Evaluation 2012 des dosages des PSA du marché français

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23ème Journées Nationales du CNBH
Paris 30-31 janvier 2014

Problématique en 2011

- Dépistage or not ?
- Surdiagnostic. Surtraitement
- Biopsies “inutiles”

Recommandation sur stratégies de dépistage / EBM

- **Qui dépister ?**
  - A partir de 45 ans pour populations à risque
  - 50 / 55 - 65 ans : dépistage recommandé
  - 65 - 75 ans : dépistage individuel
  - > 75 ans : dépistage inutile
- **A quel rythme ?**
  - A définir, fonction PSA initial et cinétique d’évolution
  - Plus espacé
  - PSA < 1ng/ml : tous les 3 à 4 ans

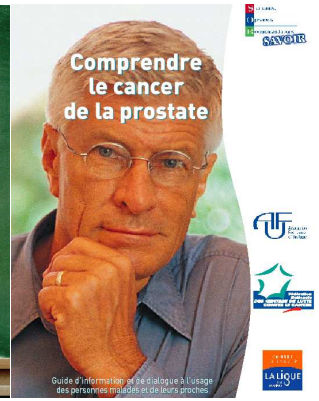
Association Française d'Urologie
www.urofrance.org

et des opposants systématiques …

Touche pas à ma prostate !
Manifeste pour un moratoire sur le dépistage du cancer de la prostate

Que faire ?

- PAIR
- Programme pilote HAS-AFU
- Recommandations HAS-INCa-AFU
- Information (patients et médecins)



Programme d’actions intégrées de recherche

Entre dépistage controversé et sur-traitement avéré

Utilisation clinique du PSA

- Détection précoce du cancer de la prostate
  - » Seuil unique de décision (aide au diagnostic, biopsie) : variable selon les standardisations des dosages (4 - 3 - 2 µg/L)
  - » Performances différentes des techniques : équimolarité, exactitude
- Suivi thérapeutique
  - » PSA indétectable après traitement radical
  - » Sensibilité différente des dosages :
    - PSA LDA 0,1 µg/L (seuil de « **récidive biologique** » pour les urologues)
    - PSA sensible : LDA 0,05 µg/L
    - PSA ultrasensible : LDA 0,01 µg/L
    - LDA 10^{-5} ?

Seuil de PSA et standardisation

- Avant 90 standard Yang (Pros-Check PSA)
  - » Seuil de décision mal défini (4 ng/mL)
- 90 : standard Hybritech (Tandem-R PSA)
  - » Seuil de décision 4 ng
  - » 2 ng/mL sur Hybritech = 4 ng/mL sur Yang
- 1994 : 2ème conférence de Stanford désigne le standard international pour le PSA total WHO 96/670 (90% de PSA-ACT et 10% de PSA libre) officiellement adopté en 1999
  - » Seuil de décision 2-3-4 ng/mL (2,5 - 3,1)
  - » Cas de Access Beckman Coulter choix du standard Hybritech ou WHO (4 sur Hybritech = 3 sur WHO)

Utilisation clinique du PSA

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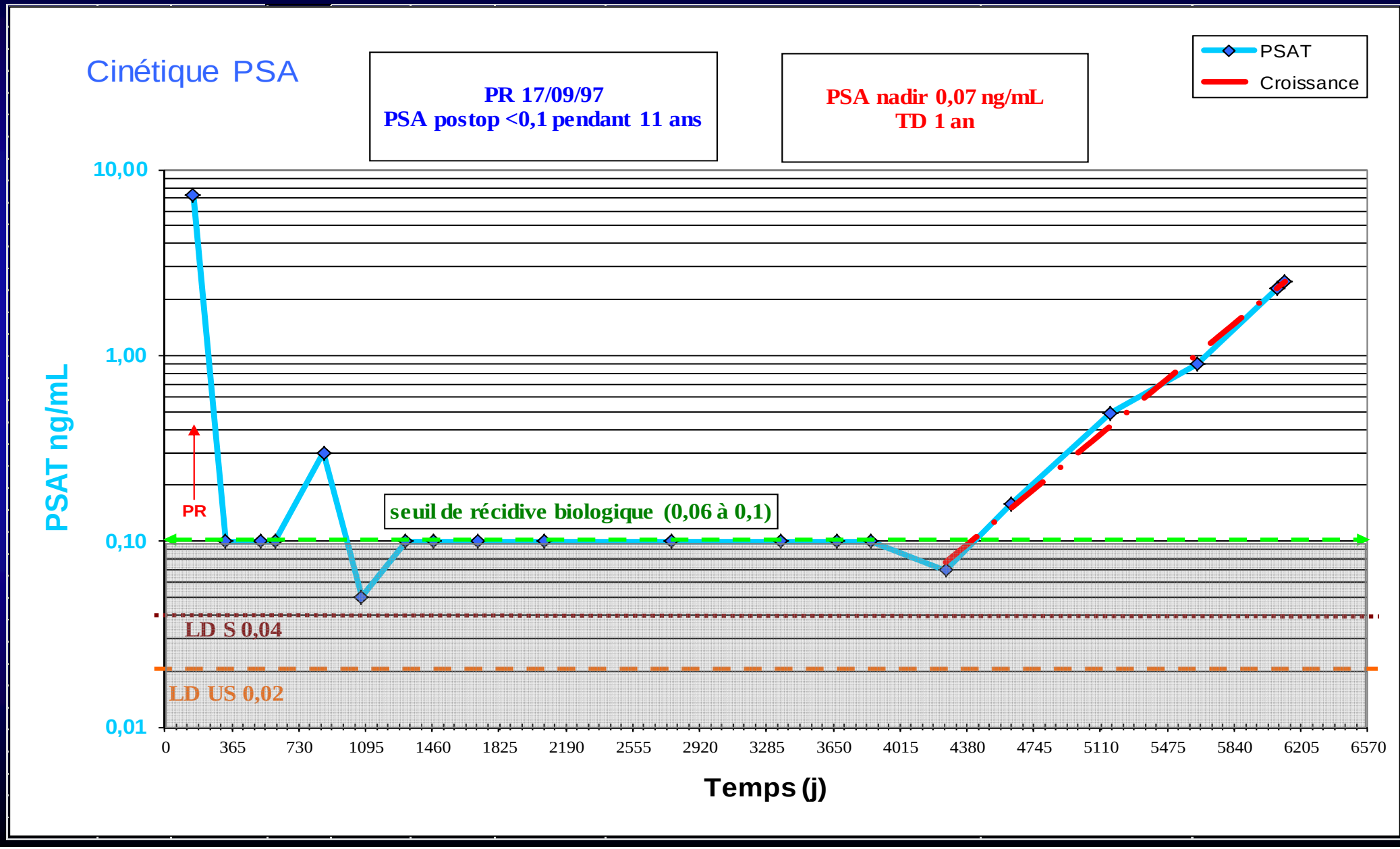
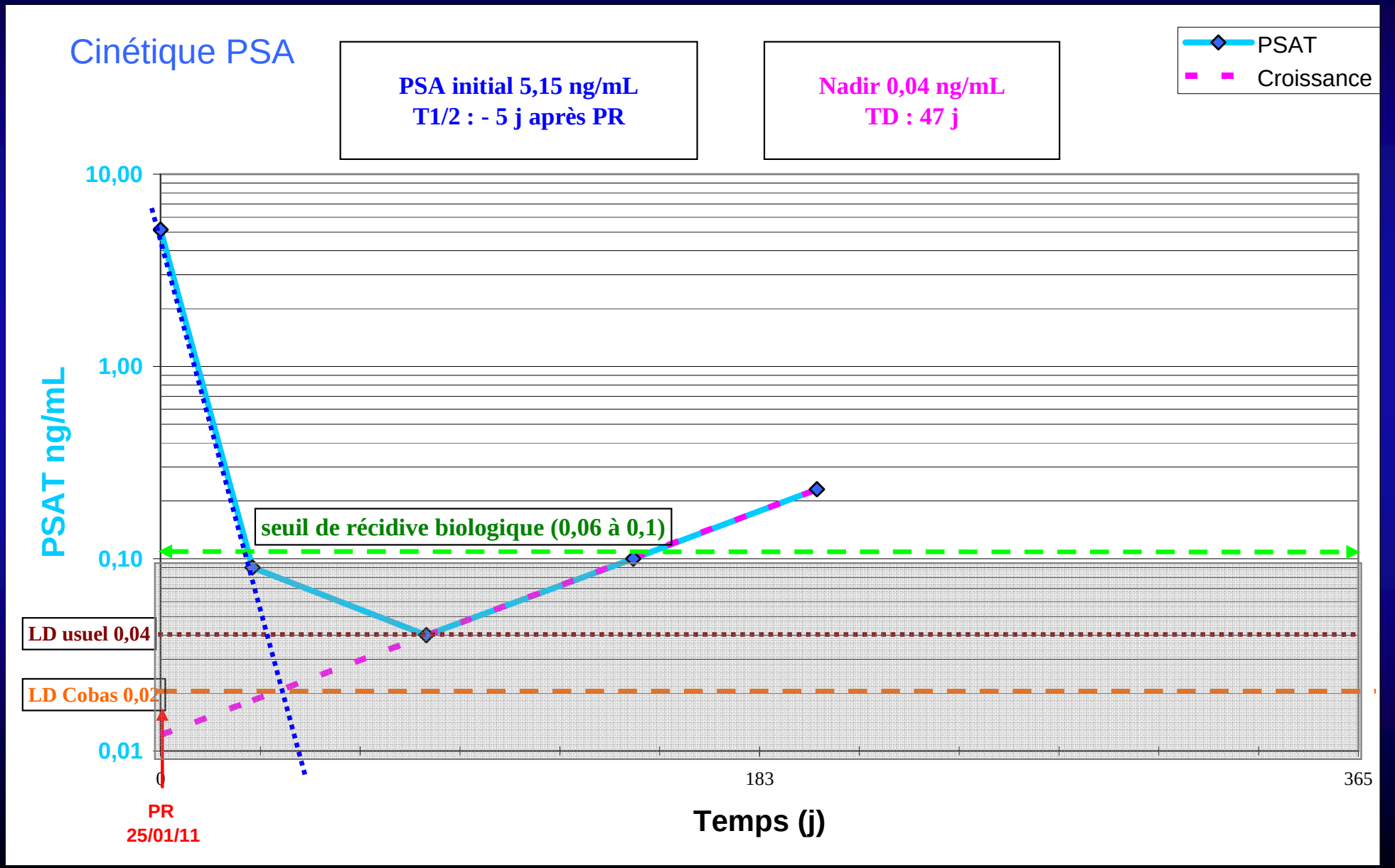
    - LDA 10^{-5} ?

Récidive biologique : seuil ?



Récidive biologique : seuil ?



