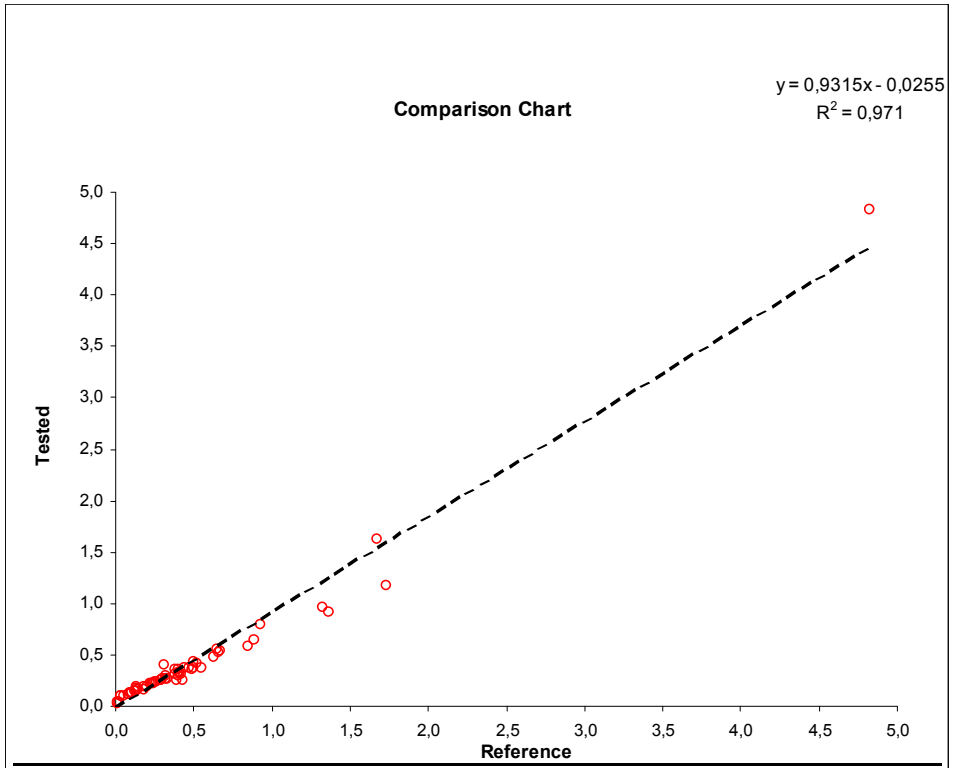
Coefficiente di correlazione: r = 0,9954
Campioni: n. 60

