Prostate Cancer: PSA; Hormone Therapy and Other Considerations

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London W1W 5EE

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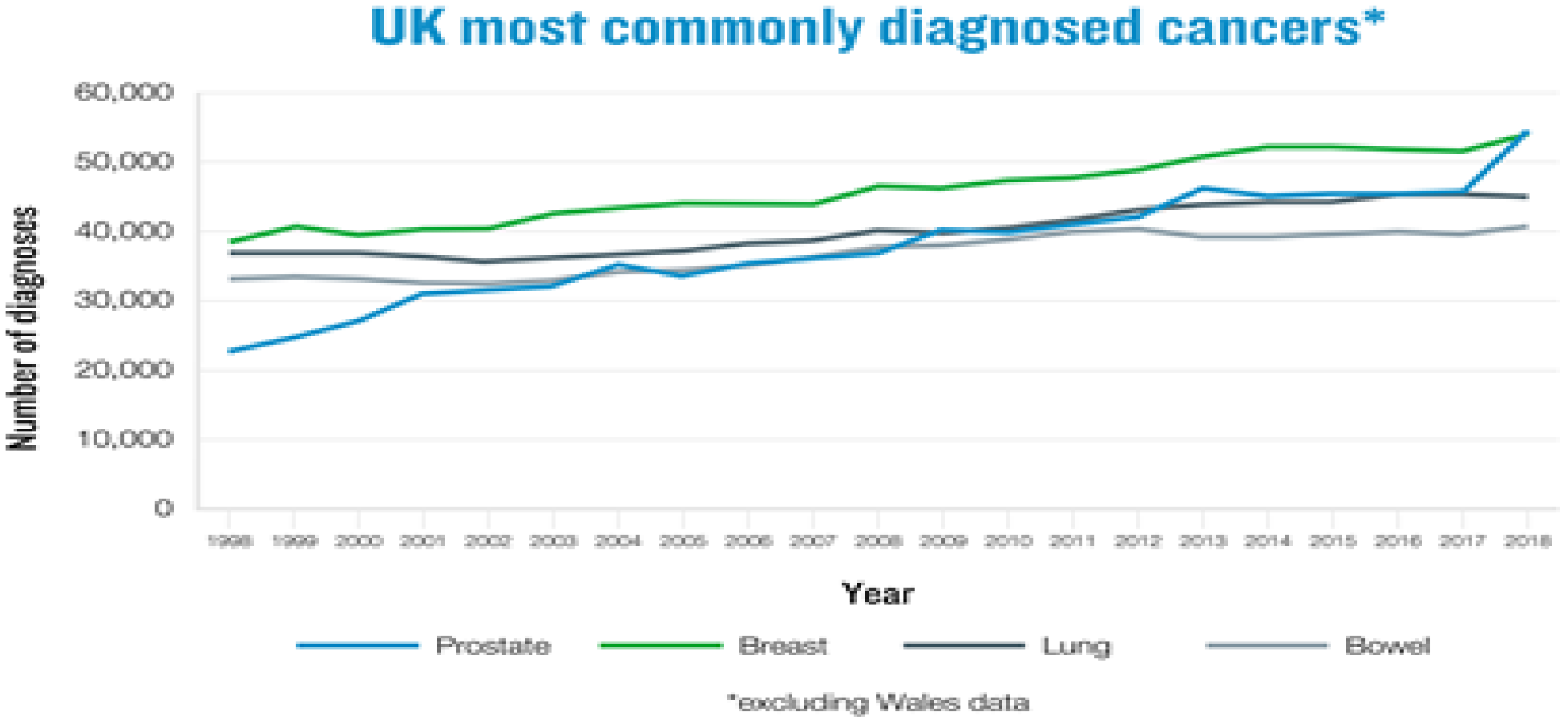
Disclosures

- Professor Mike Kirby has received funding for research, conference attendance, lecturing and advice from the pharmaceutical industry including Astellas, Pfizer, Takeda, Bayer, Besins, MSD, BI, Lilly, GSK, AZ and Menarini.
- Editor Trends in Urology & Men's Health
- Also on several NHS advisory boards including the Prostate cancer Risk Management Programme and the Prostate Cancer advisory Group
- Member of the National Prostate Cancer Audit Group

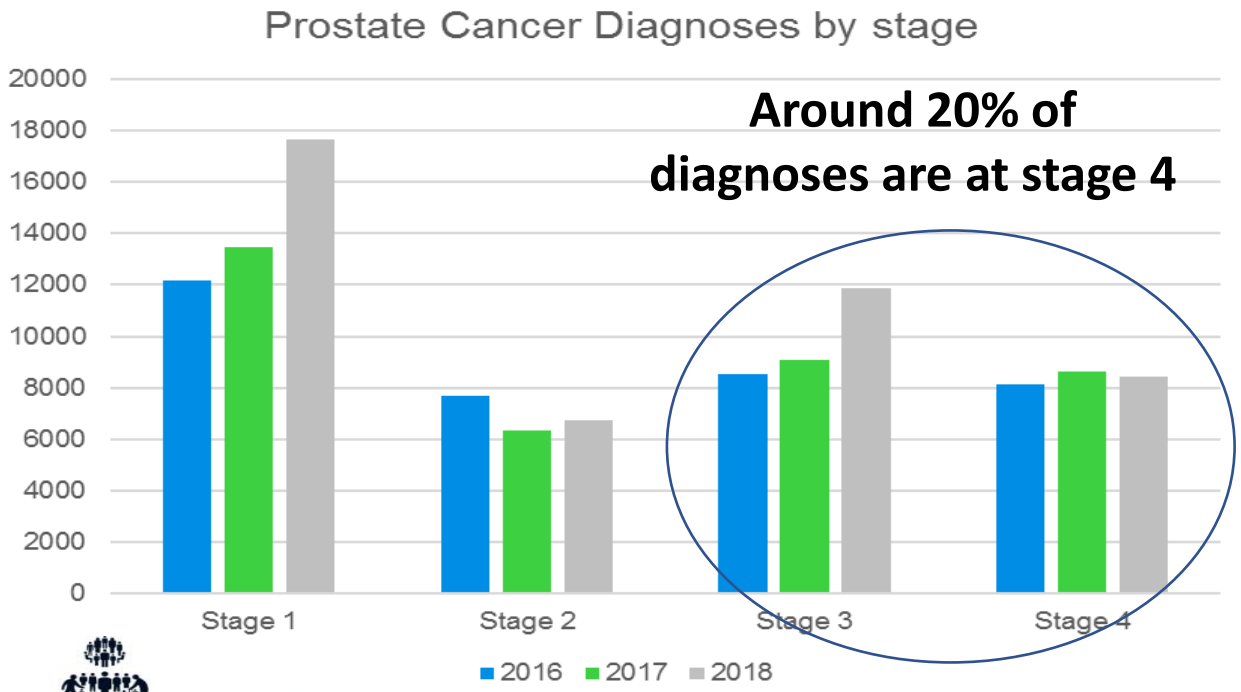
Latest figures for cancer diagnoses in England, Scotland, Northern Ireland and Wales, when combined, bring the total number **of Prostate cancer diagnoses in the UK to 57,192, exceeding those of breast, lung and bowel cancers**.



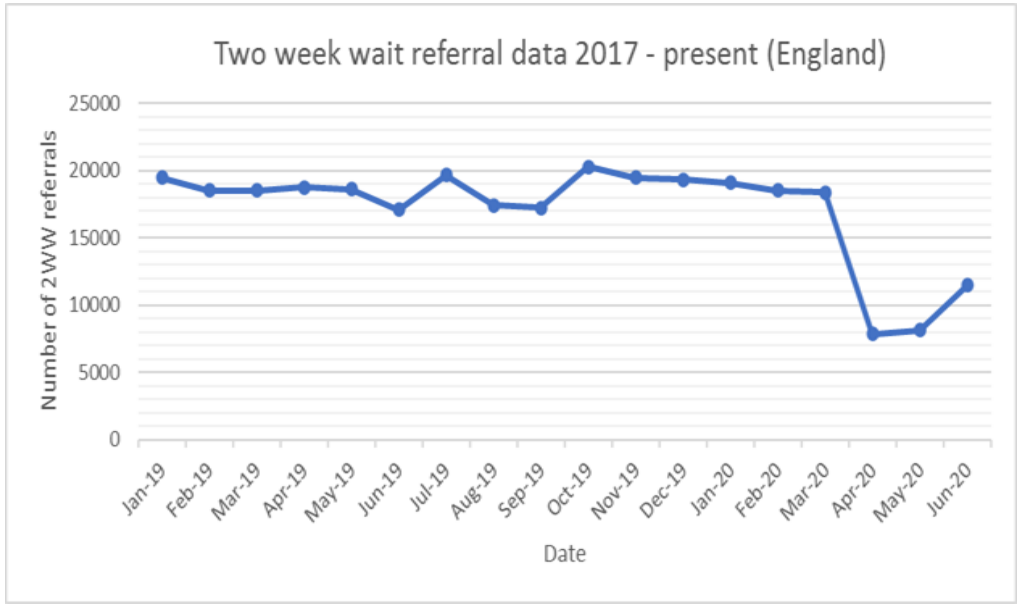
https://prostatecanceruk.org/about-us/news-and-views/2020/6/most-common-cancer-in-uk?utm_source=Adestra&utm_medium=email&utm_content=header&utm_campaign=Men%20Utd%20-%20June%204%20-%20most%20common%20story

Why is this a priority?