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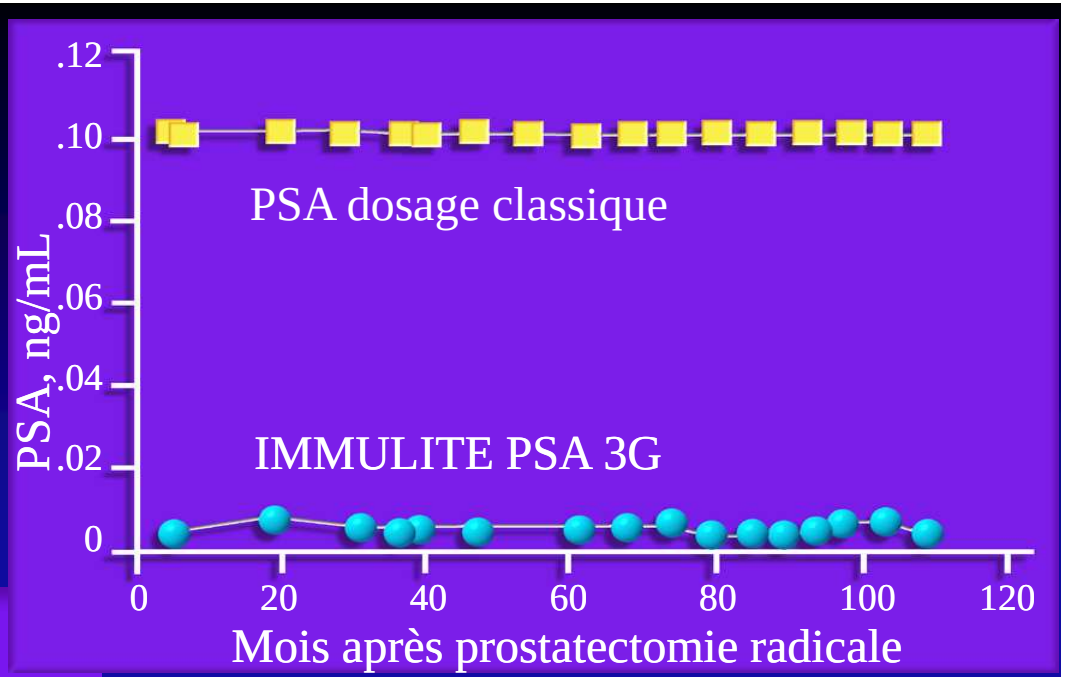
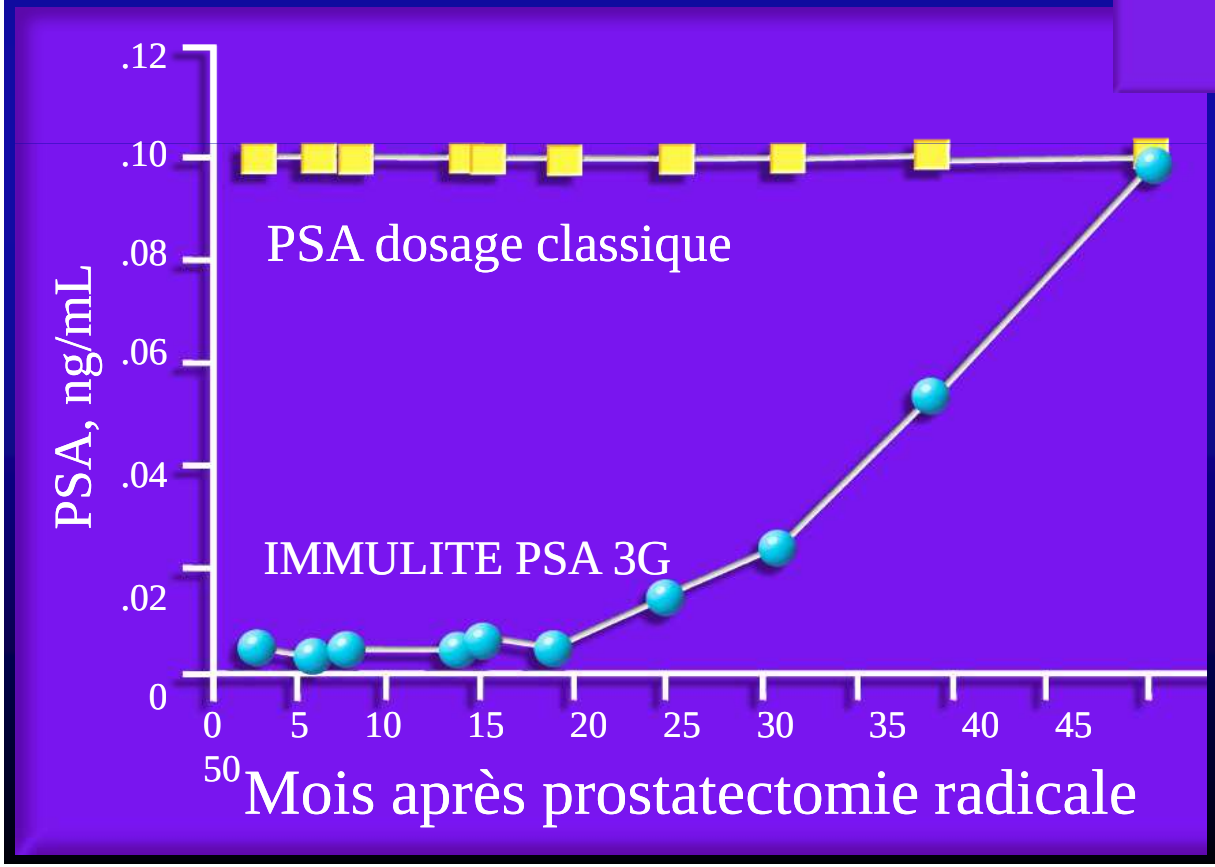
Patient 2 (73 ans)

- Symptômes urinaires, douleurs lombaires, prostate indurée
- PSA : 6,4 ng/mL
- Biopsie positive, scintigraphie osseuse négative
- Prostatectomie radicale
- Cancer étendu lobe G sans invasion capsulaire
- Pas d'envahissement/ ganglion, vésicules séminales, marge
- PSA post-opératoire : 0,004 ng/mL
- Monitorage pendant 4,2 ans avec PSA atteignant 0,10 ng/mL





Patient 1 en rémission

PSA ultra-sensible

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Performances cliniques

PSA Valeur seuil	Sensibilité	Spécificité
2 ng/mL	94%	44%
4 ng/mL	70-80%	60-80%
10 ng/mL	40-50%	80-90%

- Objectifs : améliorer la sensibilité et la spécificité des moyens de dépistage du cancer de prostate et diminuer le nombre de biopsies “inutiles”

Qualité

Le PSA autrement

- Améliorations techniques des dosages utilisés

- Optimisation conceptuelle : 1 seuil unique de décision ou évolution dynamique, analyse probabiliste données clinico-biologique combinées

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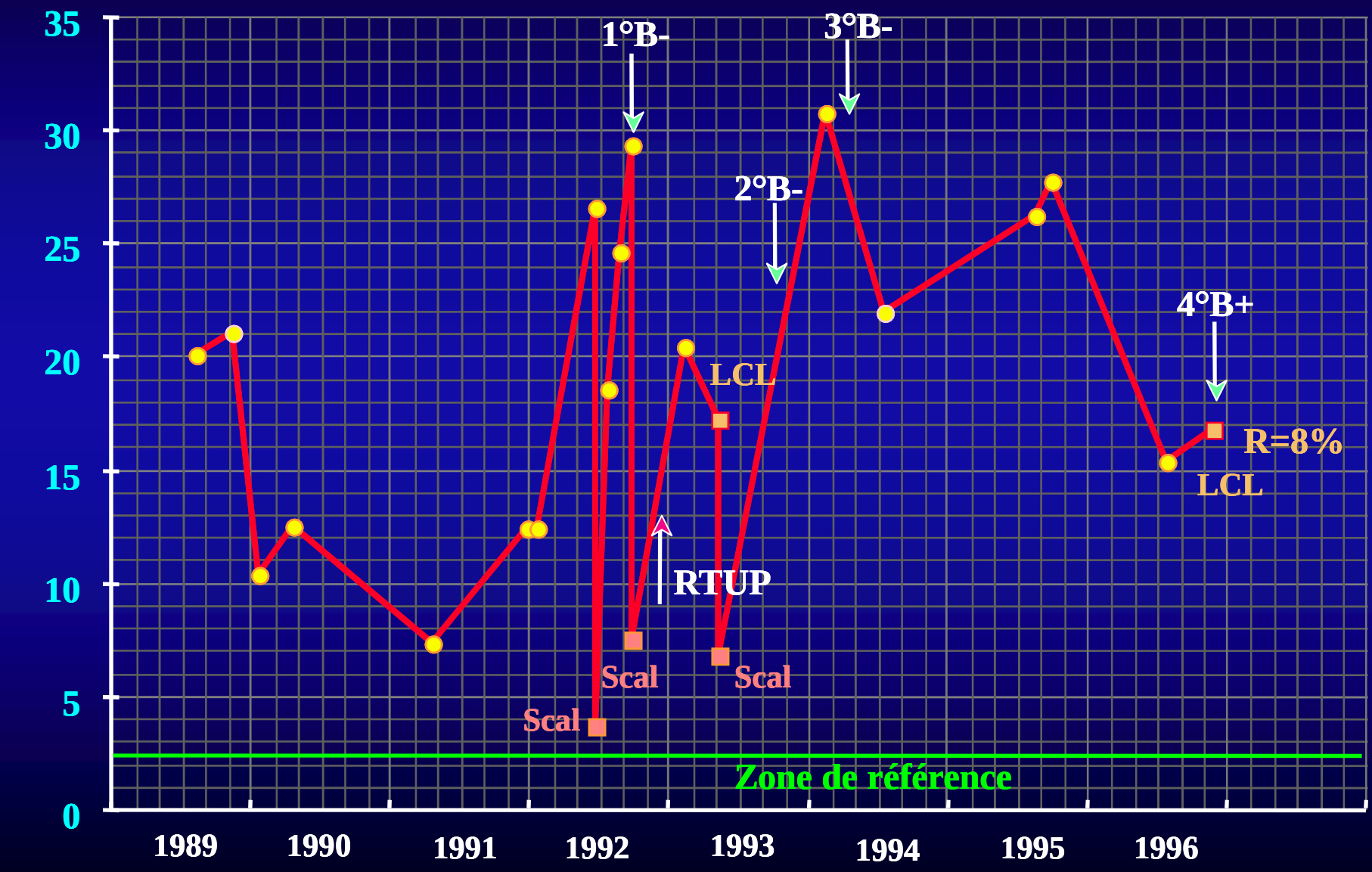
Causes de variabilité du PSA

- Individu : variation physiologique (10-30 %)
- Circonstances : manipulations prostatiques (médicales, sports) ; traitements (finastéride)
- Techniques : reconnaissance épitopique des formes circulantes, standardisations

Suivi de PSA total (W… , 1927)



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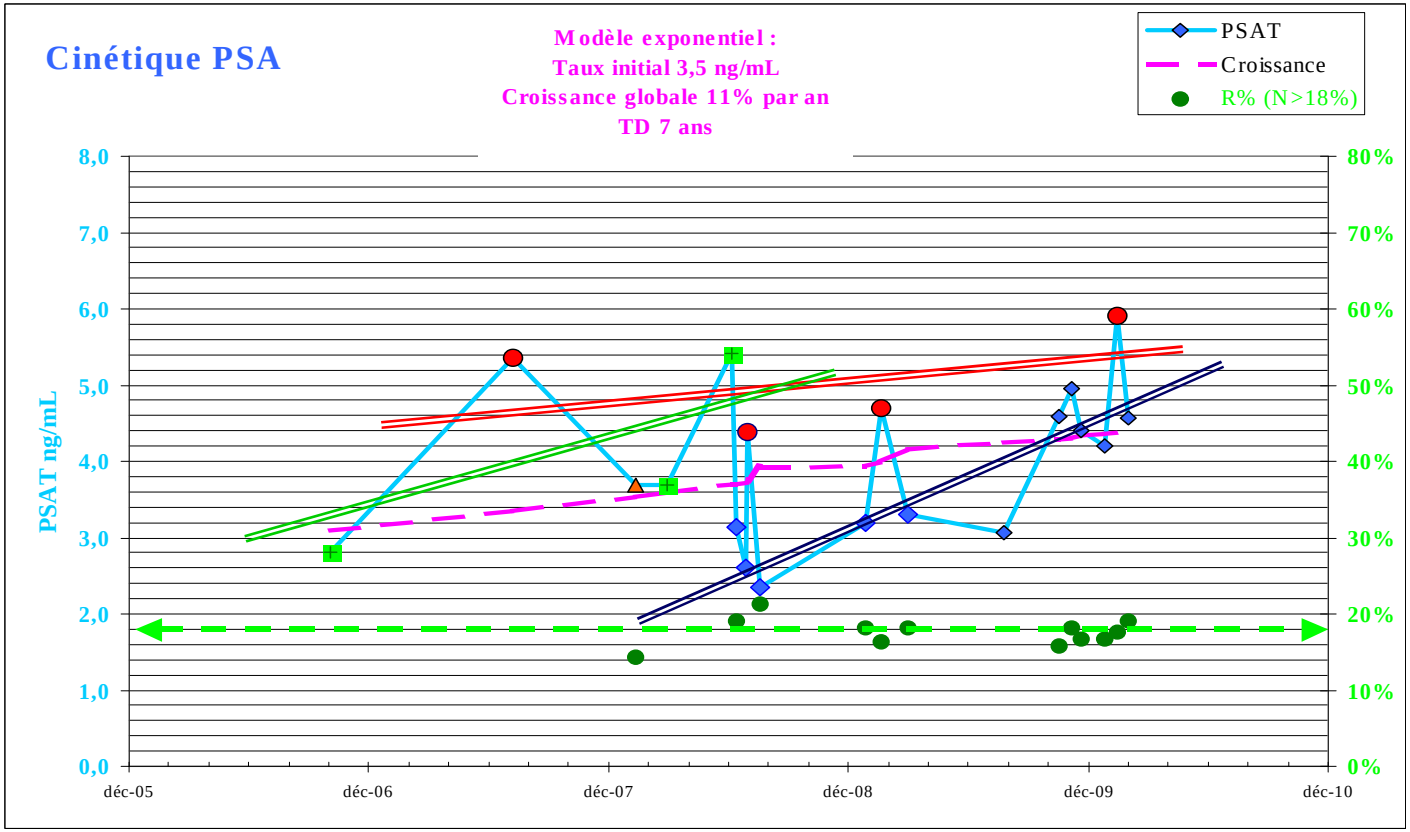
Variations techniques

PSAT	PSAL	Labo	R% (N>18%)
2,8		Axsym	
5,35		Vidas	
3,69	0,53	Modular	14%
3,68		Axsym	
5,42		Architect	
3,13	0,6	Centaur/Cis	19%
2,61	0,6	Centaur/Cis	
4,38		Vidas	
2,35	0,5	Centaur/Cis	21%
3,2	0,58	Centaur/Cis	18%
4,7	0,77	Vidas	16%
3,3	0,60	Centaur/Cis	18%
3,07		Centaur/Cis	
4,58	0,72	Centaur/Cis	16%
4,95	0,9	Centaur/Cis	18%
4,41	0,74	Centaur/Cis	17%
4,2	0,7	Centaur/Cis	17%
5,9	1,04	Vidas	18%
4,57	0,87	Centaur/Cis	19%

