CASE STUDY 3: PSA-STANDARDISATION & VARIABILITY COMPARATIVE STUDY IN HOSPITALS

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JCTLM Meeting
BIPM, Sevres,France
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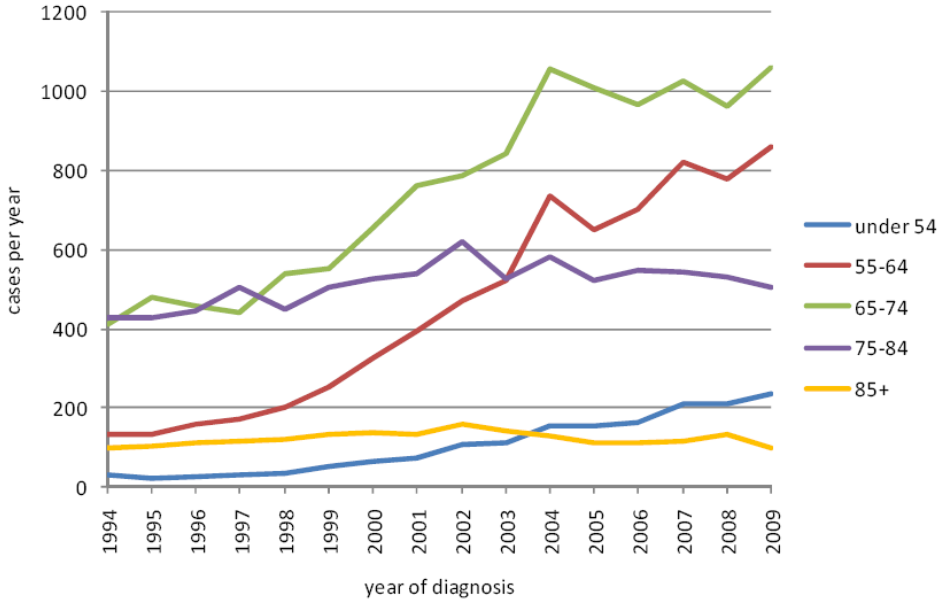
Prostate Cancer in Ireland

- Most common non-cutaneous cancer in males
- 1 in 11 Irish men diagnosed in their lifetime
- Between 1994 to 2009 – increased incidence in all age groups
  - 55 to 64 years (134 cases to 859)

National Cancer Registry Ireland



Prostate Cancer in Ireland

- Incidence is predicted to increase by 140% during 2008-2030
- Incidence is rising and survival is increasing, more men are living longer with PCa
- Over 2,500 men are diagnosed with prostate cancer each year.
- The cumulative risk of a man developing prostate cancer before the age of 50 is 1 in 485 and before the age of 70 is 1 in 13

National Cancer Forum 2006

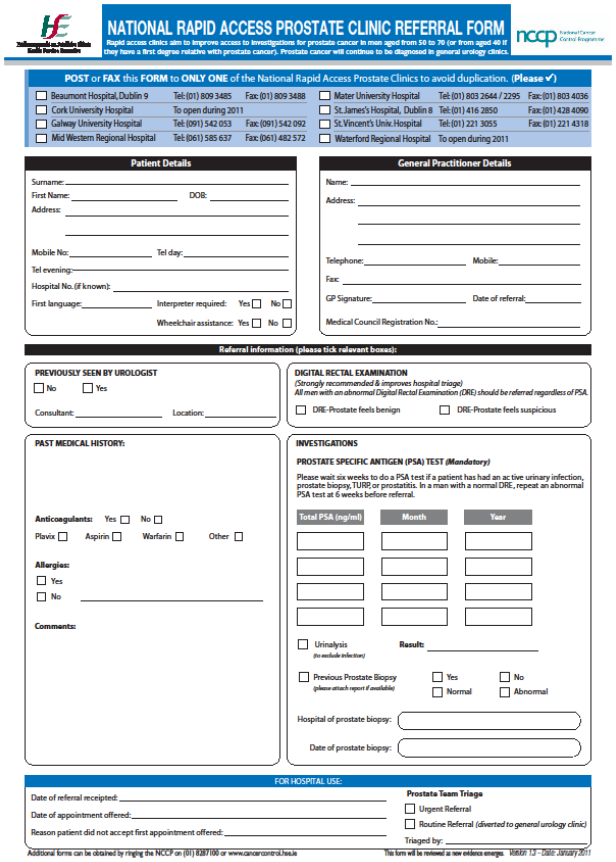
- Each year approximately 20,000 Irish people develop cancer and 7,500 die of the disease
- Recommended that Cancer Centres should be networked together in Managed Cancer Control Networks
- The National Cancer Control Programme (NCCP) was set up
  - to provide a comprehensive programme of cancer control in Ireland,
  - to transform how cancer care is delivered,
  - ensure that cancer services meet the highest standards.
- 8 Specialist Cancer Centres were set up and networked within each of the four HSE administration regions.
- Patients suspected of having PCa are assessed and diagnosed through a single integrated care pathway

Specialist Cancer Centres

- Each Specialist Cancer Centre must serve a population of at least 500,000
- Rare and complex cancers should be treated by a subset of the eight cancer centres
- Cancer Centres must be well supported

GP Electronic Cancer Referral

- Electronic referral for Breast, Prostate and Lung cancer is available free for GPs using the following ICGP accredited software systems:
  - Socrates,Complete GP,Helix Practice Manager & HealthOne



NATIONAL RAPID ACCESS PROSTATE CLINIC REFERRAL FORM

Rapid access clinics aim to improve access to investigations for prostate cancer in men aged from 50 to 70 (or from aged 40 if they have a first degree relative with prostate cancer). Prostate cancer will continue to be diagnosed in general urology clinics.