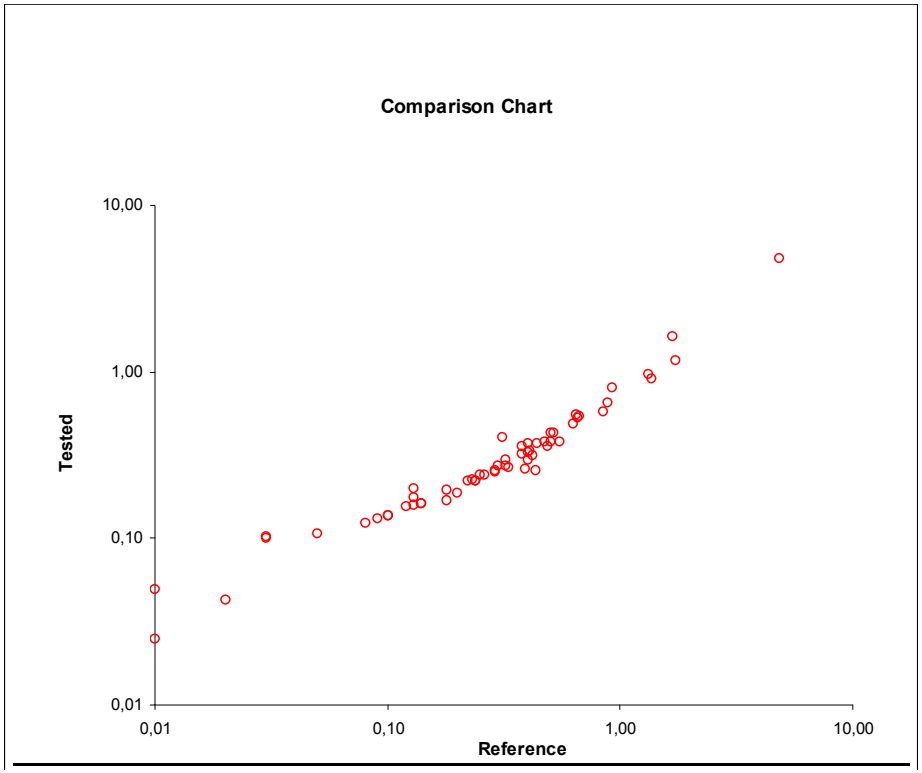




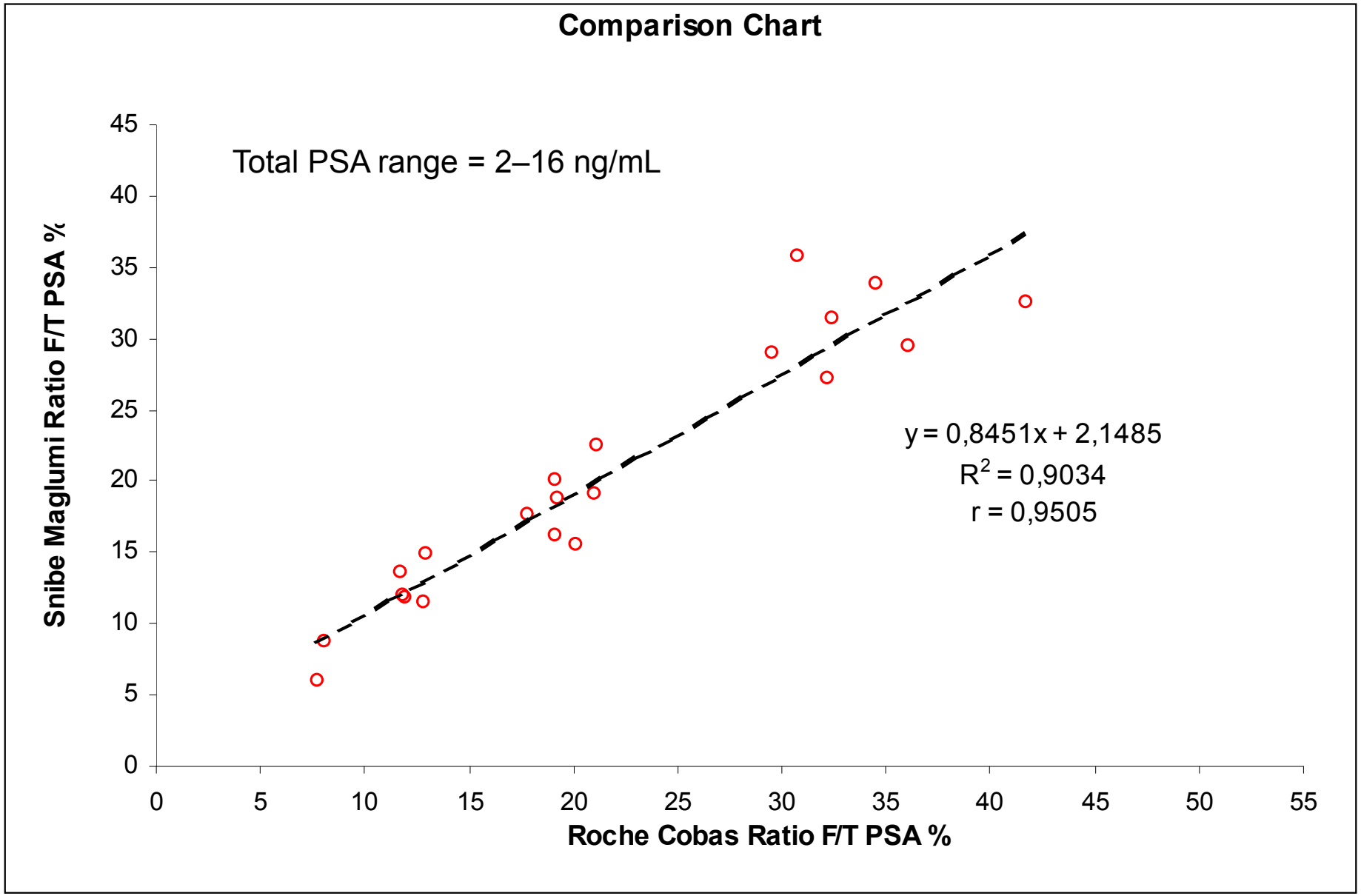
Correlazione Free PSA Maglumi vs test Roche Elecsys
Dati in File, Medical Systems S.p.A.