Dosages différents

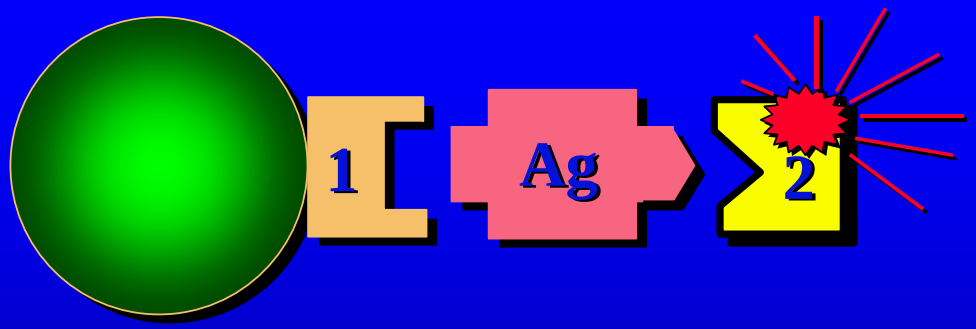


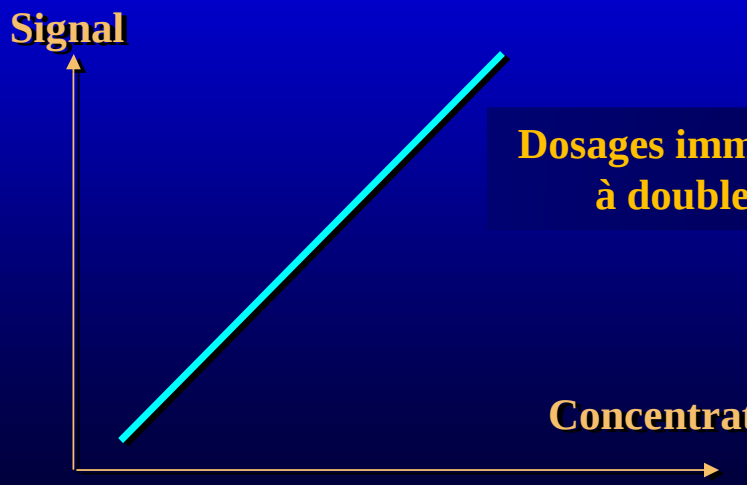
Différences entre méthodes

Causes techniques de variabilité

- Standardisation : Yang, Hybritech, WHO
- Origine du PSA étalon : liq. Séminal, tumeur, PSA humain recombinant (WHO)
- Composition du standard : PSAL 100 % ou x %
- Matrices de dilution : tampon PBS, sérum animal
- Spécificité des AC (poly, mono) : EQM

- Standardisation
  - 2°IC on PSA Stanford (Sept 1994)
  - Standard International (WHO)
  - PSA total : standard WHO 96/670
  - PSA libre : standard WHO 96/668
- Composition des standards
  - 90% PSA-ACT + 10% PSA libre





Dosages immunométriques à double anticorps

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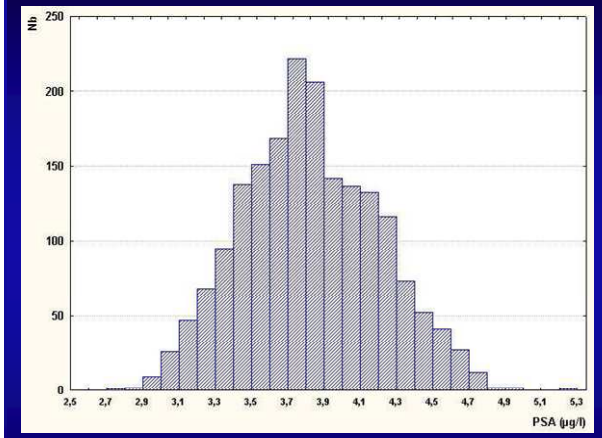
Contrôle National de Qualité ANSM

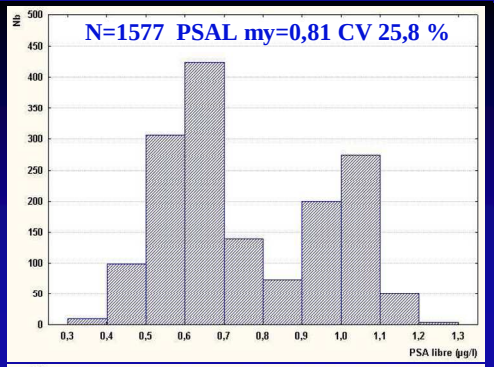
PSAT 3,85 µg/L et R 20,6 %

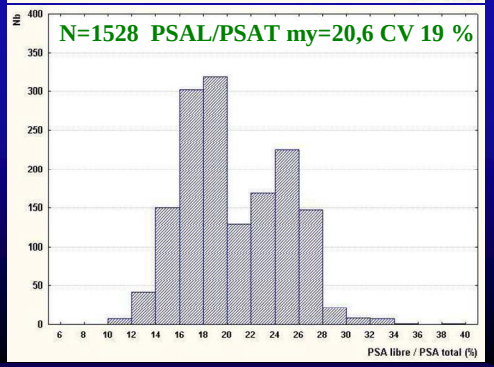
PSAT 3,58 µg/L et R 11,9 %

Afssaps 2009 : IA59

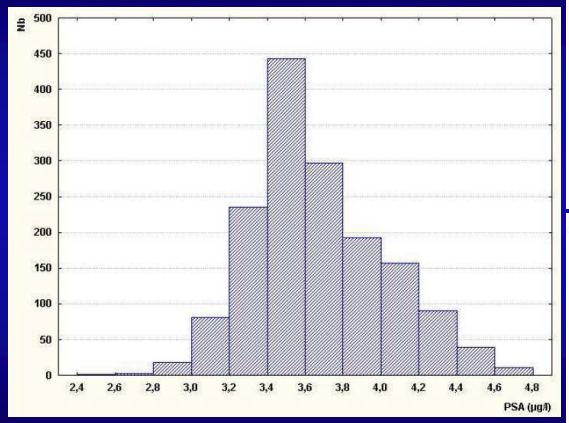


N=1873 PSAT my=3,85 CV 8,5 %

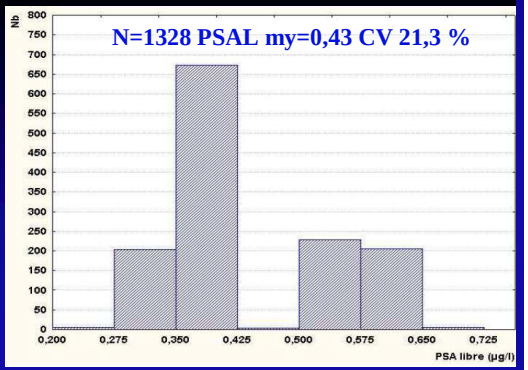


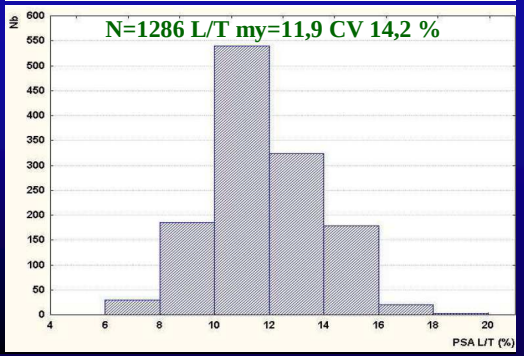


Afssaps 2011 : IA61



N=1568 PSAT my=3,58 ng/mL CV 8,2 %





ANSM 2012 : IA65 rapport 12MTU1 consultable sur le site de l'ANSM www.ansm.sante.fr (M. Noël)

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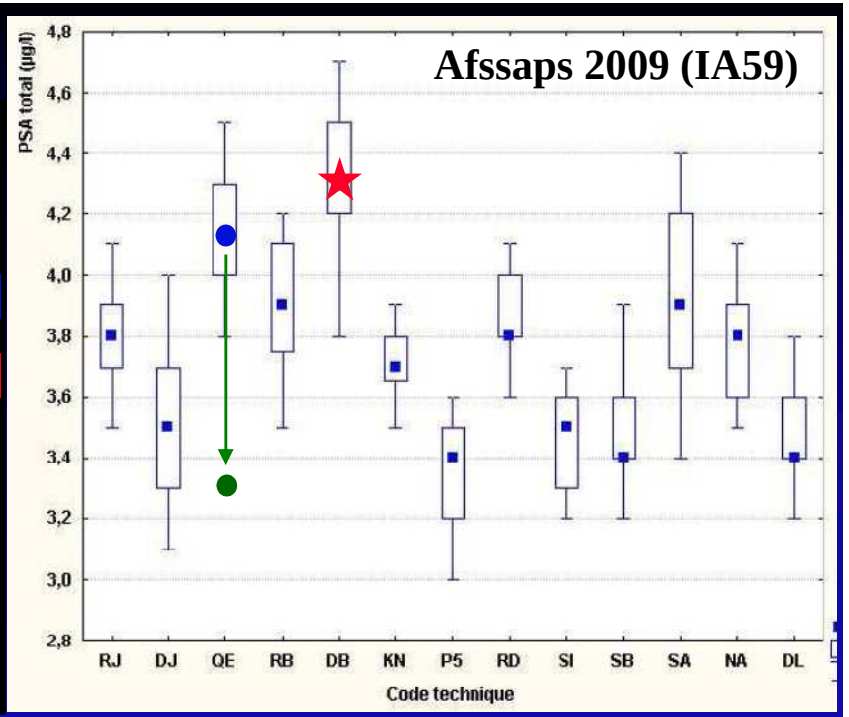
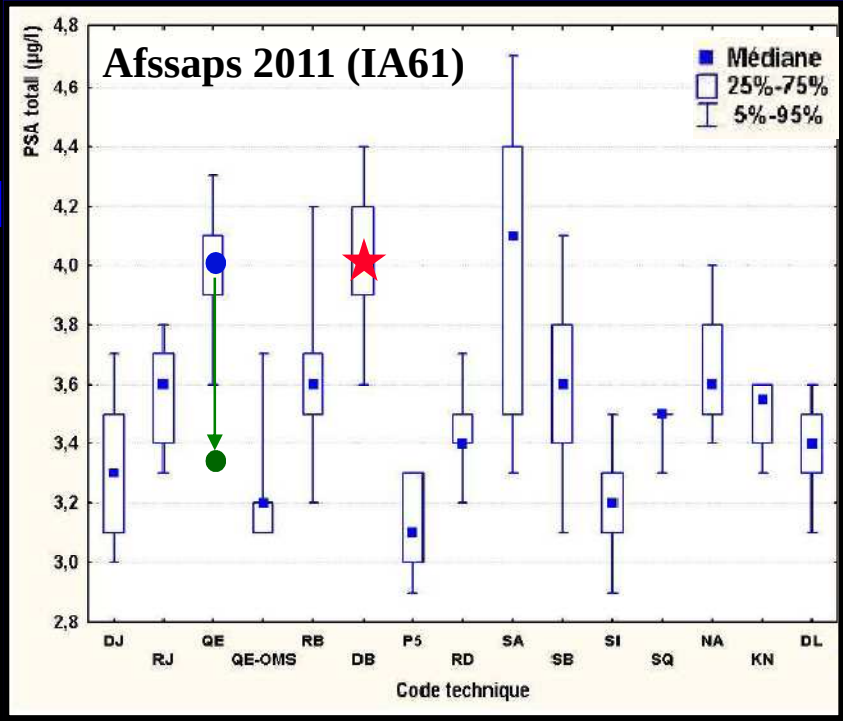
*** 224 Access standardisation Hybritech médiane 4,15 ng/mL**
5 Access standardisation WHO médiane 3,3 ng/mL).

Code	Distributeur	Nom	Nb	Mtr	CVtr %
		Moyenne toutes techniques	**1873**	**3,85**	**8,5**
RJ	ABBOTT DIAGNOSTIC	Architect PSA	279	3,79	4,4
DJ	ABBOTT DIAGNOSTIC	Axsym PSA	218	3,49	6,0
QE	BECKMAN COULTER	Access Hybritech PSA *	224	4,15	3,9
RB	BIOMERIEUX	Vidia TPSA	34	3,89	5,7
DB	BIOMERIEUX	Vidas TPSA	386	4,33	5,2
KN	BRAHMS FRANCE	Kryptor total PSA	28	3,73	3,7
P5	ORTHO CLIN. DIAG.	Vitros ECI PSA	19	3,34	5,6
RD	ROCHE DIAGNOSTICS	Elecsys PSA	345	3,85	3,4
SI	SIEMENS MED. SOL. DIAG.	Advia CentaurPSAT EQM	106	3,44	5,0
SB	SIEMENS MED. SOL. DIAG.	Immulite 2000/ Immulite 2500 PSA 3G	57	3,46	5,3
SA	SIEMENS MED. SOL. DIAG.	Immulite 2000/ Immulite 2500 PSA	41	3,93	7,3
NA	SIEMENS MED. SOL. DIAG.	Dimension flex TPSA	24	3,77	5,0
DL	TOSOH BIOSCIENCE	AIA pack/Stat AIA pack PA	99	3,45	3,9



Code	Distributeur	Nom	Nb	Mtr	CVtr %
		Moyenne toutes techniques	**1568**	**3,58**	**8,2**
DJ	ABBOTT DIAGNOSTIC	Axsym PSA	115	3,33	5,4
RJ	ABBOTT DIAGNOSTIC	Architect PSA	297	3,55	3,9
QE	BECKMAN COULTER	Access PSA étalon Hybritech	196	3,99	4,1
QE	BECKMAN COULTER	Access PSA étalon OMS	7	3,36	10,4
RB	BIOMERIEUX	Vidia TPSA	15	3,57	3,3
DB	BIOMERIEUX	Vidas TPSA	253	4,02	5,3
P5	ORTHO CLIN. DIAG.	Vitros ECI PSA	14	3,12	4,6
RD	ROCHE DIAGNOSTICS	Elecsys PSA	350	3,45	3,6
SA	SIEMENS MED. SOL. DIAG.	Immulite 2000/ 2500 PSA	34	4,01	12,1
SB	SIEMENS MED. SOL. DIAG.	Immulite 2000/ 2500 PSA 3G	47	3,58	7,0
SI	SIEMENS MED. SOL. DIAG.	Advia CentaurPSAT EQM	94	3,17	4,1
SQ	SIEMENS MED. SOL. DIAG.	LOCI PSA	8	3,50	0,0
NA	SIEMENS MED. SOL. DIAG.	Dimension flex TPSA	26	3,63	3,7
KN	THERMO FISHER	Kryptor total PSA	22	3,54	2,5
DL	TOSOH BIOSCIENCE	AIA pack/Stat AIA pack PA	82	3,40	3,6



UK-Neqas aout 2011

UK NEQAS for PROSTATE SPECIFIC AG.