POST or **FAX** this **FORM** to **ONLY ONE** of the National Rapid Access Prostate Clinics to avoid duplication. **(Please ✓)**

☐ Beaumont Hospital, Dublin 9	Tel: (01) 809 3485	Fax: (01) 809 3488	☐ Mater University Hospital	Tel: (01) 803 2644 / 2295	Fax: (01) 803 4036
☐ Cork University Hospital	To open during 2011		☐ St. James's Hospital, Dublin 8	Tel: (01) 416 2850	Fax: (01) 428 4090
☐ Galway University Hospital	Tel: (091) 542 053	Fax: (091) 542 092	☐ St. Vincent's Univ. Hospital	Tel: (01) 221 3055	Fax: (01) 221 4318
☐ Mid Western Regional Hospital	Tel: (061) 585 637	Fax: (061) 482 572	☐ Waterford Regional Hospital	To open during 2011	

Patient Details

Surname: _____

First Name: _____ DOB: _____

Address: _____

Mobile No: _____ Tel day: _____

Tel evening: _____

Hospital No. (if known): _____

First language: _____ Interpreter required: Yes ☐ No ☐

Wheelchair assistance: Yes ☐ No ☐

General Practitioner Details

Name: _____

Address: _____

Telephone: _____ Mobile: _____

Fax: _____

GP Signature: _____ Date of referral: _____

Medical Council Registration No.: _____

Referral information (please tick relevant boxes):

PREVIOUSLY SEEN BY UROLOGIST

☐ No ☐ Yes

Consultant: _____ Location: _____

DIGITAL RECTAL EXAMINATION

(Strongly recommended & improves hospital triage)

All men with an abnormal Digital Rectal Examination (DRE) should be referred regardless of PSA.

☐ DRE-Prostate feels benign ☐ DRE-Prostate feels suspicious

PAST MEDICAL HISTORY:

Anticoagulants: Yes ☐ No ☐

Plavix ☐ Aspirin ☐ Warfarin ☐ Other ☐

Allergies:

☐ Yes

☐ No _____

Comments:

INVESTIGATIONS

PROSTATE SPECIFIC ANTIGEN (PSA) TEST (Mandatory)

Please wait six weeks to do a PSA test if a patient has had an active urinary infection, prostate biopsy, TURP or prostatitis. In a man with a normal DRE, repeat an abnormal PSA test at 6 weeks before referral.

Total PSA (ng/ml)	Month	Year

☐ Urinalysis *(to exclude infection)* **Result:** _____

☐ Previous Prostate Biopsy *(please attach report if available)* ☐ Yes ☐ No ☐ Normal ☐ Abnormal

Hospital of prostate biopsy: _____

Date of prostate biopsy: _____

FOR HOSPITAL USE:

Date of referral receipted: _____

Date of appointment offered: _____

Reason patient did not accept first appointment offered: _____

Prostate Team Triage

☐ Urgent Referral

☐ Routine Referral *(diverted to general urology clinic)*

Triaged by: _____

Additional forms can be obtained by ringing the NCCP on (01) 8287100 or www.cancercontrol.ie/rau.ie

This form will be reviewed as new evidence emerges. Version 1.2 - Date: January 2011

NATIONAL PROSTATE CANCER GP REFERRAL GUIDELINES

Rapid access clinics aim to improve access to investigations for prostate cancer in men aged from 50 to 70 (or from aged 40 if they have a first degree relative with prostate cancer). Prostate cancer will continue to be diagnosed in general urology clinics.

Prostate cancer is the leading cause of cancer in men (excluding skin cancer). Over 2,500 men are diagnosed with prostate cancer in Ireland each year. The cumulative risk of a man developing prostate cancer before the age of 50 is 1 in 485 and before the age of 70 is 1 in 13.

Data Source: National Cancer Registry, Ireland.

Risk Factors: Family history of prostate cancer, age (risk of prostate cancer increases after 50 years), and men of African ethnicity.

Prostate Specific Antigen (PSA) Testing

- PSA testing of asymptomatic men or **PSA screening is not national policy**
- Prostate assessment consists of a digital rectal examination (DRE) and a PSA test
- PSA testing should only be carried out after full advice and provision of information. (Patient information leaflet about prostate assessment is available from the National Cancer Control Programme on (01) 8287100 or can be downloaded by logging onto www.cancercontrol.hse.ie)
- All men with an abnormal DRE should be referred to a urologist regardless of PSA results

GENERAL RECOMMENDATIONS

A patient who presents with symptoms or signs suspicious of prostate cancer should be referred for rapid access prostate assessment. Primary healthcare professionals should encourage all men over 50 years of age, or men over 40 who have a first degree relative with prostate cancer or those of African ethnicity to be aware of prostate health issues, in order to minimise delay in presentation of disease.

To make a referral, **FAX**, or **POST** a **NATIONAL RAPID ACCESS PROSTATE CLINIC REFERRAL FORM** or submit an electronic prostate cancer referral form via healthlink. **Electronic referral systems are currently being developed, go to the following website www.healthlink.ie for further updates**.

Additional prostate cancer referral forms can be obtained by ringing the National Cancer Control Programme on **(01) 8287100** or by logging onto **www.cancercontrol.hse.ie**

NATIONAL RAPID ACCESS PROSTATE CLINICS *(please refer to only one clinic)*

Beamount Hospital, Dublin 9	Tel: (01) 809 3485	Fax: (01) 809 3488
Cork University Hospital	Tel: (021) 492 2113	Fax: (021) 492 2391
Galway University Hospital	Tel: (091) 542 053	Fax: (091) 542 092
Mid Western Regional Hospital, Limerick	Tel: (061) 585 637	Fax: (061) 482 572
Mater Hospital, Dublin 7	Tel: (01) 803 2644 / 2295	Fax: (01) 803 4036
St. James's Hospital, Dublin 8	Tel: (01) 416 2850	Fax: (01) 428 4090
St. Vincent's University Hospital, Dublin 4	Tel: (01) 221 3055	Fax: (01) 221 4318
Waterford Regional Hospital	Tel: (051) 842 044	Fax: (051) 848 844

Patient Advice:	Guidance on PSA Testing
• Prostate assessment involves a blood test and a rectal examination • A normal assessment does not rule out cancer • A biopsy can be uncomfortable. Side effects such as bleeding, infection or urinary retention may occur but less than 1% require hospital admission	• Patients should be counselled before they have a PSA test • Patients with an abnormal PSA result should have a repeat PSA at six weeks. If the patient also has an abnormal DRE, the PSA test does not need to be repeated and they should be referred directly • Finasteride/ dutasteride reduce PSA results by 50%, therefore the PSA result should be doubled in these patients • DRE performed before the PSA does not raise the result

A Digital Rectal Examination (DRE) should be performed on every patient who is having a prostate assessment.