Too many men are diagnosed late



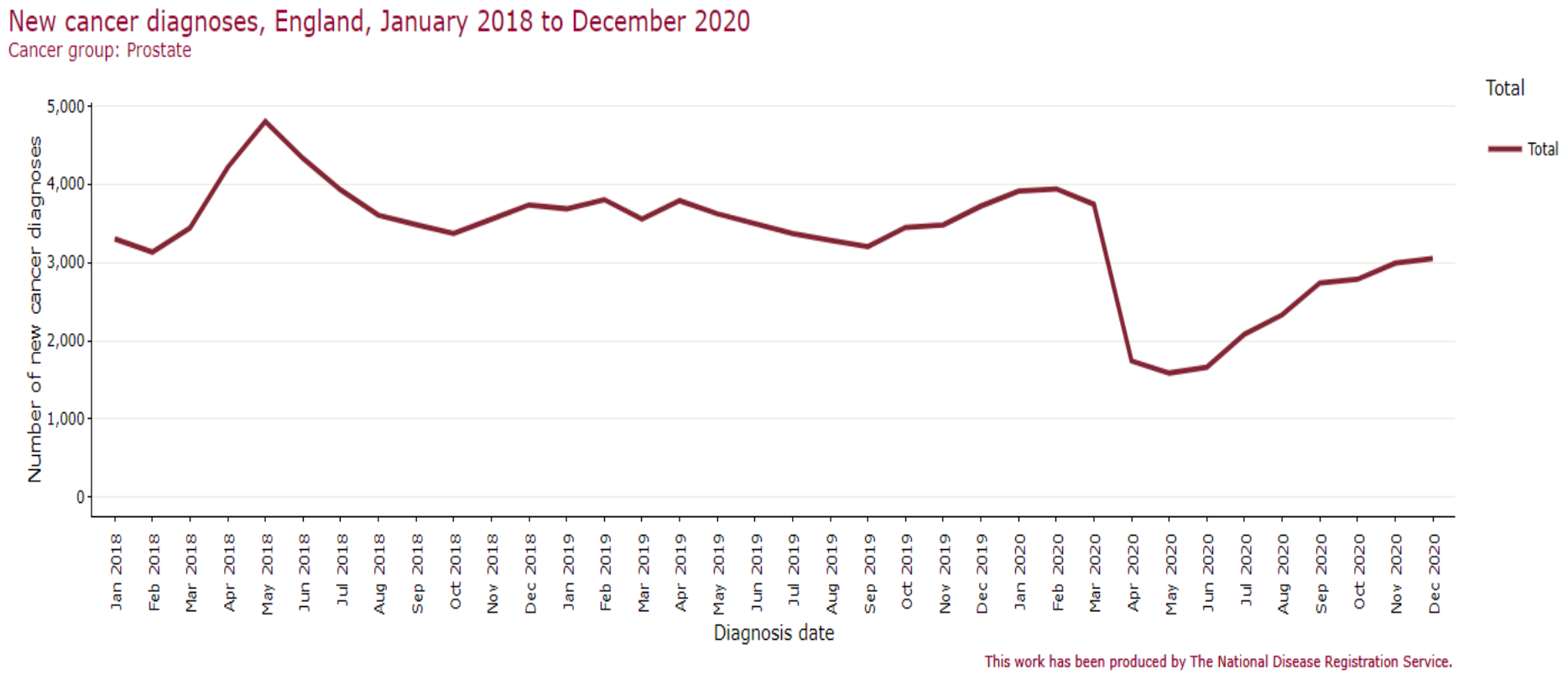
Due to Covid-19, we expect this situation to get worse



PROSTATE CANCER UK

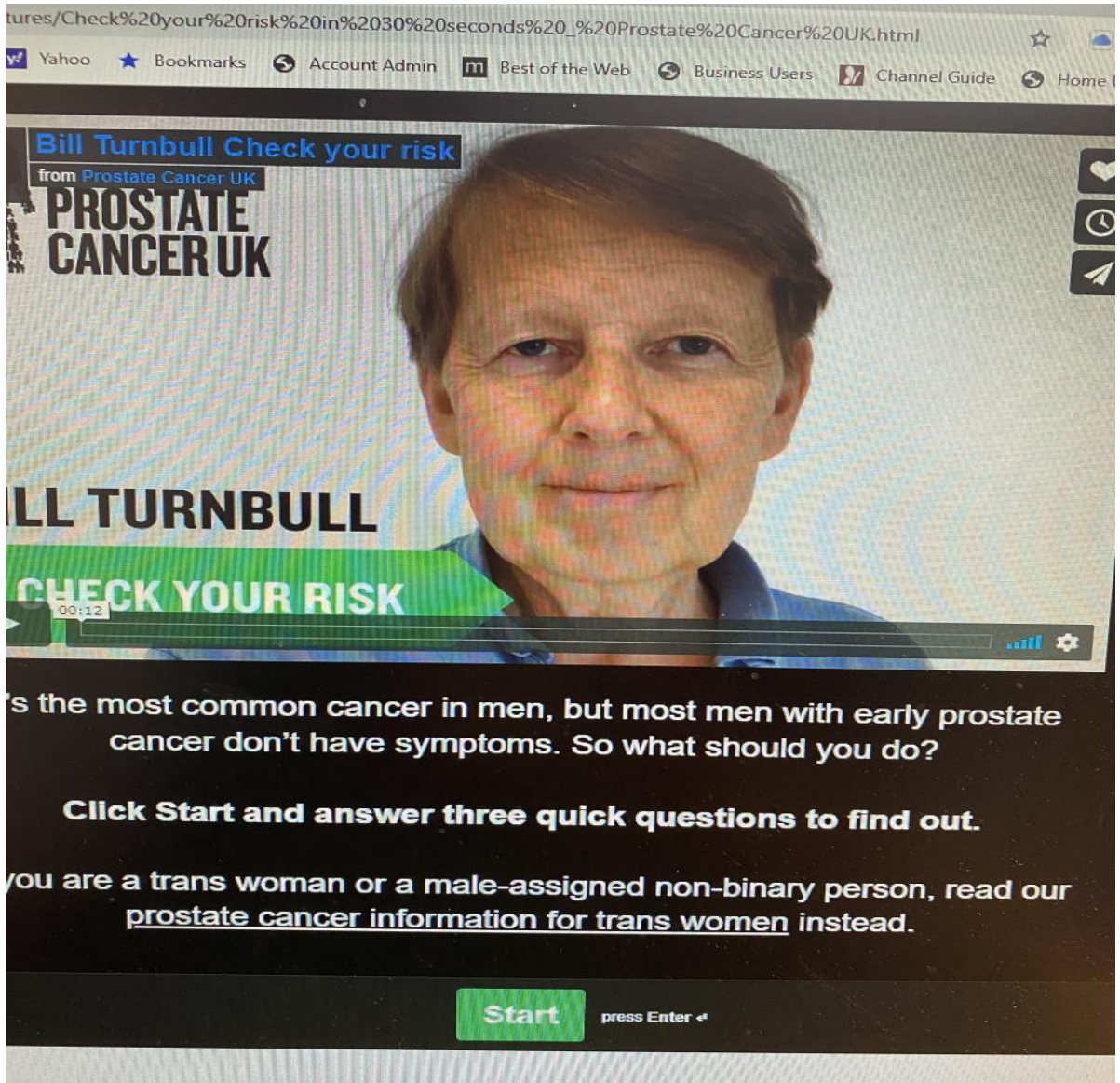
10,000 fewer diagnoses of prostate cancer

10,000 men to find before they advance!!!!



https://www.cancerdata.nhs.uk/covid-19/rcrd

https://prostatecanceruk.org/risk-checker



Risk Factors for Prostate Cancer

2.5x

A man is two and half times more likely to get prostate cancer if his father or brother has been diagnosed with it, compared to a man with no family history

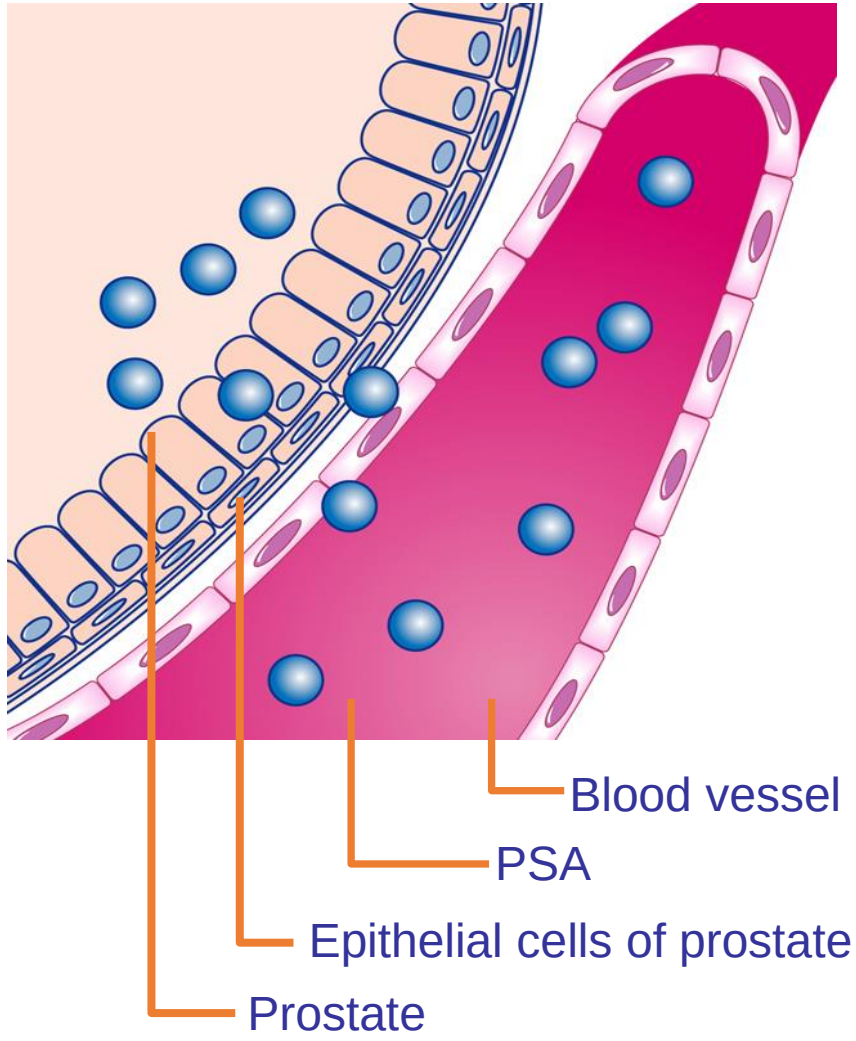
A man's risk of prostate cancer may be increased if he has a close relative with breast cancer – if the breast cancer is linked to faults in the genes BRCA1 or BRCA2