Distribution : 118 Date : 30-Aug-2011

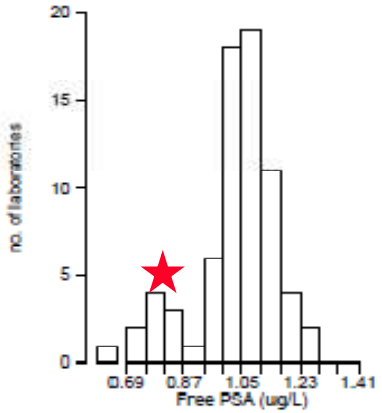
Analyte : Free PSA (ug/L)

Sample 118-1 was prepared from a single donor serum (with a high PSA concentration) diluted with pooled NBS serum. Sample 118-2 was a 1 in 2 dilution of sample 118-1.

☐ All methods

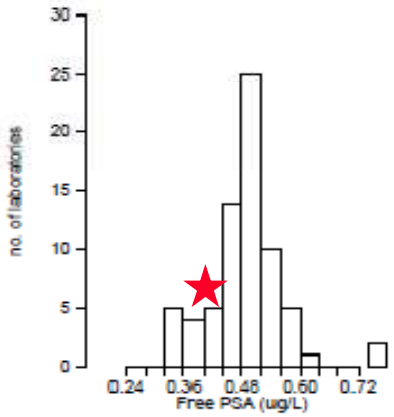
Specimen : 118-1

	n	Mean	SD	CV(%)
All methods	71	1.05	0.11	10.2
Abbott Architect	16	1.03	0.06	6.0
Beckman Access (WHO)	5	1.07	0.07	6.6
Roche E-170	25	1.06	0.06	5.3
Roche ELECSYS	7	1.13	0.08	7.0
SMS Diag. Ltd- Immulite 2000	8	0.81	0.05	5.7



Specimen : 118-2

	n	Mean	SD	CV(%)
All methods	71	0.49	0.06	12.6
Abbott Architect	16	0.47	0.03	7.1
Beckman Access (WHO)	5	0.50	0.03	5.1
Roche E-170	25	0.51	0.03	5.3
Roche ELECSYS	7	0.54	0.04	8.3
SMS Diag. Ltd- Immulite 2000	8	0.38	0.03	8.3



UK NEQAS for PROSTATE SPECIFIC AG.

Distribution : 118 Date : 30-Aug-2011

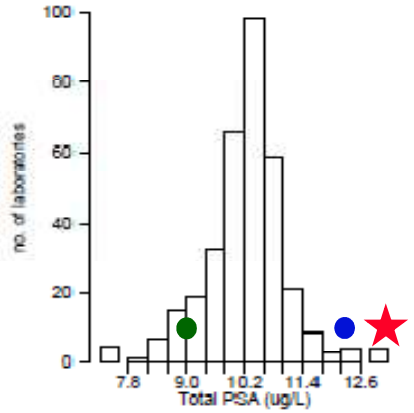
Analyte : Total PSA (ug/L)

Sample 118-1 was prepared from a single donor serum (with a high PSA concentration) diluted with pooled NBS serum. Sample 118-2 was a 1 in 2 dilution of sample 118-1.

☐ All methods

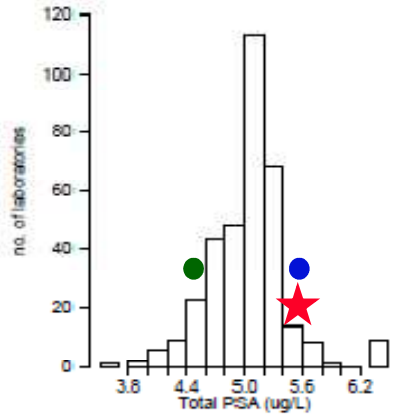
Specimen : 118-1

	n	Mean	SD	CV(%)
All methods	344	10.3	0.7	6.9
Abbott Architect	76	10.6	0.5	5.0
Abbott AxSYM	4	10.1	0.7	7.1
Beckman Access-Hybritech standard	6	12.0	1.0	8.2
Beckman Access-WHO standard	26	9.1	0.7	7.2
Ortho Vitros	9	9.1	0.3	3.5
Roche COBAS-Core EIA	10	10.6	0.3	3.0
Roche E-170	115	10.5	0.3	3.0
Roche ELECSYS	11	10.6	0.4	4.2
SMS Diag. -Immulite 2000 3rd Gen.	14	10.5	1.1	10.9
SMS Diagnostics- Immulite 2000	4	13.4	3.6	26.9
SMS Diagnostics-ADVIA Centaur	57	9.9	0.5	4.6



Specimen : 118-2

	n	Mean	SD	CV(%)
All methods	345	5.0	0.3	6.8
Abbott Architect	77	5.1	0.3	5.9
Abbott AxSYM	4	4.7	0.4	7.6
Beckman Access-Hybritech standard	6	5.5	0.4	6.5
Beckman Access-WHO standard	26	4.5	0.3	5.8
Ortho Vitros	9	4.5	0.1	3.0
Roche COBAS-Core EIA	10	5.2	0.1	2.8
Roche E-170	115	5.2	0.1	2.7
Roche ELECSYS	11	5.3	0.2	4.4
SMS Diag. -Immulite 2000 3rd Gen.	14	5.1	0.4	8.2
SMS Diagnostics- Immulite 2000	4	6.5	1.6	24.9
SMS Diagnostics-ADVIA Centaur	57	4.8	0.2	4.5



US-CAP 2011

Total Prostate Specific Antigen (Total PSA) - ng/mL (µg/L)	K-20				K-21			
METHOD	NO. LABS	MEAN	S.D.	C.V.	NO. LABS	MEAN	S.D.	C.V.
ABBOTT ARCHITECT i	230	6.489	0.348	5.4	228	13.183	0.645	4.9
ABBOTT AXSYM	40	6.215	0.377	6.1	41	12.697	0.799	6.3
BECKMAN ACCESS (WHO)	14	6.420	0.904	14.1	13	13.012	1.754	13.5
BECKMAN ACCESS/2	339	7.053	0.312	4.4	341	14.738	0.657	4.5
BECKMAN UNICEL Dxl	342	6.941	0.413	6.0	339	14.410	0.815	5.7
BECKMAN UNICEL Dxl (WHO)	9	-	-	-	10	11.076	0.549	5.0
ROCHE e411/ELECSYS	100	5.964	0.348	5.8	98	11.978	0.649	5.4
ROCHE e600 SER/E170	341	6.029	0.228	3.8	341	12.171	0.432	3.6
SIEMENS ADV CNTR/XP	446	5.810	0.308	5.3	447	11.801	0.622	5.3
SIEMENS ADVIA CENTR CP	43	5.705	0.343	6.0	43	11.525	0.700	6.1
SIEMENS DIMENSION HM	295	6.480	0.403	6.2	295	13.465	0.794	5.9
SIEMENS DIMENSION VISTA	13	6.178	0.141	2.3	13	12.619	0.412	3.3
SIEMENS IMMULITE 1000	10	7.207	0.799	11.1	10	14.880	1.652	11.3
SIEMENS IMMULITE 2000	76	6.685	0.485	7.3	78	13.503	0.967	7.2
SIEMENS IMMULITE 2500	17	6.765	0.401	5.9	17	13.803	1.013	7.3
SIEMENS IMMULT 2K/2500 3G	11	6.499	0.422	6.5	11	12.836	0.661	5.1
TOSOH ST AIA-PACK	40	6.336	0.284	4.5	40	12.681	0.545	4.3
VITROS 3600,5600,ECi/ECiQ	284	5.632	0.327	5.8	286	11.483	0.648	5.6

Complexed Prostate Specific Antigen (cPSA) - ng/mL (µg/L)	K-20				K-21			
METHOD	NO. LABS	MEAN	S.D.	C.V.	NO. LABS	MEAN	S.D.	C.V.
SIEMENS ADV CNTR/XP	47	4.881	0.238	4.9	48	10.583	0.399	3.8

Free Prostate Specific Antigen (Free PSA) - ng/mL (µg/L)	K-20				K-21			
METHOD	NO. LABS	MEAN	S.D.	C.V.	NO. LABS	MEAN	S.D.	C.V.
ABBOTT ARCHITECT i	81	0.950	0.044	4.6	81	1.333	0.078	5.9
ABBOTT AXSYM	13	0.818	0.035	4.3	14	1.200	0.072	6.0
BECKMAN ACCESS/2	90	1.227	0.050	4.1	92	1.703	0.070	4.1
BECKMAN UNICEL Dxl	158	1.215	0.065	5.4	161	1.697	0.087	5.1
ROCHE e411/ELECSYS	31	0.910	0.035	3.9	32	1.287	0.058	4.5
ROCHE e600 SER/E170	139	0.887	0.038	4.4	142	1.243	0.062	5.0
SIEMENS DIMENSION HM	37	0.854	0.045	5.3	36	1.231	0.051	4.1
SIEMENS IMMULITE 2000	53	0.778	0.052	6.7	54	1.110	0.077	7.0

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Réactifs PSA utilisés et systèmes majoritaires

	Nombre de réactifs utilisés sur le marché français (CNQ ANSM)				
Dosages	2008	2009 (N=1873)	2011 (N=1568)	2012 (N=1225)	Eval. 2012 (19 sites)
PSAT	17	18	17	15	14
PSAL	14	15	15	14	13

(Afssaps 2009)

- Biomérieux (Vidas, mini-Vidas) 27,5 %
- Abbott 24,8 %
  (AxSym 13%, Architect 11,8%)
- Roche 11,1 %
  (Elecsys 2,9%, Modular 1,4%, Cobas 6,8%)
- Beckman 9,5 %
  (Access 5,1%, DxI 4,4%)
- Siemens 8,4 %
  (Centaur 5,4%, Immulite 3%)
- Tosoh 5,9 %

(Afssaps 2011)

- Biomérieux (Vidas, mini-Vidas) 23,3 %
- Abbott 23 %
  (AxSym 7,9%, Architect 15,1%)
- Roche 16,2 %
  (Elecsys 1,6%, Modular 4%, Cobas 10,6%)
- Beckman 10,3 %
  (Access 4,5%, DxI 5,8%)
- Siemens 10,2 %
  (Centaur 6,2%, Immulite 4%)
- Tosoh 4,2 %

(ANSM 2012)

- Roche 25,1 %
- Abbott 21,3 %
- Siemens 15,7%
- Beckman 12,6 %
- Biomérieux 10,8 %
- Thermofisher 3,1 %
- Tosoh 1,9 %

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Protocole technique

* Dosage des échantillons 2, 4 et 10 ng/ml de PSA total présentant des taux de 0, 25, 50, 75 et 100% de PSA libre
* Ces échantillons ont été préparés à partir des standards (PSA libre, PSA complexé) de l'Université de Stanford (Stamey), dilués dans du tampon PBS + BSA 1%
* Dosage en triple par site (45 dosages/trousse)

Environ 1800 dosages réalisés

Résultats Exactitude

PSA total

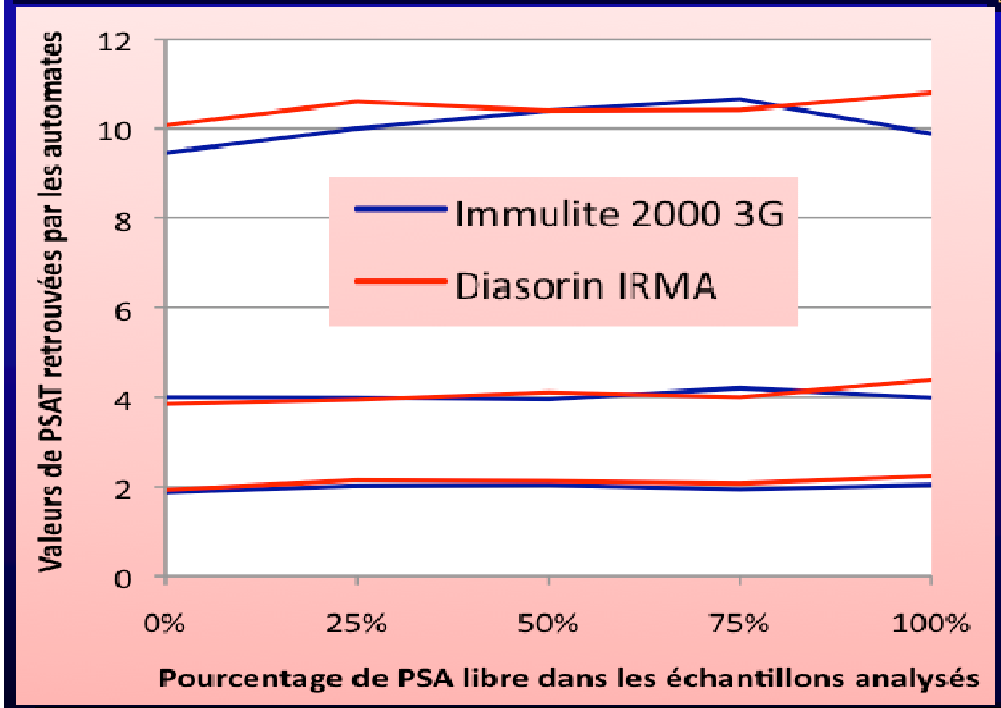
8 dispositifs sur 21 présentent des résultats satisfaisants selon experts

* ADVIA CENTAUR PSA (Siemens)
* ACS 180 PSA (Siemens)
* ADVIA IMS PSA (Siemens)
* KRYPTOR PSA Total (Brahms),
* TPSA FLEX DIMENSION (Siemens)
* PSA Total IRMA (Diasorin),
* IMMULITE 2000 PSA 3G (Siemens)
* PROSTATUS AUTODELFIA PSA libre/PSA total (Perkin Elmer)

PSA libre

8 dispositifs sur 19 présentent des résultats satisfaisants selon experts

* ARCHITECT PSA Libre (Abbott)
* IMX PSA Libre (Abbott)
* AXSYM PSA Libre (Abbott)
* ACS 180 CPSA (Siemens)
* TANDEM HYBRITECH R PSA Libre (Beckman)
* PROSTATUS AUTODELFIA PSA libre/PSA total (Perkin Elmer)
* FREE PSA ELECSYS (Roche)
* AIA PACK UCPA (Tosoh).