This guideline represents the view of the NCCP, which was arrived at after careful consideration of the evidence available. Health professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of health professionals to make decisions appropriate to each patient. This guideline will be reviewed as new evidence emerges, and supersedes all previous HSE/NCCP prostate cancer GP referral guidelines. Version 4 –Date: January 2012

REFERRALS FOR SUSPECTED PROSTATE CANCER

PATIENTS SHOULD RECEIVE FULL ADVICE PRIOR TO PSA TESTING

Patient is aged from 50 to 70 years (or from 40 to 70 years if he has a first degree relative with prostate cancer or is of African ethnicity).

ASYMPTOMATIC MEN

Advise patients on the advantages and disadvantages of PSA testing

If prostate assessment requested perform the following:

- DRE – Digital Rectal Examination
- PSA – Prostate Specific Antigen

SYMPTOMATIC MEN

Male patient presents with:
Any of the following features when unexplained:

- Lower urinary tract symptoms e.g. dysuria, urgency, nocturia
- Unexplained back pain

RECOMMENDED INVESTIGATIONS

- DRE – Digital Rectal Examination
- PSA – Prostate Specific Antigen
- Creatinine
- Hb
- Urinalysis

If normal DRE and PSA manage symptoms in Primary Care or refer to urology clinic as clinically indicated.

Refer Patient to Rapid Access Clinic if he has

- A second abnormal PSA at 6 weeks after the first PSA test
- Abnormal hard Prostate on DRE

PSA ADVICE

WHEN TO DELAY PSA TEST

PSA test should be delayed by 6 weeks if patient has any of the following:
active urinary tract infection, prostate biopsy, TURP or prostatitis.

WHEN TO REPEAT PSA TEST

- Repeat an abnormal PSA test at 6 weeks before referral. The result can vary by up to 30%

HOW THE NORMAL PSA RAISES WITH AGE

Age	PSA Caucasian Reference Ranges
40-49 years	0-2.5ng/ml
50-59 years	0-3.5ng/ml
60-69 years	0-4.5ng/ml
70-79 years	0-6.5ng/ml

Corresponding reference ranges for men of African ethnicity are 0-2.0ng/ml(40-49yrs), 0-4.0ng/ml(50-59yrs), 0-4.5ng/ml(60-69yrs) and 0-5.5ng/ml(70-79yrs).

- Double the PSA result if the patient is on finasteride / dutasteride (These drugs halve the PSA level)
- Please refer to your local PSA reference ranges as some assays give slightly different results

REFERRAL

Ir J Med Sci (2008) 177:317–323
DOI 10.1007/s11845-008-0216-1

ORIGINAL ARTICLE

Major inter-laboratory variations in PSA testing practices: results from national surveys in Ireland in 2006 and 2007

F. J. Drummond · L. Sharp · H. Comber

Ir J Med Sci
DOI 10.1007/s11845-013-1022-y

ORIGINAL ARTICLE

The number of tPSA tests continues to rise and variation in testing practices persists: a survey of laboratory services in Ireland 2008–2010

F. J. Drummond · E. Barrett · R. Burns · C. O'Neill · L. Sharp

National Cancer Registry Ireland

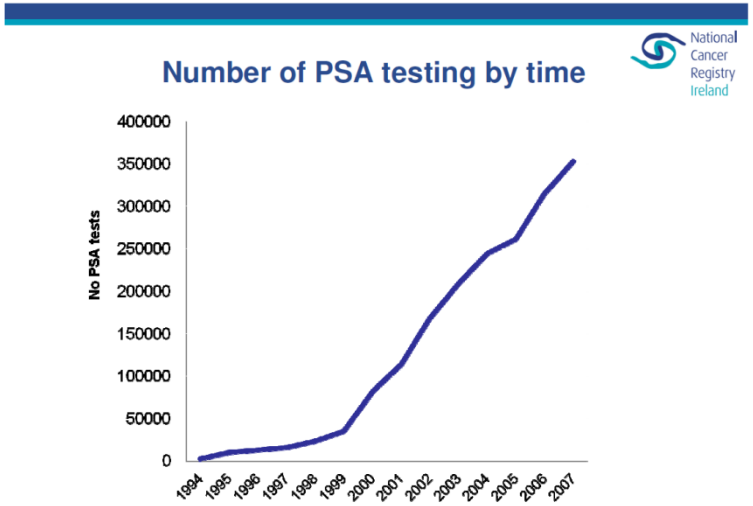


Table 1 PSA workload in laboratories in Ireland, 2006 and 2007

	No. labs Measuring PSA	Mean no. tests/lab *N* (range) 2006	No. tests January–March 2006[a]	Total no. tests 2006[c]	Mean no. tests/lab *N* (range) 2007	No. tests January–March 2007[b]	Total no. tests 2007[c]
tPSA	36/55	2,656 (100–11,000)	95,622	382,488	2,843 (25–12,900)	102,345	409,380
fPSA	14/55	865 (10–5,500)	12,116	48,464	637 (25–4,600)	8,923	35,692

[a] measured between 1 January and 31 March 2006

[b] measured between 1 January and 31 March 2007

[c] Estimated annual workload was extrapolated from the responses on numbers of tests conducted during the first quarter of each year

Table 3 Age-specific PSA values used by laboratories in Ireland

Age (years)				No. lab
40–49	50–59	60–69	>70	
PSA level (ng/ml)				
<2.5	<3.5	<4.5	<6.5	6
<2.1	<3.1	<4.1	<4.9[a]	4
<1.7	0.24–3.0	0.27–4.8	0.27–4.8[a]	2
<4.0	<4.0	<5.3	<6.16	1
<2.4	<3.5	<4.5	<6.5	1
<2.5	<4.0	<4.0	<4.0[b]	1