Black men are more likely to get prostate cancer than other men. In the UK, about 1 in 4 Black men will get prostate cancer at some point in their lives

Prostate Specific Antigen (PSA)

- PSA is a glycoprotein responsible for liquefying semen and allowing sperm to swim freely

- PSA is expressed in both benign and malignant processes involving epithelial cells of the prostate



PSA testing

- On the 20th July 2009 Sir Liam Donaldson the Chief Medical Officer wrote to all the GPs in the UK about a Revised Prostate Cancer Risk Management Programme (PCRMP) which gives the opportunity for all men over 50 yrs who have concerns about prostate cancer, to have the right to a Prostate Specific Antigen (PSA) blood test free on the NHS.
- This right should be exercised in the context of genuinely balanced information from their GP about the pros and cons of this test.

NICE CKS

When should I offer PSA testing for prostate cancer?

Before offering prostate-specific antigen (PSA) testing, ensure that the man has carefully considered the benefits and limitations of PSA tests.

Offer PSA testing to:

Men older than 50 years of age who request a PSA test.

Consider a PSA test in men with:

Lower urinary tract symptoms (LUTS), such as nocturia, urinary frequency, hesitancy, urgency or retention.

Erectile dysfunction.

Visible haematuria.

Unexplained symptoms that could be due to advanced prostate cancer (for example lower back pain, bone pain, weight loss).

Routine screening for prostate cancer is not national policy because the benefits have not been shown to clearly outweigh the harms.

PSA testing should not be offered to asymptomatic men.

- During the “PSA era” in the United States, the proportion of patients having advanced disease at diagnosis has decreased by 80%, and the age-adjusted prostate cancer **mortality rate has decreased by more than 42%** [1].

- Statistical modelling studies have estimated that 45%–70% of this mortality decrease is **attributed directly to PSA screening** [2], [3].

- **Similar trends** have been observed in countries that have adopted widespread PSA screening but not in those that have not adopted PSA screening [4].

- Two large prospective, randomized clinical trials in Europe have demonstrated a **21% and 44%, respectively, decrease in prostate cancer-specific mortality** associated with PSA screening [5], [6].

1. http://seer.cancer.gov/faststats/selections.php?#Output.
2. Etzioni R., Tsodikov A., Mariotto A., Szabo A., Falcon S., Wegelin J. Quantifying the role of PSA screening in the US prostate cancer mortality decline. Cancer Causes Control. 2008;19:175–181.
3. Etzioni R., Gulati R., Tsodikov A., Wever E.M., Penson D.F., Heijnsdijk E.A. The prostate cancer conundrum revisited: treatment changes and prostate cancer mortality declines. Cancer. 2012;118:5955–5963.
4. Bouchardy C., Fioretta G., Rapiti E., Verkooijen H.M., Rapin C.H., Schmidlin F. Recent trends in prostate cancer mortality show a continuous decrease in several countries. Int J Cancer. 2008;123:421–429.
5. Schröder F.H., Hugosson J., Roobol M.J., Tammela T.L., Ciatto S., Nelen V. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med. 2012;366:981–990.
6. Hugosson J., Carlsson S., Aus G., Bergdahl S., Khatami A., Lodding P. Mortality results from the Göteborg randomized population-based prostate-cancer screening trial. Lancet Oncol. 2010;11:725–732

Testing at younger age?

- Some suggest measuring PSA for men in their **40s:**
  - Less contamination: BPH, prostatitis etc

Baseline prostate-specific antigen (PSA) has been proposed as a possible marker to detect those who would be at increased risk for developing prostate cancer.

- The concept of baseline PSA began when Gann et al. (1995) showed the role of this test as a predictor of prostate cancer in men with PSA > 1.0 ng / mL at a median age of 62.9
-
- In a subgroup of The European Randomized study of Screening for Prostate Cancer (ERSPC), subjects with baseline PSA > 1.0 ng / mL and > 2.0 ng / mL had an increased hazard ratio for prostate cancer specific mortality (4.0 - fold and 7.6 - fold respectively) compared with those who had < 1.0 ng / mL levels

PSA at a younger age?

- >20,000 Swedish men aged 27-52
- Bloods at baseline in 1974-84, thawed in study
- Baseline PSA **very strong predictor** of future Pca
- PSA < 0.5 at 44-50y: very low risk at 25 yrs follow-up
- PSA 2-3 *(near 'normal'??):* increase odds 19-fold

Lilja et al. J Clin Oncol. 2007 ;25(4):431-6.

A secondary analysis of a cohort in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. (JAMA 2020)

There were 10,968 men aged 55-60 years (median age 57 years) at study enrolment who received long-term follow-up. The actuarial 13-year incidences of clinically significant PCa diagnosis among the participants with a baseline PSA of:

≤0.49ng/ml was	0.4%
0.50-0.99ng/ml	1.5%
1.00-1.99 ng/ml	5.4%
2.00-2.99ng/ml	10.6%
3.00-3.99ng/ml	15.3%
≥4.00ng/ml	29.5%.

During the 13-year follow-up, only 15 PCa-specific deaths occurred and 60% of those (n=9) were among men with a baseline PSA of ≥2.00ng/ml.

Kova E, Carlsson SV, Lilja H, et al. Association of baseline prostatespecific antigen level with long-term diagnosis of clinically significant prostate cancer among patients aged 55 to 60 years: A secondary analysis of a cohort in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. JAMA Netw Open 2020;3(1):e1919284.

A secondary analysis of a cohort in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. (JAMA 2020)

- The authors concluded that in men aged 55-60 years, baseline PSA levels were associated with long-term risk of clinically significant Pca.

- This suggests that repeated screening can be less frequent in in men in this age group who have a low baseline PSA (<2.00ng/ml) and possibly discontinued in those with a baseline PSA <1.00ng/ml.

Screening at younger age?

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

(2013)

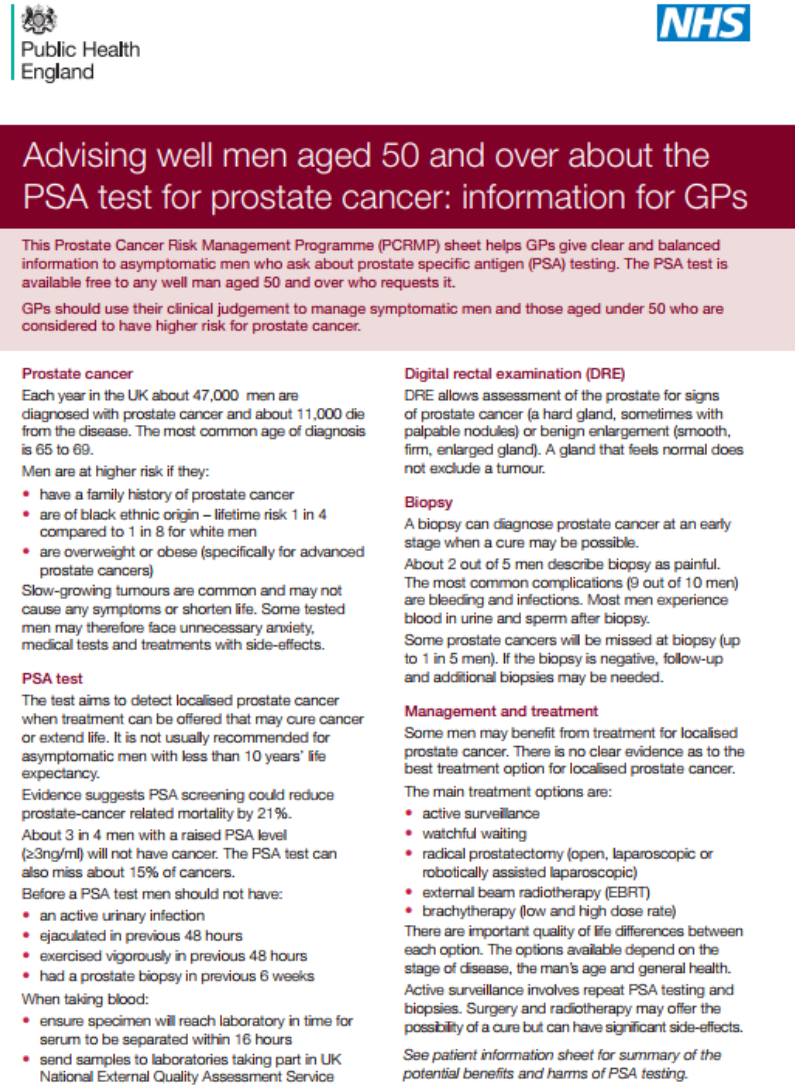
Platinum Opinion – Prostate Cancer

Early Detection of Prostate Cancer: European Association of Urology Recommendation

Conclusions: A baseline serum PSA should be offered to all men 40–45 yr of age to initiate a risk-adapted follow-up approach with the purpose of reducing PCa mortality and the incidence of advanced and metastatic PCa. In the future, the development and

Guidance on using the PSA test for prostate cancer detection

- The Prostate Cancer Risk Management Programme
- “The PSA Test is available free to any well man over 50 who requests it”
  - Younger men with high risk at the GP’s clinical judgement
- Other factors influencing a high PSA
- 10 years’ life expectancy
- Sensitivity and specificity
- Currently being reviewed



Public Health England

NHS

Advising well men aged 50 and over about the PSA test for prostate cancer: information for GPs

This Prostate Cancer Risk Management Programme (PCRMP) sheet helps GPs give clear and balanced information to asymptomatic men who ask about prostate specific antigen (PSA) testing. The PSA test is available free to any well man aged 50 and over who requests it.