Résultats Equimolarité

Capacité du système à reconnaître de façon identique les formes libre et liée

8 dispositifs sur 21 présentent des résultats satisfaisants selon experts :

* ARCHITECT PSA TOTAL (Abbott)
* AXSYM PSA TOTAL (Abbott)
* TANDEM HYBRITECH R PSA (Beckman)
* PSA TOTAL IRMA (Diasorin)
* IMMULITE 2000 PSA 3G (Siemens)
* VITROS (Ortho Clinical Diagnostics)
* PROSTATUS AUTODELFIA PSA libre/PSA total (Perkin Elmer)
* AIA PACK PA (Tosoh Bioscience).

www.ansm.sante.fr

Dosages justes et équimolaires : PSA total Irma (Diasorin), Immulite 2000 PSA 3G (Siemens), Prostatus Autodelphia PSAL / PSAT (Perkin Elmer)

Ré-évaluation des dosages PSA

- Initiative des Sociétés Savantes :
  - » Biologie : SFMN, CNBH, SFBC
  - » Urologie : AFU
- Objectifs : EQM pour PSAT, exactitude pour PSAT et PSAL (pertinence pour L/T %)
- Protocole (cf Stamey 98 et Afssaps 2004) :
  - » 3 niveaux de concentration : 2 - 4 - 10 µg/L
  - » Proportions variables en PSAL : 10 - 20 - 30 - 60 - 100 %

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NIBSC 96/670 PSA total 90:10

WHO International Standard
Prostate Specific Antigen (90:10)
NIBSC code: 96/670
Instructions for use
(Version 5.0, Dated 30/11/2011)

1. INTENDED USE

This consists of a batch of vials (coded 96/670) containing seminal plasma-derived prostate-specific antigen (PSA), 90% bound to α_1-antichymotrypsin (PSA-ACT) and 10% in the free form (1), analysed by international collaborative study and established as the First International Standard for Prostate-Specific Antigen (90:10) by the Expert Committee on Biological Standardization of the World Health Organisation (2,3).

2. CAUTION

This preparation is not for administration to humans.

The preparation contains material of human origin, and either the final product or the source materials, from which it is derived, have been tested and found negative for HBsAg, anti-HIV and HCV RNA. As with all materials of biological origin, this preparation should be regarded as potentially hazardous to health. It should be used and discarded according to your own laboratory's safety procedures. Such safety procedures should include the wearing of protective gloves and avoiding the generation of aerosols. Care should be exercised in opening ampoules or vials, to avoid cuts.

3. UNITAGE

The assigned content is 1µg total PSA per vial.

Uncertainty: the International Unit of 96/670 is assigned without uncertainty. Where required, the uncertainty of the ampoule content of 96/670 may be considered to be the co-efficient of variation of the fill volume, which was determined to be 0.46%.

4. CONTENTS

Country of origin of biological material: USA.
Each vial contains the residue, after freeze-drying, of 2ml 20mM PBS, pH 7.4 solution that contained:

Bovine serum albumin	10g/L
Prostate-specific antigen (bound)	450µg/L
Prostate-specific antigen (free)	50µg/L

5. STORAGE

Unopened ampoules should be stored at –20°C

Please note: because of the inherent stability of lyophilized material, NIBSC may ship these materials at ambient temperature.

6. DIRECTIONS FOR OPENING

DIN ampoules have an 'easy-open' coloured stress point, where the narrow ampoule stem joins the wider ampoule body.
Tap the ampoule gently to collect the material at the bottom (labeled) end. Ensure that the disposable ampoule safety breaker provided is pushed down on the stem of the ampoule and against the shoulder of the ampoule body. Hold the body of the ampoule in one hand and the disposable ampoule breaker covering the ampoule stem between the thumb and first finger of the other hand. Apply a bending force to open the ampoule at the coloured stress point, primarily using the hand holding the plastic collar.
Care should be taken to avoid cuts and projectile glass fragments that might enter the eyes, for example, by the use of suitable gloves and an eye shield. Take care that no material is lost from the ampoule and no glass falls into the ampoule. Within the ampoule is dry nitrogen gas at slightly less than atmospheric pressure. A new disposable ampoule breaker is provided with each DIN ampoule.

7. USE OF MATERIAL

For practical purposes each vial contains the same quantity of PSA. The entire content of each vial should be completely dissolved in an accurately measured amount of distilled water. No attempt should be made to weigh out portions of the freeze dried powder. On reconstitution with 2ml distilled water, each vial will contain 500ng/ml total PSA. Subsequent dilutions should be carried out with an appropriate diluent. The free PSA component retains some enzymatic activity and can react with protease inhibitors so serum-based matrices should not be used. The material has not been sterilized and the vials contain no bacteriostat. Unopened vials of the IS should be stored below -20°C in the dark.

8. PREPARATION AND TRANSFER OF VIALS

The batch consists of 2000 glass vials containing 1µg of total PSA (90% PSA-ACT and 10% free PSA) prepared from seminal plasma (4). This mixture represents the average proportion of PSA-ACT and free PSA in sera of patients with cancer of the prostate (5). The material was filled at the Ciba-Corning facility in Irvine, CA, USA and lyophilized under the same controlled conditions as used for preparation of the College of American Pathologist's Survey Panels. Fill precision as measured by weight checks during filling was 0.46% and residual moisture content of the preparation was 2.23% (CV 6.3%). The vials were donated to WHO by Prof T Stamey, Stanford University, CA, USA and, after transfer to NIBSC, were coded 96/670 and stored at -20°C.

9. COLLABORATIVE STUDY

9.1 Aims of the study

The preparation in vials coded 96/670, together with a preparation of free PSA 90:10 (96/668), was evaluated by international collaborative study in which ten laboratories in six countries took part. The study was designed:

1) To compare the immunoreactivity of the preparations in immunoassay systems representative of those commonly used in clinical practice or research and assess their suitability to serve as WHO International Standards.

2) To assess the stability of the PSA in the lyophilised preparations by assay of the contents of vials which had undergone accelerated thermal degradation.

3) To compare the PSA immunoreactivity of different serum samples in the immunoassay systems included in the study in terms of both local standards and the candidate preparations.

9.2 Activity of vial contents and stability

Estimates of the contents of 96/670 by immunoassay were similar and consistent with local standards, giving a geometric mean estimate of 1.11µg/vial (95% confidence limits: 1.04 – 1.18). PSA 90:10 is representative of the ratio of the forms of PSA found in serum of patients with cancer of the prostate and use of a common standard of this preparation significantly reduced the between-laboratory GCVs for the serum samples included in the study and gave a much narrower range of potency estimates. Therefore the preparation coded 96/670 was established as the First International Standard for PSA (90:10) with a defined content of 1µg per vial (2,3). A predicted degradation rate (6) of 0.027% per year is estimated for samples stored at -20°C.

10. STABILITY

It is the policy of WHO not to assign an expiry date to their international reference materials. They remain valid with the assigned potency and status until withdrawn or amended.

Reference materials are held at NIBSC within assured, temperature-controlled storage facilities. Reference Materials should be stored on receipt as indicated on the label. For information specific to a particular biological standard, contact standards@nibsc.ac.uk.

In addition, once reconstituted, diluted or aliquoted, users should determine the stability of the material according to their own method of preparation, storage and use.

NIBSC follows the policy of WHO with respect to its reference materials.

Users who have data supporting any deterioration in the characteristics of any reference preparation are encouraged to contact NIBSC.
Although the predicted degradation rates for the two PSA International Standards [PSA (free) coded 96/668 and PSA (90:10) coded 96/670] indicated that the long term stability of these preparations was acceptable for their use as International Standards, ECBS recommended at the time of their establishment, that the PSA standards should be the suject of an ongoing stability monitoring programme, as they are filled in vials. In light of this, a recently completed study (2011) has supported the initial stability assessment and confirms the long term stability of these International Standards.

11. REFERENCES

1. Stamey T.A., Chen Z. & Prestigiacomo A.F. Reference material for PSA: the IFCC standardization study. Clin Biochem 1998 31:475-481.
2. WHO TRS 50th Report No. 904
3. Rafferty B, Rigsby P, Rose M, Stamey T & Gaines Das R (2000). Reference reagents for prostate-specific antigen (PSA): establishment of the First International Standards for free PSA and PSA (90:10). Clin Chem 46(0): 1310 1317.
4. Sensabaugh G.F. & Blake E.T. Seminal plasma protein p30: simplified purification and evidence for identity with prostate-specific antigen. J Urol 1990 144: 1523-6
5. Stamey T.A., Chen Z. & Prestigiacomo A.F. Serum prostate-specific antigen binding to α-1-antichymotrypsin: influence of cancer volume, location and therapeutic selection of resistant clones. J Urol 1004 152: 1510-1514.
6. Kirkwood T.B.L. Predicting the stability of biological standards and products. Biometrics 1977 33: 736-742.

12. ACKNOWLEDGEMENTS

We gratefully acknowledge the important contributions of all the participants, and particularly Dr T. Stamey, Stanford University School of Medicine, who kindly donated the PSA material. We would also like to acknowledge the collaboration and support of the IFCC Scientific Division Working Group on Standardisation of PSA.

13. FURTHER INFORMATION

Further information can be obtained as follows
This material: enquiries@nibsc.hpa.org.uk
WHO Biological Standards:
http://www.who.int/biologicals/en/
JCTLM Higher order reference materials:
http://www.bipm.org/en/committees/jc/jctlm/
Derivation of International Units:
http://www.nibsc.ac.uk/products/biological_reference_materials/frequently_asked_questions/how_are_international_units.aspx
Ordering standards from NIBSC:
http://www.nibsc.ac.uk/products/ordering_information/frequenty_asked_questions.aspx
NIBSC Terms & Conditions:
http://www.nibsc.ac.uk/terms_and_conditions.aspx

14. CUSTOMER FEEDBACK

Customers are encouraged to provide feedback on the suitability or use of the material provided or other aspects of our service. Please send any comments to enquiries@nibsc.hpa.org.uk

15. CITATION

In all publications, including data sheets, in which this material is referenced, it is important that the preparation's title, its status, the NIBSC code number, and the name and address of NIBSC are cited and cited correctly.

16. MATERIAL SAFETY SHEET

National Institute for Biological Standards and Control - Assuring the quality of biological medicines
Blanche Lane South Mimms Potters Bar Hertfordshire EN6 3QG United Kingdom
Tel +44 (0)1707 641000 Fax +44 (0)1707 641050 www.nibsc.ac.uk
A World Health Organization Laboratory for Biological Standards

National Institute for Biological Standards and Control - Assuring the quality of biological medicines
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Tel +44 (0) 707 641000 Fax +44 (0)1707 641050 www.nibsc.ac.uk
A World Health Organization Laboratory for Biological Standards

NIBSC 96/668 PSA libre

WHO International Standard
Prostate-Specific Antigen Free
NIBSC code: 96/668
Instructions for use
(Version 6.0, Dated 30/11/2011)

1. INTENDED USE

This consists of a batch of vials (coded 96/668) containing seminal plasma-derived prostate-specific antigen (PSA) (1) analysed by international collaborative study and established as the First International Standard for Prostate-Specific Antigen (Free) by the Expert Committee on Biological Standardization of the World Health Organisation (2,3).

2. CAUTION

This preparation is not for administration to humans.
The preparation contains material of human origin, and either the final product or the source materials, from which it is derived, have been tested and found negative for HBsAg, anti-HIV and HCV RNA. As with all materials of biological origin it should be regarded as potentially hazardous. It should be used and discarded according to your own laboratory's safety procedures. Such safety procedures probably will include the wearing of protective gloves and avoiding the generation of aerosols. Care should be exercised in opening ampoules or vials, to avoid cuts by glass and metal edges.

3. UNITAGE

The assigned content is 1µg total PSA per vial.

Uncertainty: the International Unit of 96/668 is assigned without uncertainty. Where required, the uncertainty of the ampoule content of 96/668 may be considered to be the co-efficient of variation of the fill volume, which was determined to be 0.46%.

4. CONTENTS

Country of origin of biological material: USA.
Each vial contains the residue after freeze-drying of 2ml 20mM PBS, pH 7.4 solution that contained:

Bovine serum albumin	10g/L
Prostate-specific antigen (free)	500µg/L

5. STORAGE

Unopened ampoules should be stored at –20°C
Please note: because of the inherent stability of lyophilized material, NIBSC may ship these materials at ambient temperature.