[a] Manufacture age-specific reference ranges

[b] In-house reference ranges

Reference ranges

National Cancer Registry Ireland

- 56% (n=19) tPSA ≥4 ng/mL
- 3% (n=1) tPSA ≥3.2 ng/mL; 3% (n=1) tPSA ≥3.1 ng/mL
- 38% (n=13) age-specific normal values
- 9% (n=3) unknown

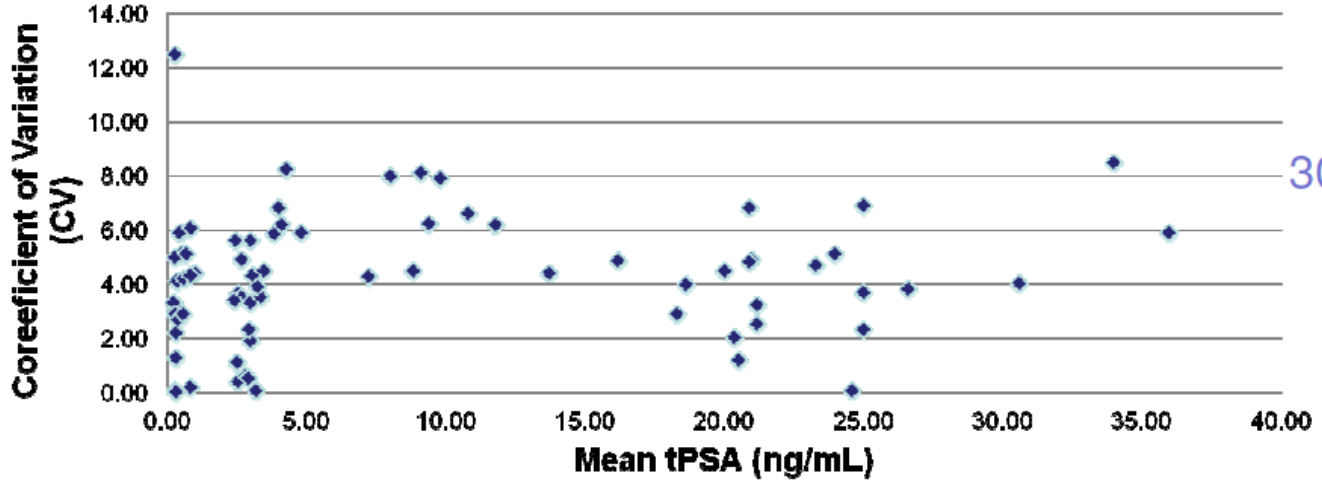
Calibration

National Cancer Registry Ireland

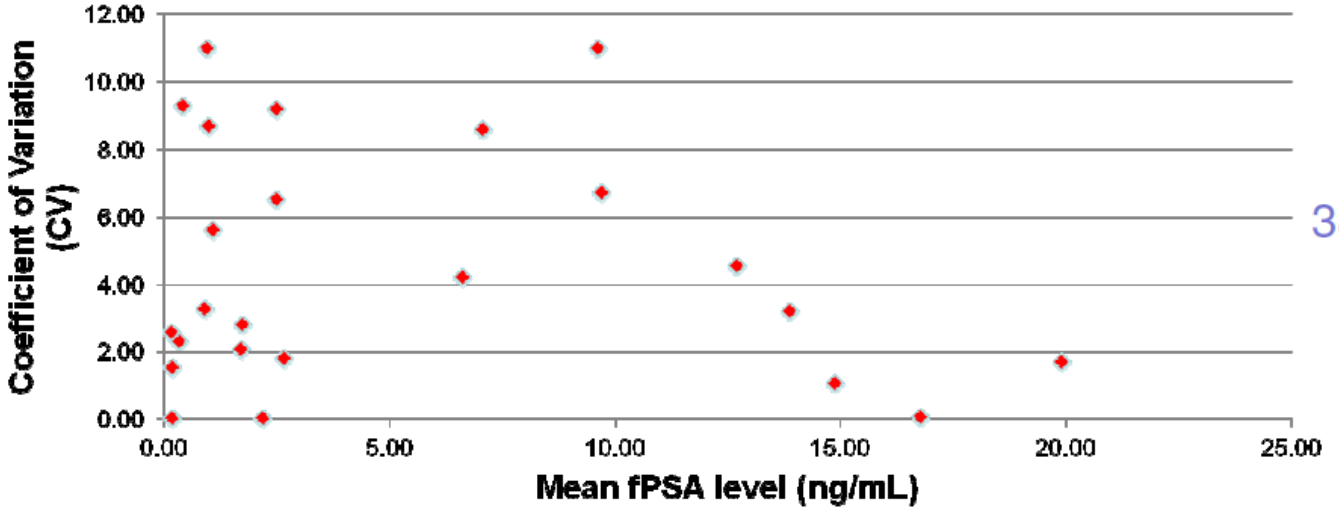
- 26% (n=11) implemented the WHO First International Standards (IRR96/670)
- 2 / 11 reduced reference limit to ≥3.2 ng/mL