GPs should use their clinical judgement to manage symptomatic men and those aged under 50 who are considered to have higher risk for prostate cancer.

Prostate cancer

Each year in the UK about 47,000 men are diagnosed with prostate cancer and about 11,000 die from the disease. The most common age of diagnosis is 65 to 69.

Men are at higher risk if they:

- have a family history of prostate cancer
- are of black ethnic origin – lifetime risk 1 in 4 compared to 1 in 8 for white men
- are overweight or obese (specifically for advanced prostate cancers)

Slow-growing tumours are common and may not cause any symptoms or shorten life. Some tested men may therefore face unnecessary anxiety, medical tests and treatments with side-effects.

PSA test

The test aims to detect localised prostate cancer when treatment can be offered that may cure cancer or extend life. It is not usually recommended for asymptomatic men with less than 10 years' life expectancy.

Evidence suggests PSA screening could reduce prostate-cancer related mortality by 21%.

About 3 in 4 men with a raised PSA level (≥3ng/ml) will not have cancer. The PSA test can also miss about 15% of cancers.

Before a PSA test men should not have:

- an active urinary infection
- ejaculated in previous 48 hours
- exercised vigorously in previous 48 hours
- had a prostate biopsy in previous 6 weeks

When taking blood:

- ensure specimen will reach laboratory in time for serum to be separated within 16 hours
- send samples to laboratories taking part in UK National External Quality Assessment Service

Digital rectal examination (DRE)

DRE allows assessment of the prostate for signs of prostate cancer (a hard gland, sometimes with palpable nodules) or benign enlargement (smooth, firm, enlarged gland). A gland that feels normal does not exclude a tumour.

Biopsy

A biopsy can diagnose prostate cancer at an early stage when a cure may be possible.

About 2 out of 5 men describe biopsy as painful. The most common complications (9 out of 10 men) are bleeding and infections. Most men experience blood in urine and sperm after biopsy.

Some prostate cancers will be missed at biopsy (up to 1 in 5 men). If the biopsy is negative, follow-up and additional biopsies may be needed.

Management and treatment

Some men may benefit from treatment for localised prostate cancer. There is no clear evidence as to the best treatment option for localised prostate cancer.

The main treatment options are:

- active surveillance
- watchful waiting
- radical prostatectomy (open, laparoscopic or robotically assisted laparoscopic)
- external beam radiotherapy (EBRT)
- brachytherapy (low and high dose rate)

There are important quality of life differences between each option. The options available depend on the stage of disease, the man's age and general health.

Active surveillance involves repeat PSA testing and biopsies. Surgery and radiotherapy may offer the possibility of a cure but can have significant side-effects.

See patient information sheet for summary of the potential benefits and harms of PSA testing.

PROSTATE CANCER UK

PSA testing and prostate cancer: advice for well men aged 50 and over

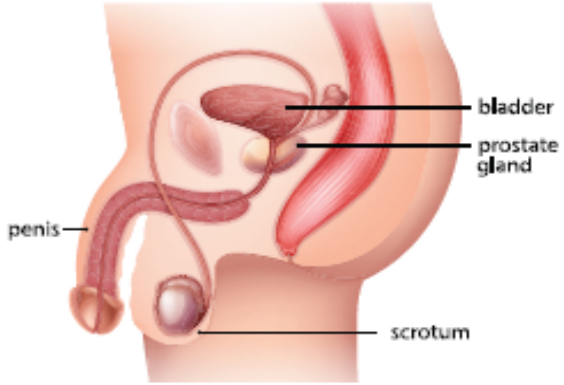
The prostate specific antigen (PSA) test may help find out if you are more likely to have prostate cancer. It is not perfect and will not find all prostate cancers.

Having a PSA test has potential harms and potential benefits.

This information should help you decide if you want to have the test or not. It is your decision. Before making your decision you may want to talk to your GP, practice nurse and your partner, family member or a friend.

Prostate cancer

The prostate gland lies just below your bladder. It helps produce healthy sperm. Problems with the prostate gland can affect how you urinate and your sexual function.



Prostate cancer is caused when some cells in the prostate start to grow out of control. Slow-growing cancers are common. They may not cause any symptoms or shorten your life.

Prostate cancer is the second most common cause of cancer deaths in UK men. Each year about 47,000 men are diagnosed with prostate cancer and about 11,000 die from the disease. Prostate cancer is rare in men under 50. The most common age of diagnosis is between 65 and 69.

Symptoms

Most early prostate cancers do not have any symptoms. If there are symptoms, many are the same as those caused by an enlarged prostate that is not cancerous.

Symptoms can include problems urinating, pain when ejaculating, pain or stiffness in the lower body, extreme tiredness and loss of appetite.

Risk

You are at higher risk of prostate cancer if you:

- have a family history of prostate cancer
- are of black ethnic origin – the lifetime risk is 1 in 4 compared to 1 in 8 for white men
- are overweight or obese

There is no clear evidence to recommend PSA testing more for high risk men than low risk men.

PSA test

The PSA blood test measures the level of PSA in your blood. A raised PSA level can mean you have prostate cancer. But it can also mean you have a condition that is not cancer, such as enlargement of the prostate or a urinary infection.

Test results and follow-up

If you have a raised PSA level you might need further tests, including a biopsy. This involves taking small samples of your prostate through your back passage and checking them for cancer.

If you have prostate cancer, your specialist will discuss options. Men with slow-growing cancers may be offered active surveillance. This involves repeat PSA tests to monitor the cancer, with treatment offered if the cancer starts to progress.

Possible treatments include surgery, radiotherapy and hormone therapy. Side effects of treatment can include problems with erections, loss of fertility and incontinence.

Find out more at www.nhs.uk/psa

Potential benefits and risks of PSA testing

	Having the PSA test	Not having the PSA test
Health	If you have the PSA test and follow-on treatment you are less likely to die of prostate cancer than men who do not have the test. Having an abnormal PSA test result means you may be offered further tests and treatments, which may harm your health.	If you do not have the PSA test you are more likely to die of prostate cancer than men who do have the PSA test. You are also more likely to experience the complications of advanced incurable prostate cancer.
Test results	The PSA test may reassure you if the result is normal. But it can miss cancer and provide false reassurance. If you have prostate cancer, you are more likely to be diagnosed and treated early. But an abnormal test result may also lead to unnecessary worry and medical tests when there is no cancer. The test cannot tell the difference between fast-growing cancers and slow-growing cancers that may not cause symptoms or shorten your life.	If you do not have the PSA test you may avoid unnecessary worry and tests after an abnormal result when there is either no cancer or a slow-growing cancer. If you have prostate cancer, you are less likely to be diagnosed and treated early.
Accuracy	About 75 out of every 100 men who have an abnormal PSA test result do not have prostate cancer. This is called a false positive result. About 15 out of every 100 men who have a normal PSA test result do have prostate cancer. This is called a false negative result.	If you do not have a PSA test, you will not get a false positive or a false negative result but the chance of early detection may be missed.
Follow-up	About 17 out of every 100 men who are tested have an abnormal test result. About 82 out of every 100 men who have an abnormal result will have a biopsy. Some men have problems or complications after a biopsy for prostate cancer. The most common complications are bleeding and infections.	If you do not have a PSA test, it is unlikely you will need to have a biopsy unless you get symptoms of prostate cancer, at which stage the cancer might be more advanced.
Treatment	If you are diagnosed with prostate cancer, you will need to decide about treatment. Potential treatments can include surgery, radiotherapy and hormone therapy. Side effects of treatments for prostate cancer can include problems with erections, loss of fertility and incontinence.	If you choose not to have a PSA test, it is unlikely you will need treatment for prostate cancer, unless you get symptoms. This means you are less likely to have any complications from treatments.

PHE gateway number 2015736

Age adjusted cut offs: **50–59: PSA = 3 ng/mL; 60–70: PSA = 4 ng/mL; ≥ 70: PSA = 5 ng/mL**

Suspected cancer: recognition and referral, NICE guideline NG12 December 2021

[A] Evidence reviews for diagnostic accuracy of prostate specific antigen (PSA) thresholds for referring people with suspected prostate cancer
NICE guideline NG12 December 2021

The committee recommended the use of age-specific thresholds, which are already established in current practice and were recommended in the previous version of the guideline. **Because of regional variations in practice (particularly in the 50 to 69 age range), the committee decided to define the age-specific PSA thresholds.**

The committee agreed that the thresholds used in the reviewed studies on people with symptoms of possible prostate cancer should be used in the absence of evidence to support alternative values, because these studies were most applicable to the population that the recommendation applies to.

No evidence was available specifically for people under 40 or over 79, and so the committee recommended that clinical judgement is used when deciding whether to refer people in these groups to secondary care.