6. DIRECTIONS FOR OPENING

DIN ampoules have an 'easy-open' coloured stress point, where the narrow ampoule stem joins the wider ampoule body.
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8. PREPARATION AND TRANSFER OF VIALS

The batch consists of 2000 glass vials containing 1µg of free PSA prepared from seminal plasma (4). The material was filled at the Ciba-Corning facility in Irvine, CA, USA and lyophilized under the same controlled conditions as used for preparation of the College of American Pathologist's Survey Panels. Fill precision as measured by weight checks during filling was 0.46% and residual moisture content of the preparation was 2.23% (CV 6.3%). The vials were donated to WHO by Prof T Stamey, Stanford University, CA, USA and, after transfer to NIBSC, were coded 96/668 and stored at -20°C.

9. COLLABORATIVE STUDY

9.1 Aims of the study

The preparation in vials coded 96/668, together with a preparation of PSA 90:10 (96/670), was evaluated by international collaborative study in which ten laboratories in six countries took part. The study was designed:

1) To compare the immunoreactivity of the preparations in immunoassay systems representative of those commonly used in clinical practice or research and assess their suitability to serve as WHO International Standards.

2) To assess the stability of the PSA in the lyophilised preparations by assay of the contents of vials which had undergone accelerated thermal degradation.

3) To compare the PSA immunoreactivity of different serum samples in the immunoassay systems included in the study in terms of both local standards and the candidate preparations.

9.2 Activity of vial contents and stability

Estimates of the contents of 96/668 by immunoassay were similar and consistent with local standards, giving a geometric mean estimate of 1.10 µg/vial (95% confidence limits: 0.99 – 1.21). Therefore the preparation coded 96/668 was established as the First International Standard for PSA (free) with a defined content of 1 microgram per vial (2,3). A predicted degradation rate (5) of 0.042% per year is estimated for samples stored at -20°C.

It is the policy of WHO not to assign an expiry date to their international reference materials. They remain valid with the assigned potency and status until withdrawn or amended.

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This material: enquiries@nibsc.hpa.org.uk
WHO Biological Standards:
http://www.who.int/biologicals/en/
JCTLM Higher order reference materials:
http://www.bipm.org/en/committees/jc/jctlm/
Derivation of International Units:
http://www.nibsc.ac.uk/products/biological_reference_materials/frequently_asked_questions/how_are_international_units.aspx
Ordering standards from NIBSC:
http://www.nibsc.ac.uk/products/ordering_information/frequently_asked_questions.aspx
NIBSC Terms & Conditions:
http://www.nibsc.ac.uk/terms_and_conditions.aspx

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13. CITATION

In all publications, including data sheets, in which this material is referenced, it is important that the preparation's title, its status, the NIBSC code number, and the name and address of NIBSC are cited and cited correctly.

14. MATERIAL SAFETY SHEET

Physical and Chemical properties	
Physical appearance: White lyophilised powder	Corrosive: No
Stable: Yes	Oxidising: No
Hygroscopic: Yes	Irritant: No
Flammable: No	Handling: See caution, Section 2
Other (specify):	Contains material of human origin
Toxicological properties	
Effects of inhalation:	Not established, avoid inhalation
Effects of ingestion:	Not established, avoid ingestion
Effects of skin absorption:	Not established, avoid contact with skin
Suggested First Aid	
Inhalation:	Seek medical advice
Ingestion:	Seek medical advice
Contact with eyes:	Wash with copious amounts of water. Seek medical advice
Contact with skin:	Wash thoroughly with water.
Action on Spillage and Method of Disposal	
Spillage of ampoule contents should be taken up with absorbent material wetted with an appropriate disinfectant. Rinse area with an appropriate disinfectant followed by water. Absorbent materials used to treat spillage should be treated as biological waste.	

15. LIABILITY AND LOSS

Information provided by the Institute is given after the exercise of all reasonable care and skill in its compilation, preparation and issue, but it is provided without liability to the Recipient in its application and use.

It is the responsibility of the Recipient to determine the appropriateness of the standards or reference materials supplied by the Institute to the Recipient ("the Goods") for the proposed application and ensure that it has the necessary technical skills to determine that they are appropriate.

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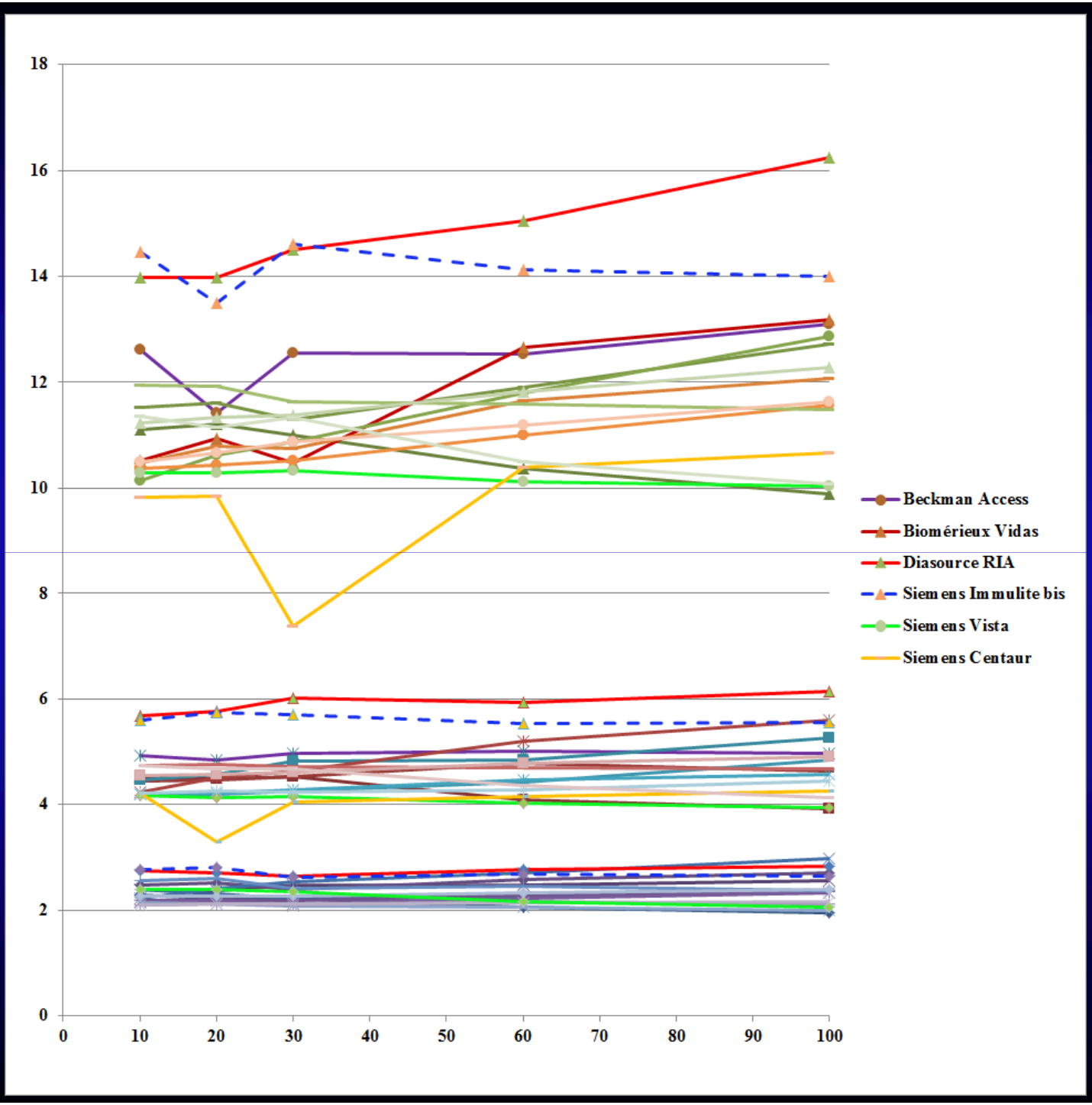
A World Health Organization Laboratory for Biological Standards

Panels

- Préparation à Lyon (Anne Charrié)
  - » Standards NIBSC : PSAT 90:10 (96/670) et PSAL (96/668)
  - » Tampon de dilution : PBS-BSA 5 %
- Envoi aux sites évaluateurs (Corinne Sault, Biomnis)
- Dosages : en triple avec tous les dispositifs utilisés en France (exclus TDR)
  - » PSAT : 14
  - » PSAL : 13 (dont 1 PSAC)
- Sites experts (19) : biologistes Public et Privé (volontariat). Si possible 2 sites pour chaque dispositif.

			PSAT	PSAL	PSAC	
Fournisseur	**Système**	**Standardisation**	**27**	**26**	**1**	**Sites Evaluateurs**
ABBOTT	Architect	WHO	1	1		F. Boux, CHU Angers
	Architect ci-8200	WHO	1	1		D. Brault-S. Bailleul, Tenon Paris
BECKMAN COULTER	Access	Hybritech	1	1		PJ. Lamy, CRLC Montpellier
	DXI 600	Hybritech	1	1		P. Deleplanque, CH Niort
	DXI 800	Hybritech	1	1		M. Capdeville, CH Neufchâteau
	DXI 800	Hybritech	1	1		A. Georges, CHU Bordeaux
BIOMERIEUX	Vidas	WHO	1	1		C. Claise, CH Melun
CISBIO	RIA Cisbio	WHO	1	1		PJ. Lamy, CRLC Montpellier
	RIA Cisbio	WHO	1	1		AS. Gauchez, CHU Grenoble
DIASORIN	Liaison	WHO	1	1		C. Sault, Biomnis Lyon
	Liaison	WHO	1	1		C. Massart, CHU Rennes
DIASOURCE	RIA Diasource	WHO	1			AS. Gauchez, CHU Grenoble
ROCHE	Cobas 8000	WHO	1	1		C. Sault, Biomnis Lyon
	Cobas 6000	WHO	1	1		PJ. Lamy, CRLC Montpellier
	Cobas 6000	WHO	1	1		Y. Cano, CH Vannes
SIEMENS	Immulite 2000	WHO	1	1		A. Marinier, CH Versailles
	Immulite 2000 XPi	WHO	1	1		X. Heches, CH Mont-de-Marsan
	Immulite 2500	WHO	1	1		X. Heches, CH Mont-de-Marsan
	Vista 500	WHO	1	1		C. Claise, CH Melun
	Vista 500	WHO	1	1		M. Marchaison, CH Hyères
	Centaur	WHO	1	1	1	C. Massart, CHU Rennes
THERMO FISCHER	Kryptor	WHO	1	1		MP. Moineau, CHU Brest
	Kryptor Compact	WHO	1	1		MP. Moineau, CHU Brest
	Kryptor	WHO	1	1		N. Reix, CHU Strasbourg
	Vitros 5600	WHO	1	1		X. Heches, CH Mont-de-Marsan
TOSOH	AIA 2000	WHO	1	1		JC. Monboisse, CHU Reims
	AIA 2000	WHO	1	1		G. Méchin, CH Eaubonne-Montmorency



PSAT

EQM

Justesse

- EQM variable
- Ciblage variable vs L/T%
- Ecart augmente avec PSA
- Surdosage global PSAT