Imprecision of tPSA and fPSA assays

National Cancer Registry Ireland

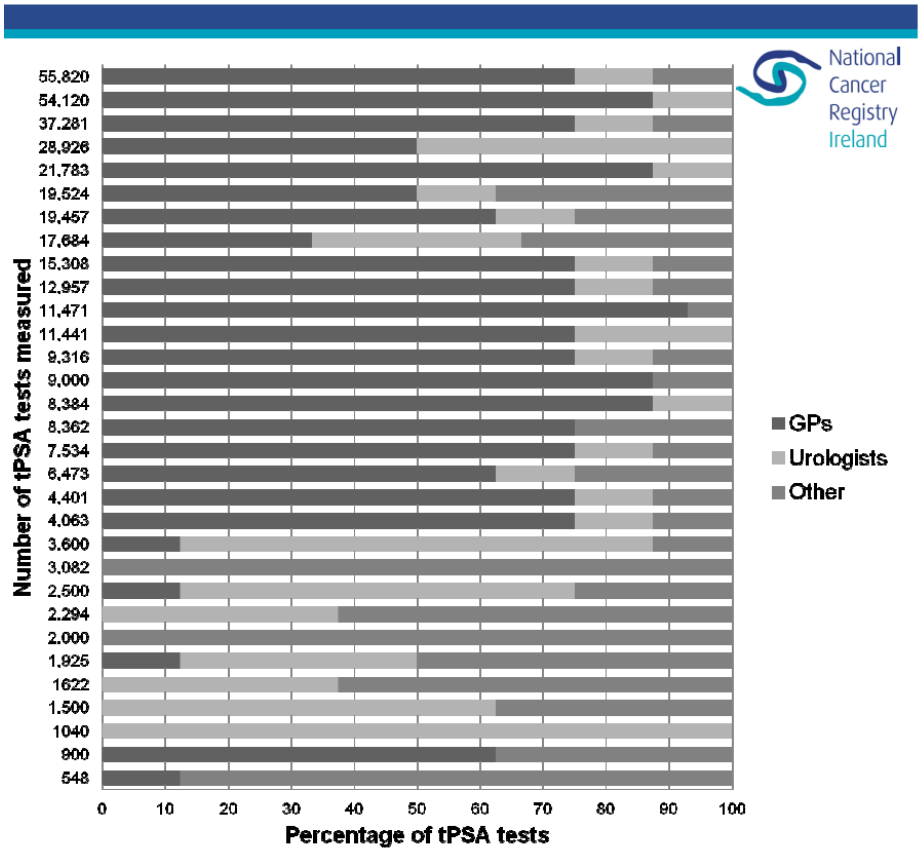


30% > 5%



38% > 5%

- Most PSA tests originate from GPs
- Opportunistic case finding has led to a decrease in age at PCa diagnosis and a shift towards more localised disease at diagnosis



Ir J Med Sci (2010) 179:43–49
DOI 10.1007/s11845-009-0376-7

ORIGINAL ARTICLE

Trends in prostate specific antigen testing in Ireland: lessons from a country without guidelines

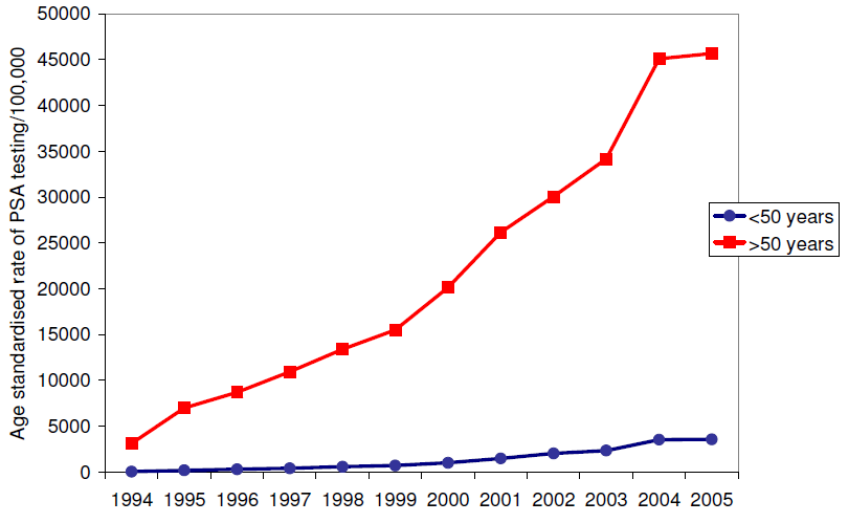
F. J. Drummond · A.-E. Carsin · L. Sharp · H. Comber

- In Ireland there are no national guidelines on PSA testing.
- In 2006 the National Cancer Forum recommended against the introduction of population-based prostate cancer screening

- There was a 19-fold increase in the number of PSA tests performed, 1994–2005.
- The rate of PSA testing increased by 39% in men younger than 50 years and by 25% annually in men aged 50 years and older
- Men outside the recommended age groups (<50 and >70 years) are having regular PSA tests, despite the fact that this has not been shown to be clinically beneficial

Age standardised rate of PSA testing by time

National Cancer Registry Ireland



Sources of Variation

- Assays used
- Reference ranges
- Calibration methods
- Turnaround times
- Imprecision
- Workload

BJUI
BJU INTERNATIONAL

Standardization of assay methods reduces variability of total PSA measurements: an Irish study

James C. Forde*†, Laure Marignol†, Ophelia Blake‡, Ted McDermott*, Ronald Grainger*, Vivien E. Crowley‡ and Thomas H. Lynch*

*Department of Urology, St James's Hospital, †Prostate Molecular Oncology Research Group, St James's Hospital and Trinity College, and ‡Department of Clinical Biochemistry, St James's Hospital, Dublin, Ireland

NCCP - Working Group on PSA Harmonisation – using patient samples to compare variability across the country