Coefficiente di correlazione: r = 0,9854
Campioni: n. 60





Correlazione Ratio F/T PSA Maglumi vs test Roche Elecsys
Dati in File, Medical Systems S.p.A.



Quando dosare il Free PSA per usare il Ratio F/T PSA% ?

Diagnosi Differenziale con Malattia Benigna e Indicazione all'Esecuzione di Biopsia Prostatica:

Raccomandato per valori PSA >4 e <10 ng/mL	(Riff. 1, 2, 3, 4, 5)
Proposto per valori PSA >2.0 e <10 ng/mL	(Riff. 6, 7)
Proposto per valori PSA >2.5 e <10 ng/mL	(Riff. 4, 8)
Proposto per valori PSA >3.0 e <10 ng/mL	(Riff. 9)
Clinicamente inutile per valori PSA >10 ng/mL	(Rif. 3)
Mai per valori PSA <2.0 e >10 ng/mL	(Riff. 1-9)

Monitoraggio di Carcinoma Prostata e Dopo Prostatectomia Radicale:

Clinicamente inutile	(Rif. 3)

1. Guidelines Prostate Cancer, National Comprehensive Cancer Network, NCCN, 2012
2. Guida all'uso clinico biomarcatori in oncologia. Gion M et al. Biochimica Clinica, 2011
3. Guidelines Prostate Cancer, European Association of Urology, EAU Guidelines 2010
4. Linee Guida Nazionali Carcinoma Prostata, Agenzia Servizi Sanitari Regionali, AgeNaS
5. Linee Guida Carcinoma della Prostata, Associazione Italiana di Oncologia Medica, AIOM
6. Linee Guida Carcinoma Prostatico, Associazione Urologi Italiani, AUrO 2008
7. Linee Guida Carcinoma della Prostata, Regione Piemonte, 2009
8. Linee Guida Biopsia Prostatica. Società Italiana di Urologia Oncologica, SIUrO, 2005
9. Appropriatezza di richiesta dosaggio FPSA con calcolo dell'indice FPSA/PSA: esperienza Az."Ist.Ospitalieri" Cremona. Rizzardi S. et al. Ligand Assay 2004 Vol.9, n°3, p.288

ALGORITMO DIAGNOSTICO DELLA PATOLOGIA PROSTATICA: IL PSA REFLEX

PSA Reflex, Delibere Regionali:

Mai dosaggio del PSA Libero per valori di PSA <2.5 e >10 ng/mL (Rif. 1)

Mai dosaggio del PSA Libero per valori di PSA <2.0 e >10 ng/mL (Riff. 2,3)

1. Regione Emilia-Romagna *(Deliberazione Giunta Regionale N.1779 del 22/11/2010)*

Nota: nel paziente che è stato sottoposto a prostatectomia la prestazione da richiedere è il solo PSA totale.
In questo caso, infatti, rilevare la presenza di PSA dopo l'intervento è in ogni caso indice di presenza di tessuto prostatico residuo, indipendentemente dalla concentrazione del PSA libero. La recidiva è, infatti, eventualmente indicata dalla ripresa della secrezione del PSA e non dalla quota non legata alle proteine vettrici.

2. Regione Lombardia *(Deliberazione Giunta Regionale N.IX/2057 del 28/07/2011)*

3. Regione Lazio *(Decreto del Commissario ad Acta N.U00156 del 20/4/2015)*