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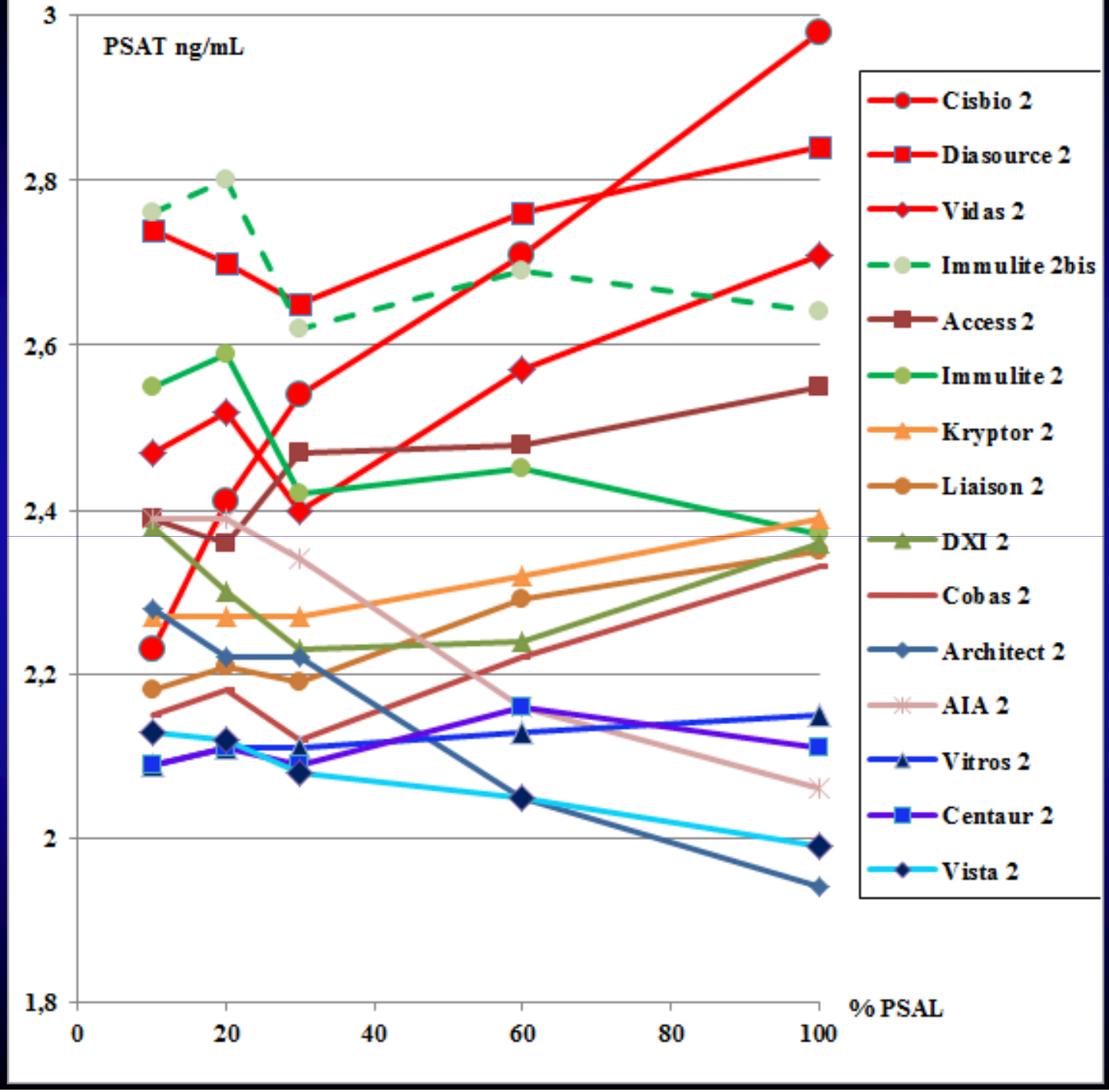
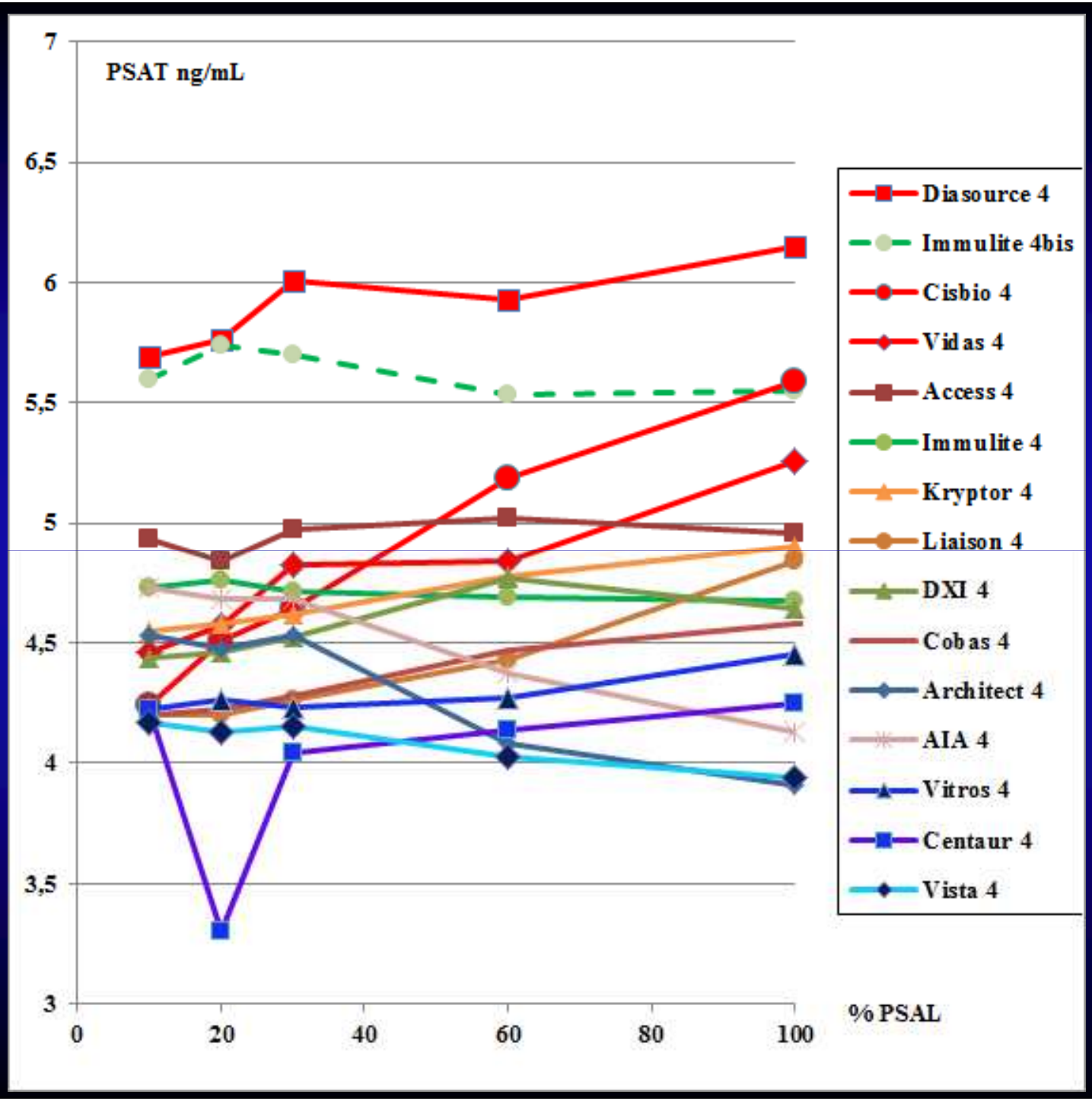
2014