ST. JAMES'S HOSPITAL

PSA study – St James's Hospital

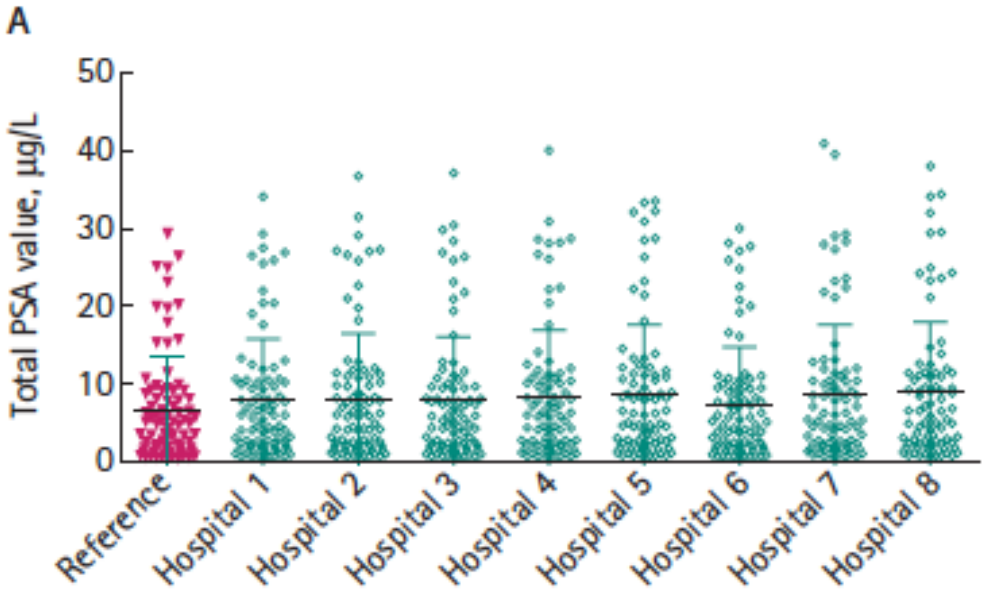
- Between July and December 2009
- 84 male patients attending the Urology OPD Clinic
- Blood sample collected and serum dispensed into 9 aliquots within 2 hours of venesection
- All aliquots stored at -20°C
- An aliquot was sent to each of the Cancer designated Laboratories throughout the country
- One spare aliquot was retained in the host Lab.

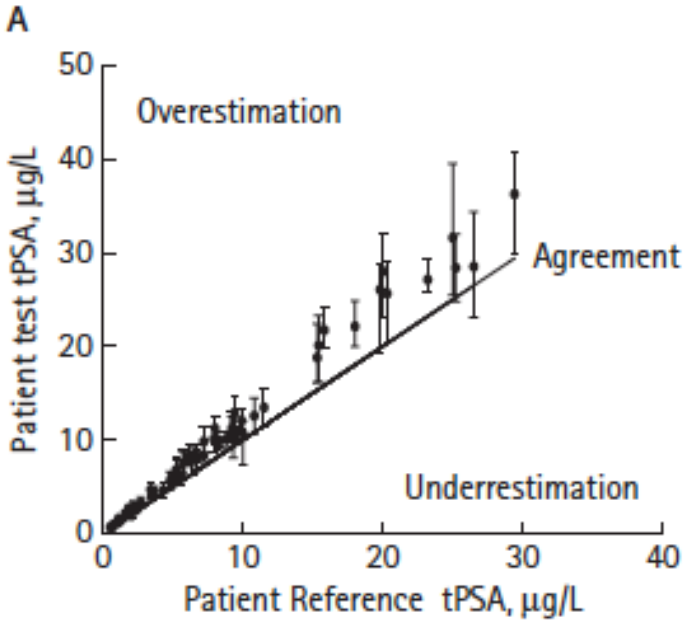
PSA study – St James's Hospital

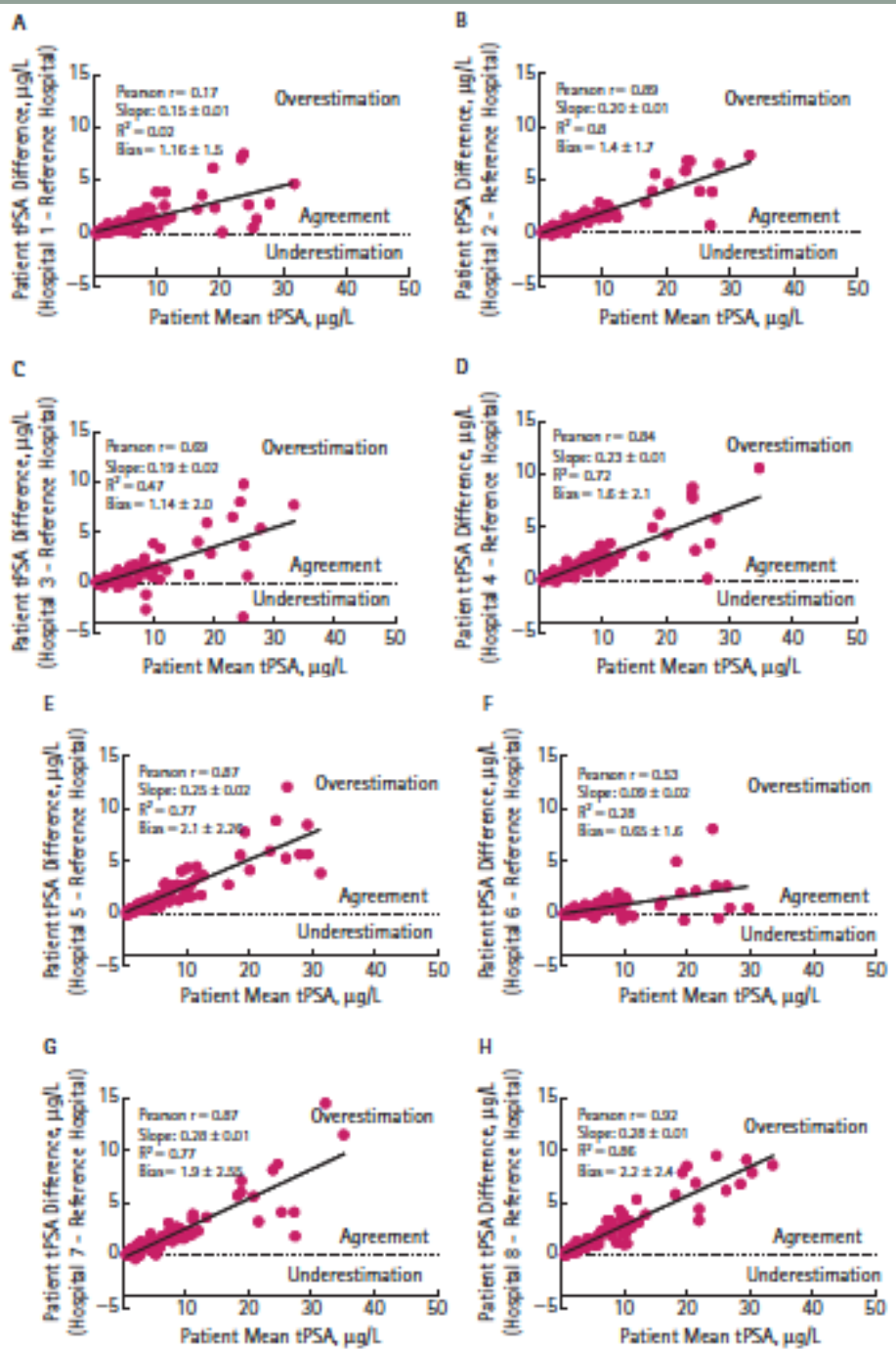
- Samples were transported and stored at -20°C
- All samples were thawed on ice and analysed within 1 hour
- Six different methods in use in the 9 laboratories
  - Beckman Coulter (Hybritech, WHO calibrated)
  - Tosoh AIA 1800
  - Roche E170 (4 laboratories)
  - Abbott AxSym
  - Immulite 2500 (2 versions 2^{nd} Gen & 3^{rd} Gen)
  - Siemens Advia Centaur