- No recommendation on values below the age of 50 which suggests the free PSA test will not be available to those aged between 40 and 49,

- and there is no recommendation to offer PSA testing to men who have a strong family history (2.5 fold increase if father has prostate cancer and 3.4 fold increase if one brother has the disease).

DAEWOO DRIVES INTO EUROPE • WHAT'S NEXT FOR HIGH-TECH STOCKS

MAY 13, 1996 NO. 9

FORTUNE

TAKING ON PROSTATE CANCER

by Andy Grove

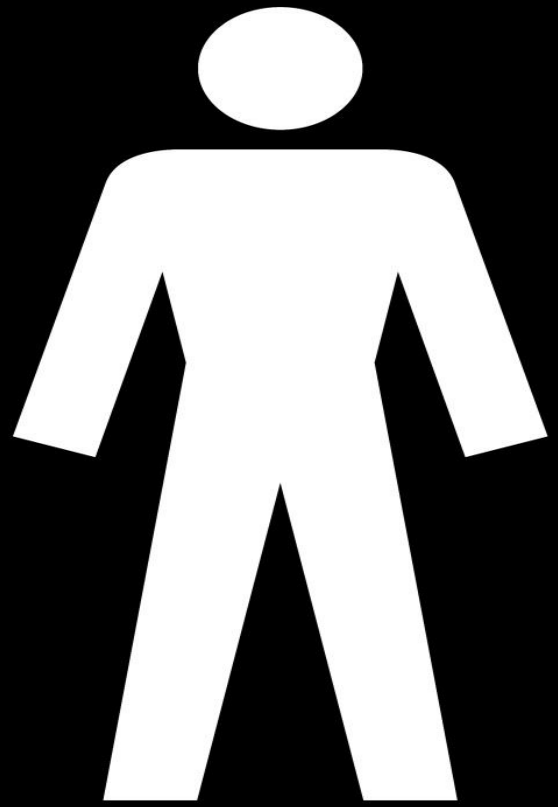
When Intel's CEO got the chilling diagnosis, he didn't just follow doctor's orders. Neither should you.

BUT:

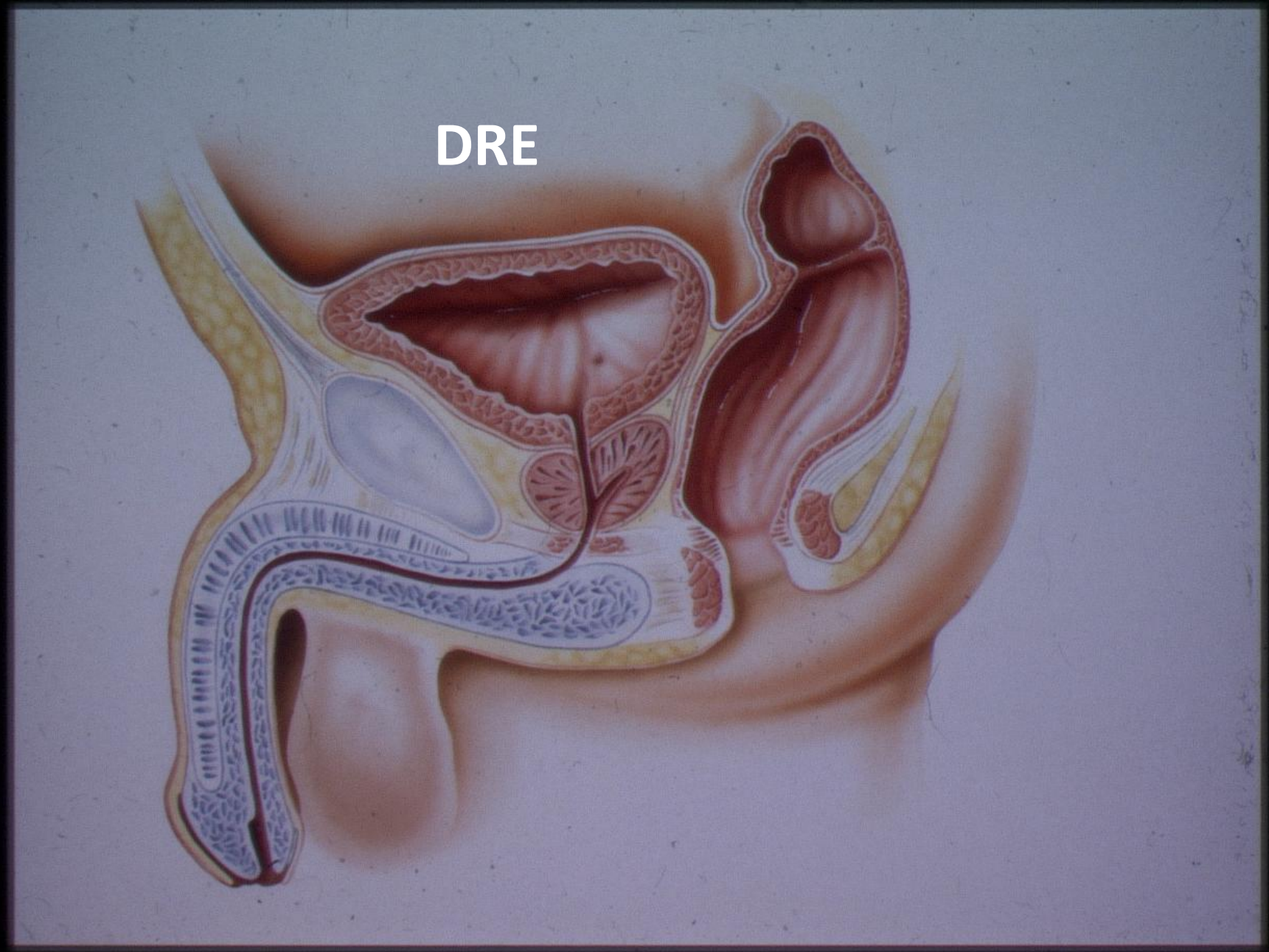
Approximately 40% of prostate cancers in England are diagnosed at a late stage (III or IV).

Early detection and treatment may reduce mortality from prostate cancer.

http://www.ncin.org.uk/publications/survival_by_stage



DRE



Digital Rectal Examination

- Symptoms are not very specific. The DRE cannot be used solely to diagnose prostate cancer. **DRE should be used in combination with PSA testing.**

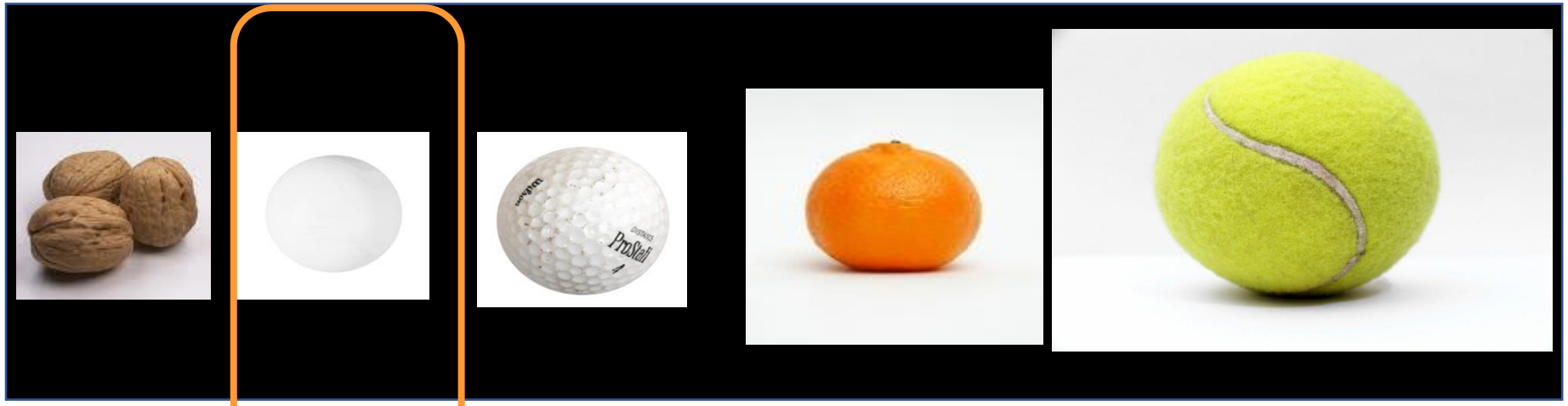
- The DRE allows assessment of the prostate for signs of prostate cancer (a hard gland, sometimes with palpable nodules) or benign enlargement (smooth, firm, enlarged gland). However, a gland that feels normal does not exclude a tumour.

- **Most prostate cancers are located in the peripheral zone of the prostate** and may be detected by DRE when the volume is about 0.2 ml or larger.

  - Men should be referred (for an appointment within 2 weeks) for suspected prostate cancer if their prostate feels malignant on DRE.