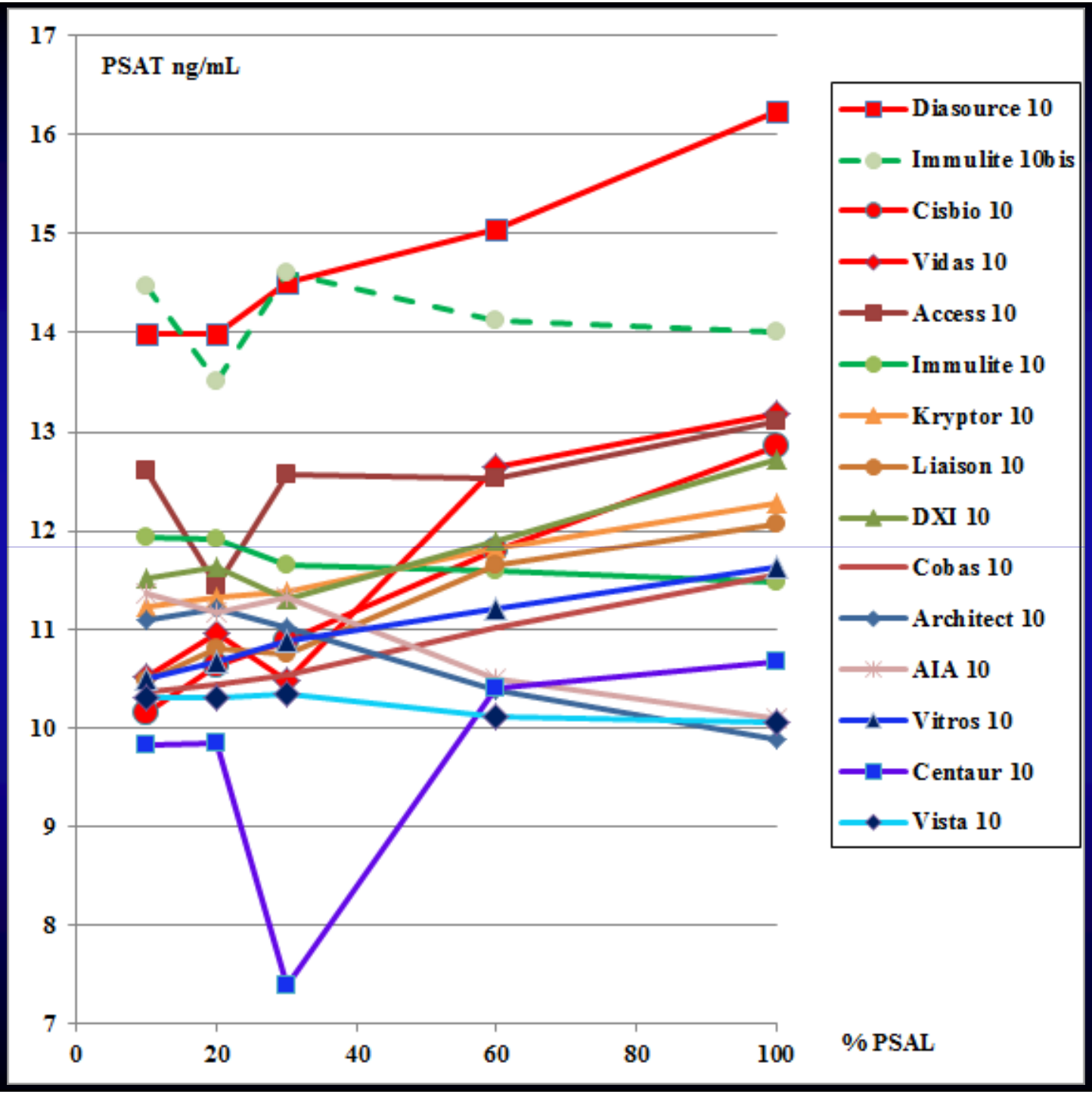
PSA cible 2 ng/mL

Fulla 2014



PSA cible 4 ng/mL

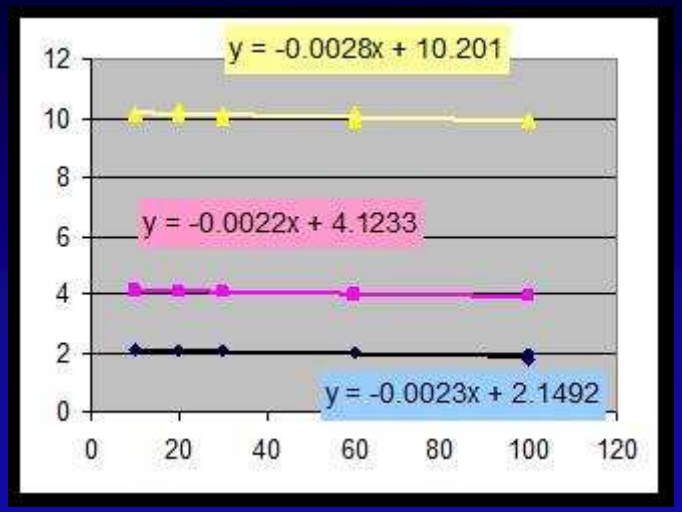
Fulla 2014



PSA cible 10 ng/mL

Fulla 2014

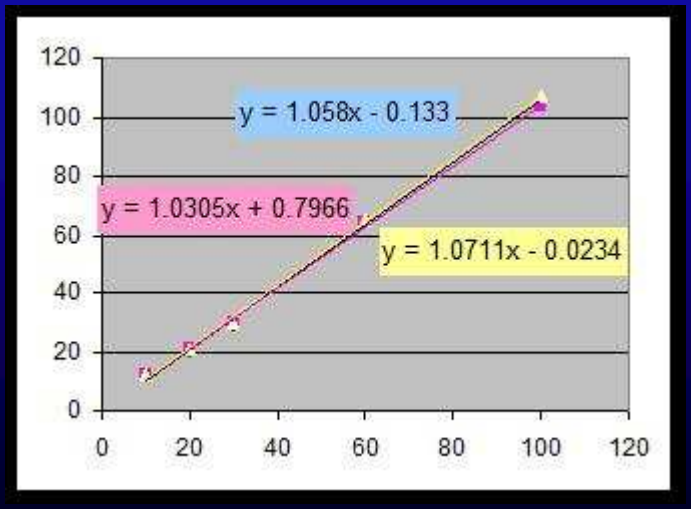
Vista



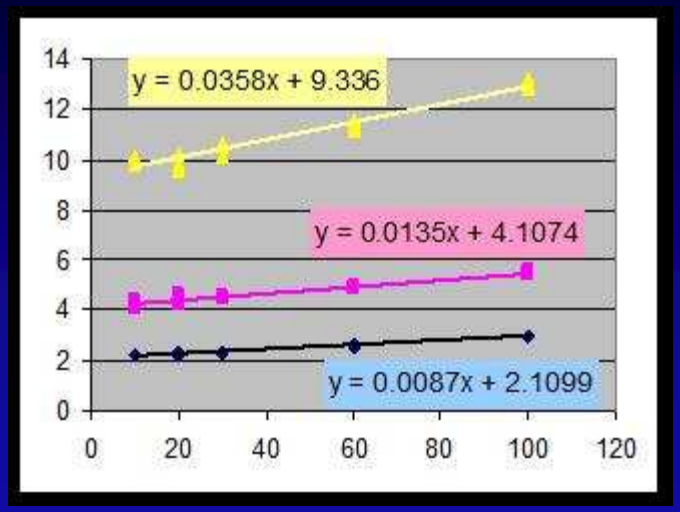
$PSAL_m = 0,97\ PSAL_{th} + 0,52$

$PSAL_m = 1,00\ PSAL_{th} + 0,06$

$PSAL_m = 0,98\ PSAL_{th} + 0,10$



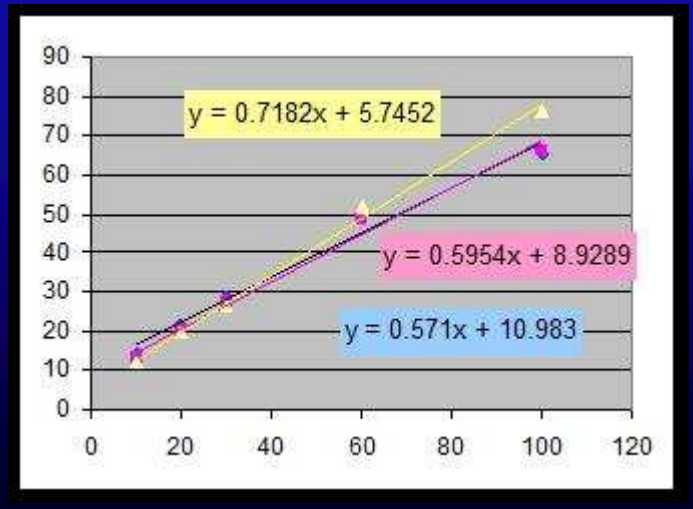
RIA



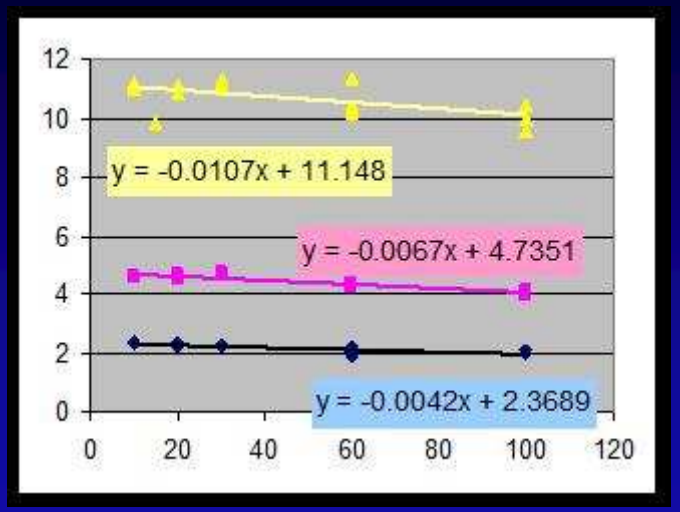
$PSAL_m = 0,92\ PSAL_{th} + 0,14$

$PSAL_m = 0,86\ PSAL_{th} + 0,22$

$PSAL_m = 0,99\ PSAL_{th} + 0,04$



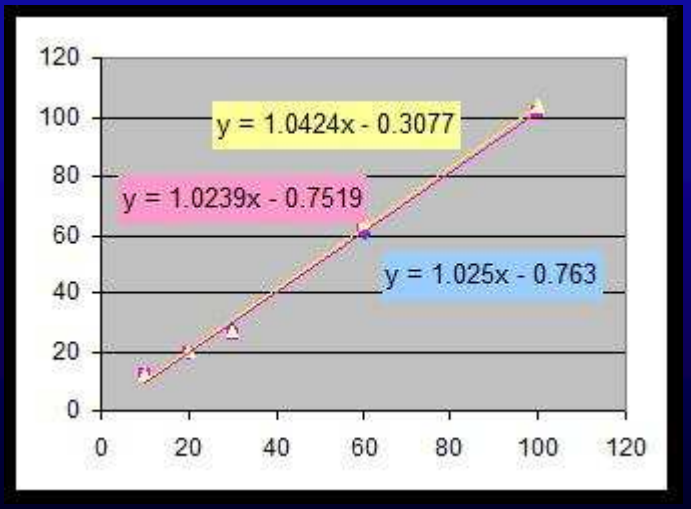
AIA



$PSAL_m = 0,99\ PSAL_{th} + 0,05$

$PSAL_m = 1,02\ PSAL_{th} + 0,09$

$PSAL_m = 1,00.PSAL_{th} + 0,29$



Fulla
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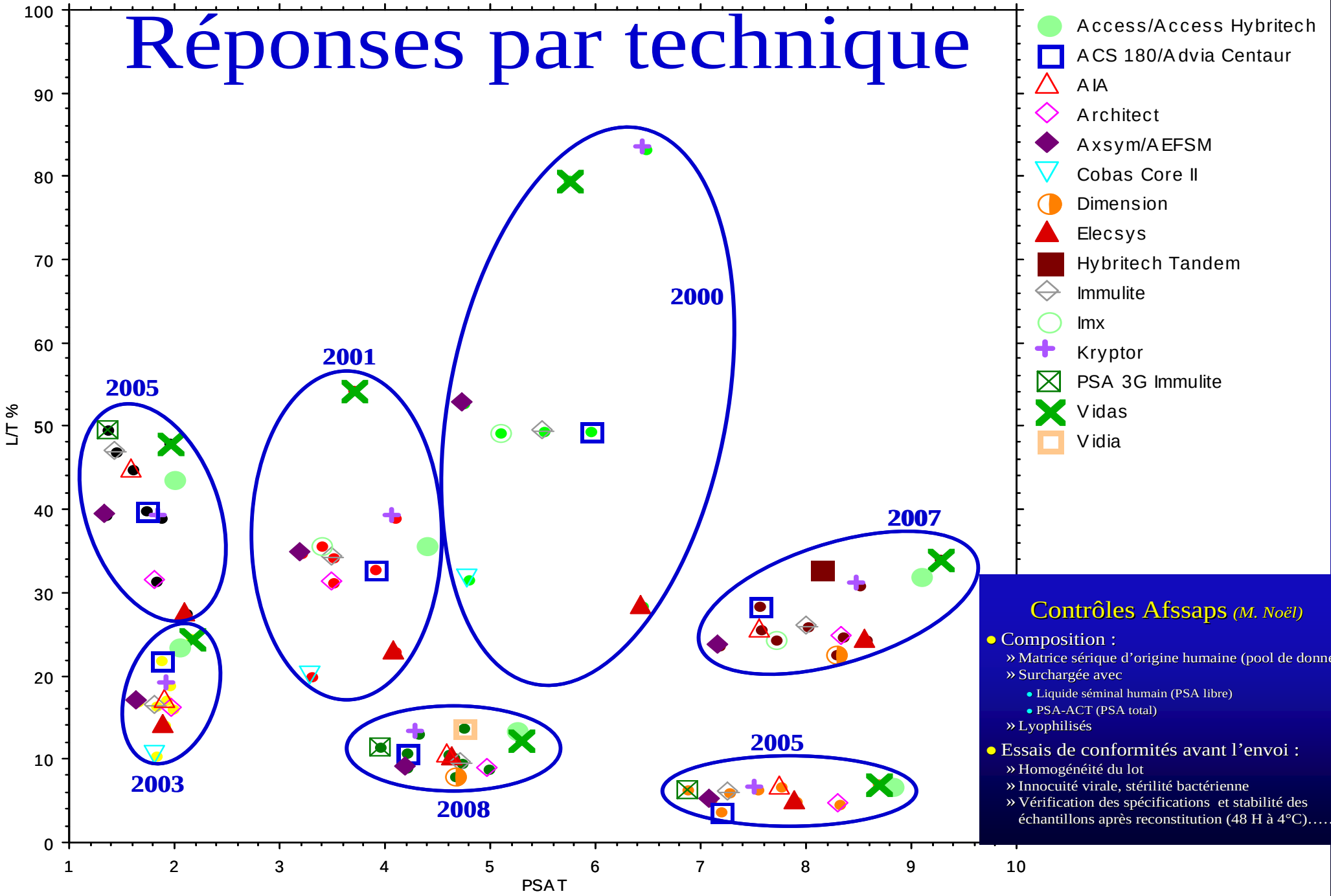
Réponses par technique



Contrôles Afssaps *(M. Noël)*

- Composition :
  - » Matrice sérique d'origine humaine (pool de donneurs)
  - » Surchargée avec
    - Liquide séminal humain (PSA libre)
    - PSA-ACT (PSA total)
  - » Lyophilisés
- Essais de conformités avant l'envoi :
  - » Homogénéité du lot
  - » Innocuité virale, stérilité bactérienne
  - » Vérification des spécifications et stabilité des échantillons après reconstitution (48 H à 4°C)……

Conséquences pour la pratique du PSA

- Abaque d'ajustement des différentes techniques ?
  - » Seuil de décision unique : équivalence de performance pour la détection précoce
  - » Cinétique : calcul pertinent des paramètres PSAV et TD sans biais de variabilité intertechnique
- Cinétique du PSAT : TD et PSAV informatifs
  - » Conditions à définir : fréquence et délai dosages, technique utilisée, modèle mathématique (croissance exponentielle, vélocité linéaire)
- Les résultats de PSA doivent être rendus avec la mention en clair du système utilisé, car les différences intertechniques augmentent avec la concentration de PSAT et la proportion de PSAL. L'interprétation d'un résultat de PSA doit tenir compte de la qualité du test utilisé
- PSAL : 2 groupe de ciblage dont l'un surdose à plus de 40%

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Conclusion

Conseils de bonne pratique

- Choix du bon dosage
  - » Détection précoce : seuil de décision unique pour prescription de biopsies (2-3-4 …ng/mL) ou cinétique attention à la variabilité des dosages de PSAT. Privilégier un dosage **exact et EQM** pour PSAT, **exact** pour PSAL (rapport L/T % correct)
  - » Suivi post-prostatectomie : seuil de récidive (0,1-0,2 ng/mL ou moins ?) privilégier un dosage **ultra-sensible** et faire une cinétique sur plusieurs valeurs successives détectables
- Messages pour sensibiliser :
  - » Biologistes : considérer la qualité face aux contraintes économiques et organisationnelles
  - » Décideurs et ingénieurs biomédicaux : dialogue rapport qualité/prix
  - » Industriels : améliorer les dosages défaillants, voire retirer les mauvais (surtout en PSA libre) pour éviter les surdosages (surtraitements)
  - » Cliniciens (Urologues, Généralistes) et Patients : exiger des dosages de qualité pour une décision diagnostique efficace et à moindre coût

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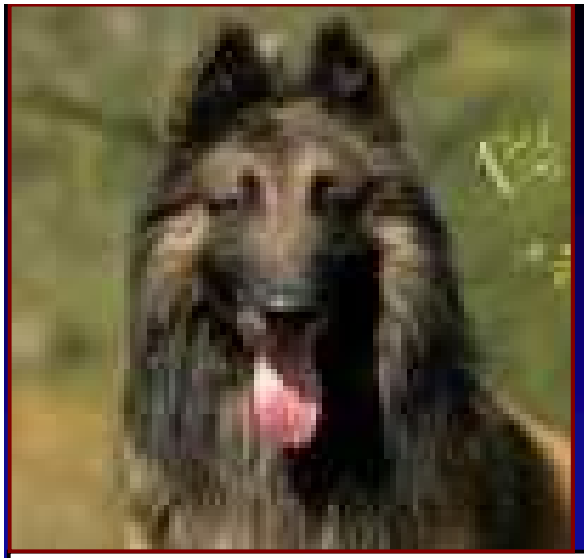

Berger Belge Chien renifleur

Des chiens capables de détecter les cancers de la prostate

Autre(s) nom(s) Malinois, Groenendael, Laekenois, Tervueren, Belgian Shepherd Dog
Origine Belgique
Groupe Bergers et Bouviers

L'odorat du chien est extrêmement développé (illustration)

France – Selon une étude menée par une équipe française et présentée à l'*American urological association*, certaines races de chiens pourraient être entraînées à détecter les cancers de la prostate.

Les médecins de l'hôpital Tenon à Paris ont entraîné ces chiens à distinguer l'urine d'hommes atteints d'un cancer de la prostate de celle d'hommes sains. Les chiens sont parvenus à identifier 63 cancers sur 66.
Les chiens possèdent un odorat extrêmement subtil, 100.000 fois plus puissant que celui de l'Homme. Ils sont déjà entraînés à détecter drogues, explosifs ou prisonniers évadés.
Une molécule contenue dans les cellules du cancer de la prostate doit libérer une odeur particulière à laquelle les malinois sont sensibles, selon Jean-Nicolas Cornu, le directeur de la recherche. Toutefois, les scientifiques n'ont pas encore identifié cette molécule. Il pourrait également s'agir d'un effet Clever Hans, phénomène par lequel un animal répond correctement à une demande, une question non pas parce qu'il connaît la réponse mais par réaction à un stimulus provoqué par l'expression du visage et/ou les mouvements de la personne "l'interrogeant". D'autres études avec un panel plus large doivent donc être menées.

Une équipe de chercheurs français a révélé cette semaine que les chiens pourraient être utiles dans la **détection du cancer de la prostate chez l'homme**. En effet, ces animaux seraient capables de **sentir la présence de produits chimiques** dans l'urine de personnes atteintes de cancer de la prostate.

Les chiens, dont l'**odorat est extrêmement développé**, seraient donc entraînés pour reconnaitre cette odeur particulière diffusée par les produits chimiques. Dans le cas d'un cancer du poumon, des produits chimiques sont également présents, et peuvent être sentis dans **l'haleine de la personne**.

Le docteur français Jean-Nicolas Cornu a entrainé un Berger belge à sentir des échantillons d'urine de personnes atteintes d'un cancer de la prostate et d'autres qui ne l'étaient pas. Sur 66 essais, les chiens ont réussi 63 fois. Les seuls erreurs étaient sur des personnes saines, que le chien avait évalué comme malades. Toutes les personnes ont été **identifiées par le Berger belge**.

Le processus d'entrainement a duré pendant environ un an et l'équipe de chercheurs est déjà en train de **former de nouveaux chiens**. Les chercheurs tentent d'identifier les produits chimiques auxquels répondent les chiens, afin de mettre au point un « nez électronique »

Décidément, les chiens ont vraiment une âme de sauveurs ! Nous parlions récemment de la bave du chien qui pourrait être utilisée pour guérir les personnes atteintes du cancer. Nos amis à quatre pattes n'en finiront jamais de nous étonner !