Results – all tPSA results (0.5-30 µg/L, N=84)

- Differences between the different methods were statistically significant (ANOVA, P<0.001)
- Differences in tPSA values were >10µg/L at the upper range





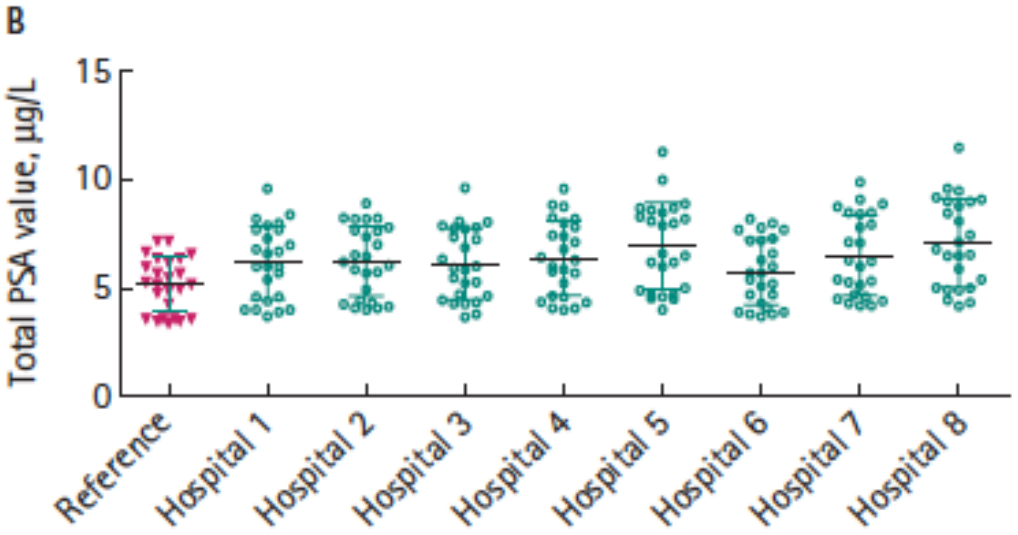


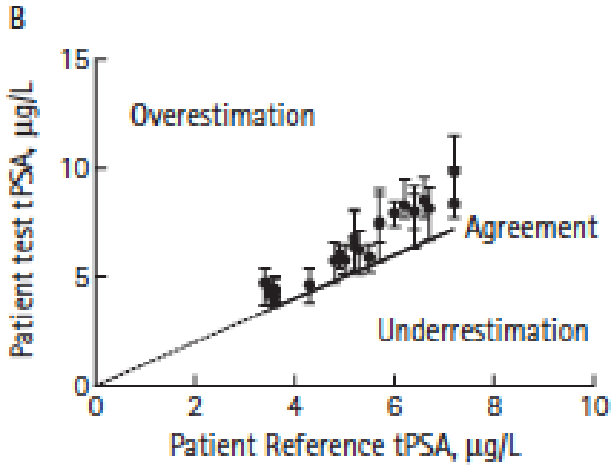
Bland –Altman plots demonstrating the agreement between the tPSA assays used by each Hospital and the reference method (Beckman Access Hybritech, WHO)

Best agreement-Hospital 6 (bias: 0.65 ± 1.6 µg/L)
Poorest agreement-Hospital 8 (bias: 2.2 ± 2.4 µg/L)

Results - TPSA (3-7 µg/L, n=25)

- Mean and SD of 5.2 ± 1.3 µg/L
- Differences between the means were statistically significant (ANOVA,P<0.001)
- Minimum variability in PSA values was 0.86µg/L
- Largest variability in PSA values was 4.3µg/L