National Institute for Health and Care Excellence (NICE). Suspected cancer: recognition and referral [NG12]. London:National Institute for Health and Clinical Excellence, 2015

Some common comparisons to help assess prostate size



Walnut	Ping Pong Ball	Golf Ball	Clementine	Tennis Ball
3.2cm diameter	4cm diameter	4.3cm diameter	5cm diameter	6.3 diameter
Approx 20cc	Approx 33cc	Approx 40cc	Approx 65cc	Approx 130 cc

- A 30 cc prostate is approximately the size of a ping pong ball

Less harm because: The prostate cancer diagnostic pathway is changing

	mpMRI	TRUS
Sensitivity	93%	48%
Specificity	41%	96%
PPV	51%	90%
NPV	89%	74%

- **No longer sending men straight to biopsy**
- mpMRI scans used before a biopsy – with greater specificity than biopsies at detecting clinically significant disease
- Enable some men – often with nothing suspicious in their prostate – to avoid an immediate, often invasive biopsy

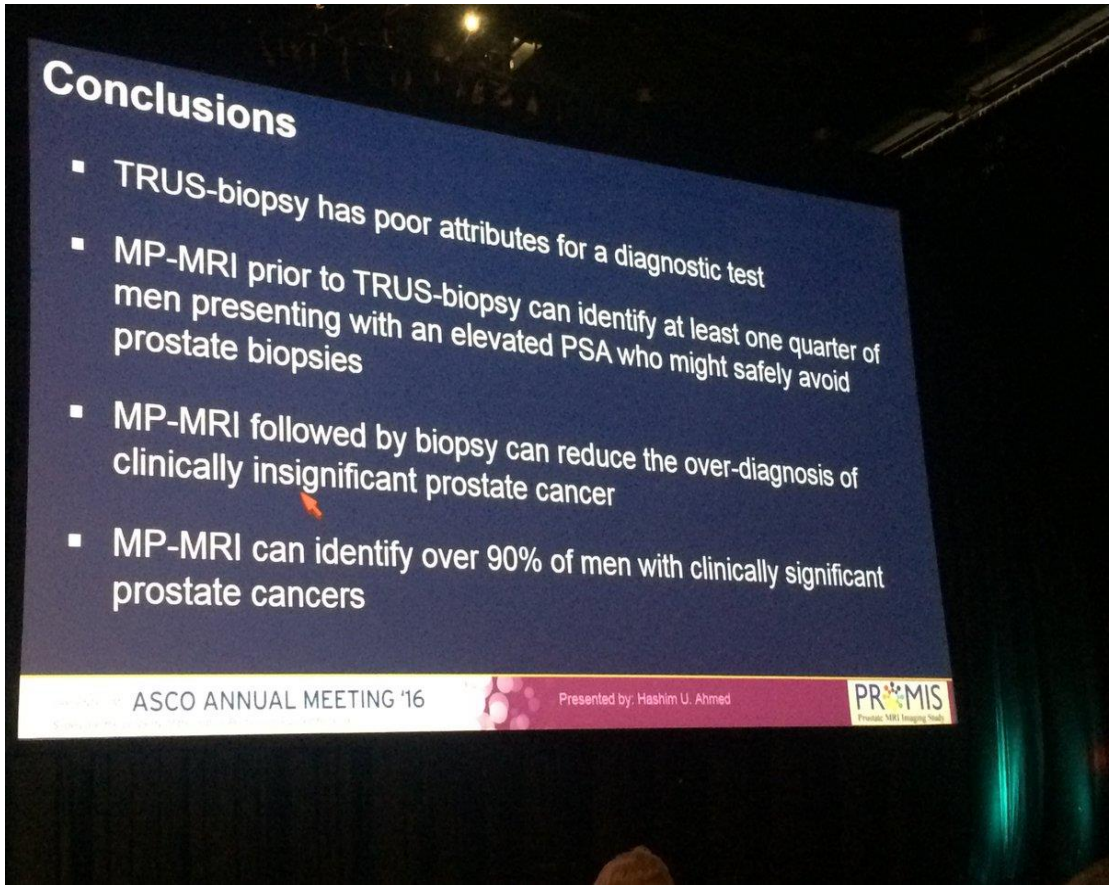
PROSTATE CANCER UK

A reduction in over-diagnosis

PROMIS

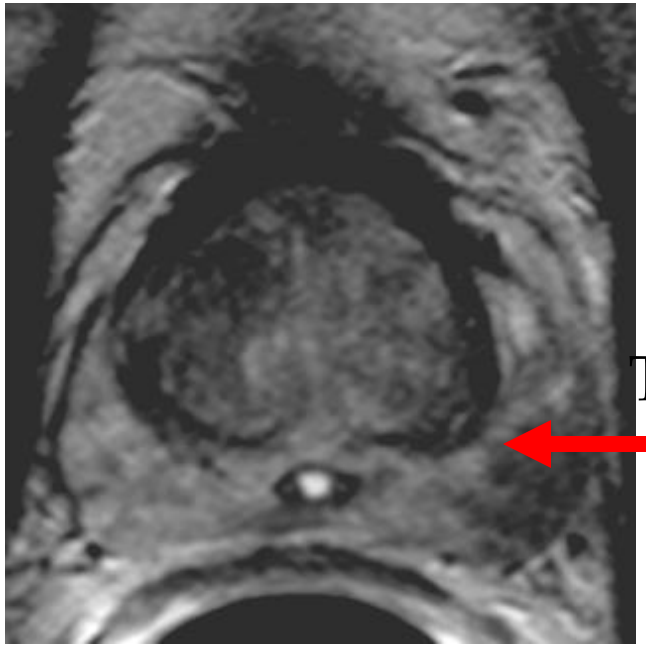
Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study

Hashim U Ahmed*, Ahmed El-Shater Bosaily*, Louise C Brown*, Rhian Gabe, Richard Kaplan, Mahesh K Parmar, Yolanda Collaco-Moraes, Katie Ward, Richard G Hindley, Alex Freeman, Alex P Kirkham, Robert Oldroyd, Chris Parker, Mark Emberton, and the PROMIS study group†



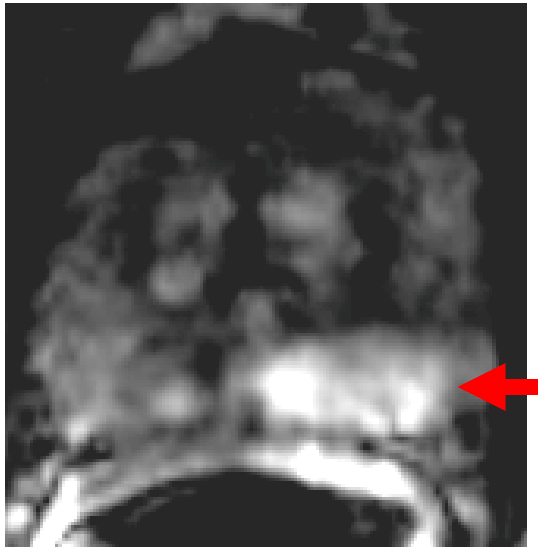
- 27% potentially saved from primary biopsy
- miss 5% of clinically significant cancer
- Sensitivity 93% vs 48%
- NPV 89 % vs 74%
- high risk patients – should probably still have prostate biopsies even in light of a normal MRI

Tailoring Nerve Sparing Based on MRI (1)



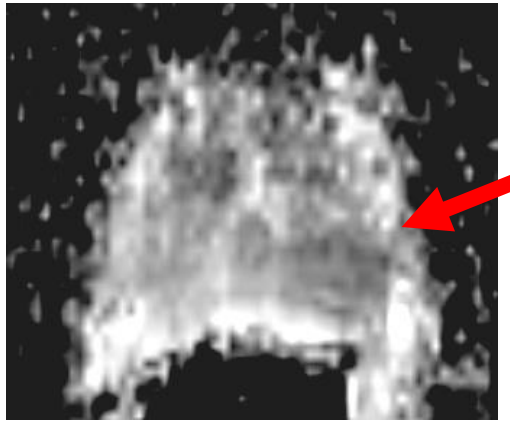
T2 weighted image

Irregular capsule



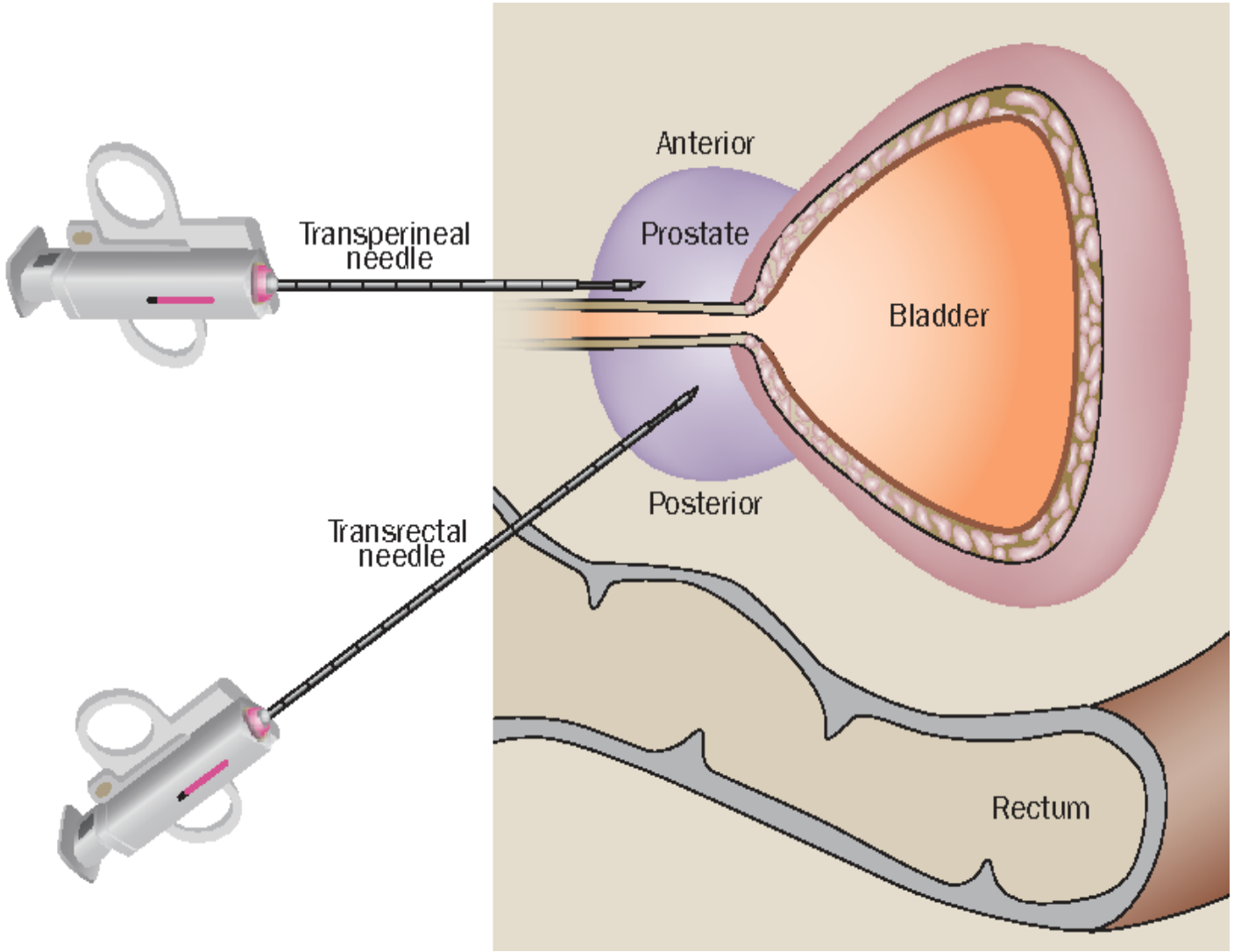
Perfusion

Diffusion



What happens after a positive MRI?

- Route
  - Transrectal
  - Transperineal
- Fusion
  - Cognitive
  - MRI software fusion
- LA vs GA



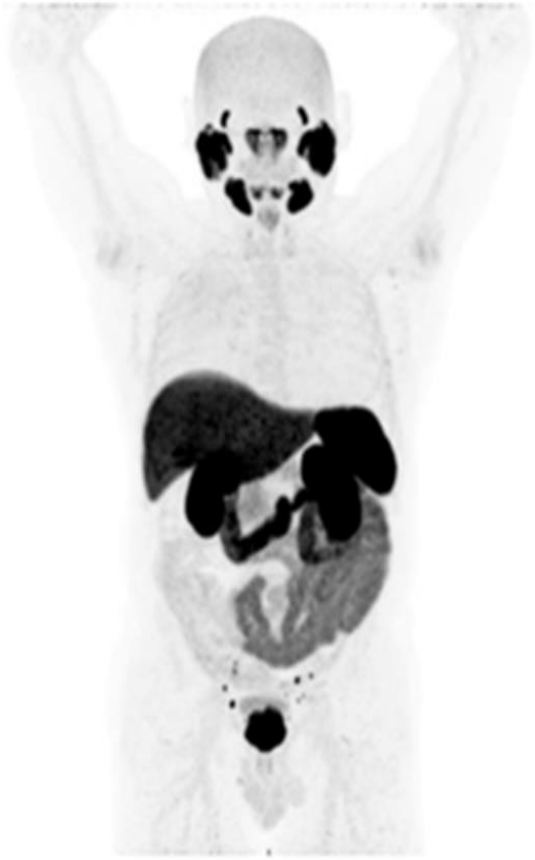
Targeted Treatment:

How can we be sure it hasn't spread?
Avoiding unnecessary surgical Rx
Cancer characteristics now much more specific
Imaging, much improved

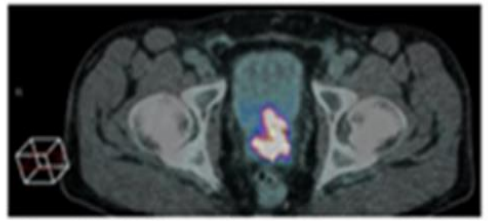
What can we do if it hasn't spread?
Try to cure it!!

Radiotherapy
External beam or Brachytherapy
Surgery
Robotic radical prostatectomy

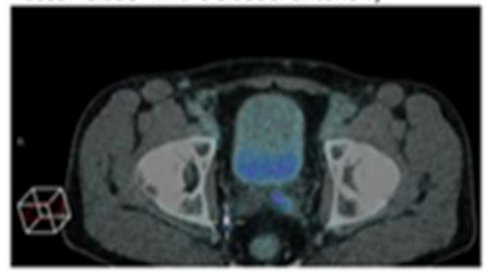
PSMA PET Scan



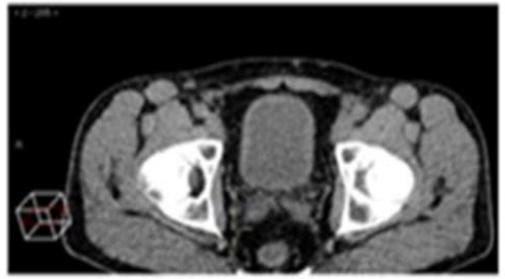
18F-PSMA-1007 MIP image showing intensely avid prostate tumour and bilateral small avid pelvic nodes



Fused PET/CT image showing intense activity in the large volume prostate tumour with minimal urinary tracer accumulation in the bladder anteriorly



Fused PET/CT image showing intense activity in a small volume right internal iliac lymph node



CT image of the right internal iliac node – only 4mm in short axis diameter (not significant by size criteria)

Principle is to kill the cancer with minimal damage to important surrounding tissues-

Balance between functional and oncological benefits

- Precision surgery- 10x magnified stereoscopic vision
- 1 night in hospital

- 1 week simple analgesia

- Low complication rate

    - High chance of cure

- Erectile dysfunction- minimize with nerve sparing

- Urinary incontinence- now a temporary phenomenon <3 months in 80%

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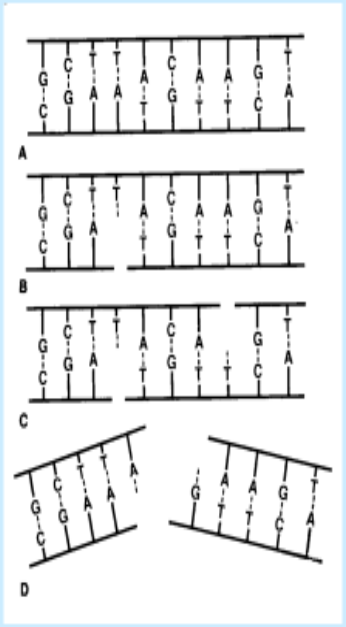
Oncological outcome surgery vs radiotherapy are the same

- Need to be fit for surgery
- Previous abdominal surgery
- Bowel disease
- Pre-existing LUTs
- If you have radiotherapy and it fails- results of surgery are poor
- If surgery fails, salvage radiotherapy is often successful

- Young fit people tend to go for surgery
- Older less fit people tend to go for radiotherapy

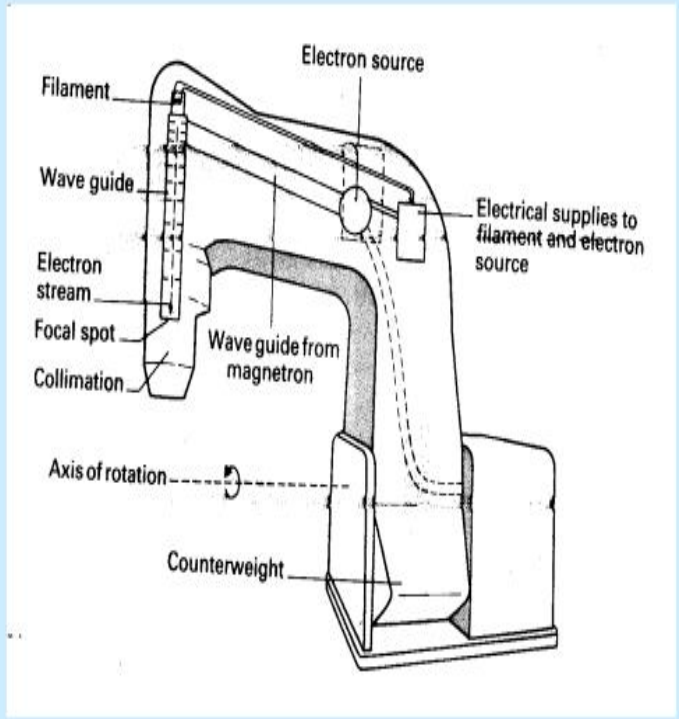
RADIOTHERAPY

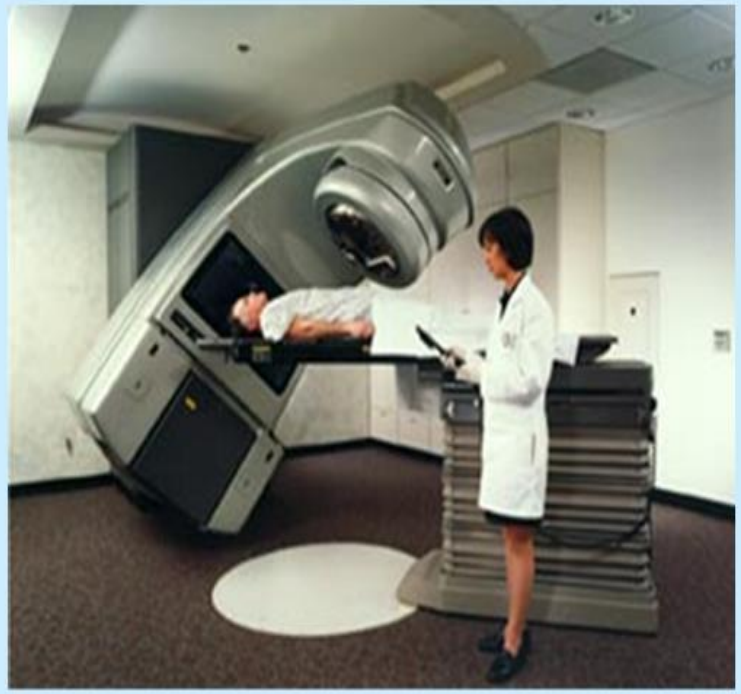
DNA Strand Breaks



- Major biological target is DNA.
- Interactions cause chemical changes in structure of DNA.
- Double strand breaks are lethal lesions that lead to cell death