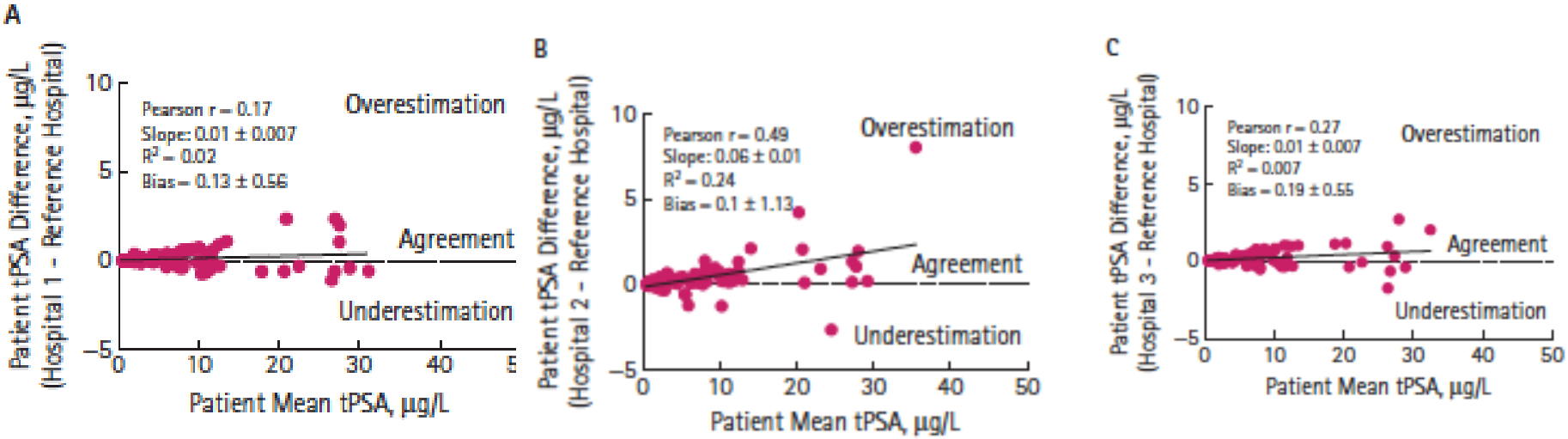


Results : PSA 3 - 7µg/L

- The difference in tPSA between the two methods increased as the mean tPSA increased in all Hospitals
- The range in individual tPSA values was
  - <1µg/L for 2/25 (8%) patients
  - between 1 and 2 µg/L for 11/25 (44%) patients
  - Excess of 2 µg/L for 12/25 (48%) patients

Results – same method

- Four hospitals used the same assay (Roche E170)
- Mean tPSA value measured by E170 in this cohort was not statistically significant (ANOVA,P=0.990)
- Agreement was excellent between these Laboratories (Bias <0.2µg/L)



Results – same assay method

- For tPSA ranging from 3 to 7µg/L
  - Minimum variability in PSA is ± 0.16 µg/L
  - Largest variability in tPSA is ± 1.77 µg/L

- Range in individual tPSA values was <0.5 µg/L for 13/25 (52%) patients

Conclusion

- PSA values varied significantly throughout the nine hospitals involved in the study
- Using the same assay method reduces this variation considerably
- Despite the availability of the WHO reference material for assay calibration, significant differences exist
- Number of PSA assays currently in use throughout the country needs to be reduced
- A significant number of patients in Ireland would be referred for biopsy simply based on the inherent variability of the assay

Setting quality specifications for PSA assay performance

- Serum/Plasma PSA: unit of measurement
- Calibration of PSA assays
- Reference values/Clinical cutoffs
- Internal Quality Control (IQC) Targets
- External Quality Assessment (EQA) targets
- Harmonisation of pre-analytical requirements
- Biological variation

Reference Standards for PSA Assays

Standards traceable to	Notes
Hybritech Standard	Tandem-R assay, first FDA approved PSA assay in 1986. Using this assay a multicentre prospective study (J Urol 1994; 152: 2037-42) validated a clinical decision point of 4.0 µg/L for early detection of prostate cancer. Many assays whose standardisation has been closely aligned to the Hybritech assay have been developed promoting the 4.0 µg/L cut-off value.
WHO International Standard Total PSA: 96/670 Free PSA: 96/668	Released in 1999 with the expectation that this standard would lead to greater consistency of PSA results as manufacturers began to use it to calibrate PSA assays.

Beckman Coulter Immunodiagnostics PSA Assay (Beckman Coulter Data)	
Total PSA (µg/L) Using Hybritech calibration	Total PSA (µg/L) Using WHO 96/670 calibration
4.0	3.1

Note: Sensitivity (81.6%) and specificity (48.0%) maintained at these cut-offs

Age related Reference Intervals

- Oesterling et al showed an age related increase in serum PSA in normal men
- This increase was mostly explained by the age related increase in prostate size
- Distribution was found to be skewed (log normal); so for a 95^{th} percentile (one tailed) cutoff for PSA , 5% of normal men will have a PSA above the cutoff (ie 95% specificity at any age)

Age (years)	Total PSA (µg/L) Oesterling et al. 1993 in current NCCP Guidelines	Total PSA (µg/L) Oesterling et al. 1993 If recalculated to WHO 96/670
40 – 49	0 – 2.5	0 – 1.9
50 – 59	0 – 3.5	0 – 2.7
60 – 69	0 – 4.5	0 – 3.5
70 – 79	0 – 6.5	0 – 5.0

Setting a target for IQC

- **Option 1:** Set as target that which is consistently attained by 80% of the participants.

- *79% of CVs are less than 4%*

IQC CV (%)	Number of values	Percent of all values
< 2	1	3
< 3	15	52
< 4	23	79
< 5	26	90
< 6	29	100

Setting a target for IQC

- **Option 2:**
- Set target for analytical precision (Cv_a) in relation to the within subject biological variation (References: Callum Fraser).
- *Within subject biological coefficient of variation (CV_i) for PSA = 14.0%*
- *(From Carmen Ricós and associates).*

- <u>Callum Fraser's proposals:</u>
- Desirable performance: $CV_a < 0.5\ Cv_i$ [< 7.0%]
- Optimum performance: $CV_a < 0.25\ Cv_i$ [< 3.5%]
- Minimum performance: $CV_a < 0.75\ Cv_i$ [< 10.5%]

Allowable limits of performance (ALP)

- The goal adopted is such that over 80% of laboratories can achieve the performance.
- This target encourages further refinement of methods particularly to achieve the tighter monitoring goals
- The format of the ALP is ± *x* from the target value where *x* may be expressed as a percent, an absolute value, or an absolute value up to a certain target value and then a percent above that value.

RCPAQAP
RCPA Quality Assurance Programs

Allowable Limits of Performance	
Reviewed January 2012	
Total PSA	± 0.4 µg/L for values up to 5.0 µg/L
	8% for values greater than 5.0 µg/L

Other issues

- Existence of antibodies to PSA in the serum of 5% of sexually active women as well as men with P Ca
- Heterophilic antibodies will affect PSA assays using the respective animal antibody
- Form of PSA used for calibrations (90:10, 80:20 or 70:30)
- Matrix of the calibrator (PBS or female sera)
- Ratio of Free to Total PSA varies in patient samples – assays with equimolar reactivity is required
- Assay architecture (monoclonal/polyclonal or monoclonal/monoclonal Abs)

Thank You

- Acknowledgements:
  - Dr James Forde
  - Dr Ned Barrett (IEQAS & NCCP)