Isocentrically mounted Linear Accelerator





Recent improvements in Radiotherapy

- Innovative techniques allow dose escalation while sparing normal tissue:

3D conformal RT (3D-CRT)
- Minimises organ damage
- Allows higher radiation dose

Intensity-modulated RT (IMRT)
- Optimised form of 3D-CRT
- Dose distribution shaped more precisely to target than 3D-CRT to spare organs at risk

Image-guided RT (IGRT)
- Fiducial markers
- Cone-beam imaging
- Tomotherapy

Hypofractionation

High dose rate (HDR) brachytherapy boost

Combined RT and ADT
- Can delay progression and improve overall survival
- Concomitant and adjuvant ADT mandatory for RT of high-risk PCa[1]

Cyberknife and Proton Beam under investigation

Hormone therapy for prostate cancer

Prostate cancer (Pca) is recognized as a hormone-dependent disease.

A clear target, the androgen receptor (AR) signalling pathway, has been identified as a primary objective for the development of effective therapies.

In healthy males, the androgens testosterone (T) and its derivative dihydrotestosterone (DHT) are essential for cell survival and function of the prostate.

However, Pca cells exhibit excess activation of the androgen signalling pathway resulting in uncontrolled proliferation of tumour cells

The role of effective ADT has been endorsed in recent years by the explosion of scientific advances confirming the importance of suppression of T activity in the management of advanced PCa.

Emergence of new therapies that target androgen signalling through modes of action other than hormonal therapy (ADT), resulting in the inactivation of the androgen signalling pathway.

Androgen-targeted therapy

Prostate Cancer and Prostatic Diseases https://doi.org/10.1038/s41391-018-0079-0

Almost all PCa tumours will initially respond to ADT, although with long-term T suppression, some cell populations become refractory and elimination of T production from the testes is no longer sufficient to fully suppress tumour cell growth.

This is referred to as castration-resistant PCa (CRPC), which is determined by a rising PSA in an environment where T levels are castrate

Ceder Y, Bjartell A, Culig Z, Rubin MA, Tomlins S, Visakorpi T. The molecular evolution of castration-resistant prostate cancer. Eur Urol Focus. 2016;2:506–513.

In CRPC, reactivation of AR pathways from multiple mechanisms occurs:

Production of androgens by the adrenal glands and PCa cells themselves

Androgen-independent activation of the AR by AR gene amplification or overexpression

Hu J, Wang G, Sun T. Dissecting the roles of the androgen receptor in prostate cancer from molecular perspectives. Tumour Biol. 2017;39:1010428317692259.

Summary

Orchidectomy: Surgically remove both testes to reduce T production

Antiandrogens : Block the androgen receptor to reduce effects of T signalling in the cell

LHRH agonist : Overstimulate the pituitary gland to downregulate the GnRH receptor and decrease LH production, which lowers T production in the testes

LHRH antagonists : Block the GnRH receptor to decrease LH production, which lowers T production in the testes

Androgen pathway inhibitors : Target the androgen pathway to inhibit T synthesis or reduce AR signalling

Antiandrogens: Bicalutamide, Flutamide, Nilutamide, Cyproterone acetate

LHRH agonists: SC-leuprolide acetate, IM-leuprolide acetate, Triptorelin, Goserelin

LHRH antagonists: Degarelix and Relugolix

Androgen pathway inhibitors: Abiraterone, Enzalutamide, Apalutamide, Darolutamide

Chemotherapy: Docetaxel & Carbazetaxel

Lutetium Lu 177, is a new radiation pharmaceutical that is administered through injection or infusion. The drug travels throughout the body and targets cancer cells with the PSMA biomarker, a protein found on most prostate cancer cells.

Abiraterone acetate (ZYTIGA®) is an oral, androgen biosynthesis inhibitor that blocks T production through inhibition of the enzyme CYP17.

It is administered in combination with prednisone and with ongoing ADT,
Effective in reducing androgen production from all sources including the testes, adrenal glands, and PCa cells.

Several trials have found that abiraterone in combination with ADT profoundly suppresses T to lower levels than are generally seen with an LHRH agonist alone

Crawford ED, Shore ND, Petrylak DP, Higano CS, Ryan CJ. Abiraterone acetate and prednisone in chemotherapy-naïve prostate cancer patients: rationale, evidence and clinical utility. Ther Adv Med Oncol. 2017;9:319–333.
Taplin ME, Montgomery B, Logothetis CJ, Bubley GJ, Richie JP, Dalkin BL, et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. J Clin Oncol. 2014;32:3705–3715

Darolutamide is an oral, nonsteroidal antiandrogen with a similar mode of action to enzalutamide and apalutamide. In a 12-week phase 2 study, darolutamide demonstrated a PSA response rate of 29% in the low, 33% in the mid, and 33% in the highest dose group.

Relugolix is an oral GnRH antagonist in phase 3 development. In healthy males the drug was readily absorbed and reduced mean serum T levels within 6 h of dosing

T recovered rapidly following cessation of treatment

Fizazi K, Massard C, Bono P, Jones R, Kataja V, James N, et al. Activity and safety of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer (ARADES): an open-label phase 1 dose-escalation and randomised phase 2 dose expansion trial. Lancet Oncol. 2014;15:975–985.
MacLean DB, Shi H, Faessel HM, Saad F. Medical castration using the investigational oral GnRH antagonist TAK-385 (Relugolix): phase 1 study in healthy males. J Clin Endocrinol Metab. 2015;100:4579–4587.

Conclusions

- The management of advanced PCa has undergone a revolution over the last decade with the emergence of new science and data in androgen-targeted therapies.

- Patients are living longer and benefit from improved outcomes with the widespread use of new drugs such as abiraterone, enzalutamide, apalutamide, darolutamide

- These drugs, in combination with ADT, dramatically inhibit the availability of T to the tumour by near complete inhibition of the androgen signalling pathway.

Prostate Cancer UK's Best Practice Pathway – prostate cancer: treatment by risk stratification

Watchful waiting: is a monitoring modality for men with localised prostate cancer who are either not suitable for, or do not ever wish to receive, curative treatment, and instead involves the deferred use of hormone therapy when symptoms of progressive disease develop.

Updated August 2019

Risk stratification	Additional treatment combinations	Active surveillance	Surgery (prostatectomy)	Radiotherapy			Hormone therapy				Chemotherapy		Radium-223
			Laparoscopic	External beam intensity modulated	Brachytherapy		Androgen deprivation therapy		Anti-androgen	Abiraterone	Docetaxel	Cabazitaxel	
					Low dose	High dose	LHRHa	GnRHa					
Low risk localised		●	●	●	●								
Intermediate risk localised	EBRT and ADT and high dose brachytherapy boost	●	●	●	●	●	●	●					
High risk localised	EBRT and ADT and high dose brachytherapy boost		●	●	●	●	●	●					
Locally advanced			●	●			●	●	●		● (High risk)		
Metastatic hormone-naive	LHRHa and anti-androgen			● .			●	●	●	●	●		
Metastatic castrate-resistant										●	●	●	●

Please note: the table above is based on men being eligible for these treatment options and having made an informed choice to have them.

KEY	
●	Treatment choice
●	Optimal treatment supported by evidence
●	Optimal treatment combination supported by evidence
	Not appropriate

*Only patients who do not have 4 bone metastases, including 1 outside the pelvis and spine or visceral metastases

Optimal treatment evidence

Active surveillance for low risk localised disease: Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med [Internet 2016 Oct 13 [cited 2016 Nov 28];375(15):1415–24

External beam radiotherapy in combination with androgen deprivation therapy for locally advanced disease: National Institute for Health and Care Excellence (2019) Prostate cancer: diagnosis and management (NG131). Available at: https://www.nice.org.uk/guidance/ng131/. http://www.nice.org.uk/guidance/CG175

Docetaxel in combination with androgen deprivation therapy for newly diagnosed advanced hormone-naïve metastatic disease:James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. The Lancet [Internet]. 2016 Mar 19 [cited 2016 Nov 7];387(10024):1163–77

Cardiovascular risk

- Evaluating cardiovascular and metabolic risk

- Older age is associated with diabetes, cardiovascular disease, and prostate cancer, so it's not surprising how often these conditions overlap.

- Indeed, cardiovascular disease is the second leading cause of death in men with prostate cancer and **the primary cause of death in men with T3 or lower-stage disease**

Chowdhury S, Robinson D, Cahill D, et al. Causes of death in men with prostate cancer: an analysis of 50,000 men from the Thames Cancer Registry. BJU Int 2013 Jul;112(2):182-189.

ABCDE approach

- **A: Awareness & aspirin where indicated**
- **B: Blood pressure, ACE, ARB**
- **C: Cholesterol, high intensity statin for pre-existing CVD or high risk of CVD**

  Cigarettes- smoking cessation
- **D: Diabetes, good control, metformin, consider SGLT2 & GLP1**

  Diet, Mediterranean, consider vitamin D & avoid xs alcohol
- **E: Exercise, 150 min moderate, 75 min vigorous/week including resistance exercise**

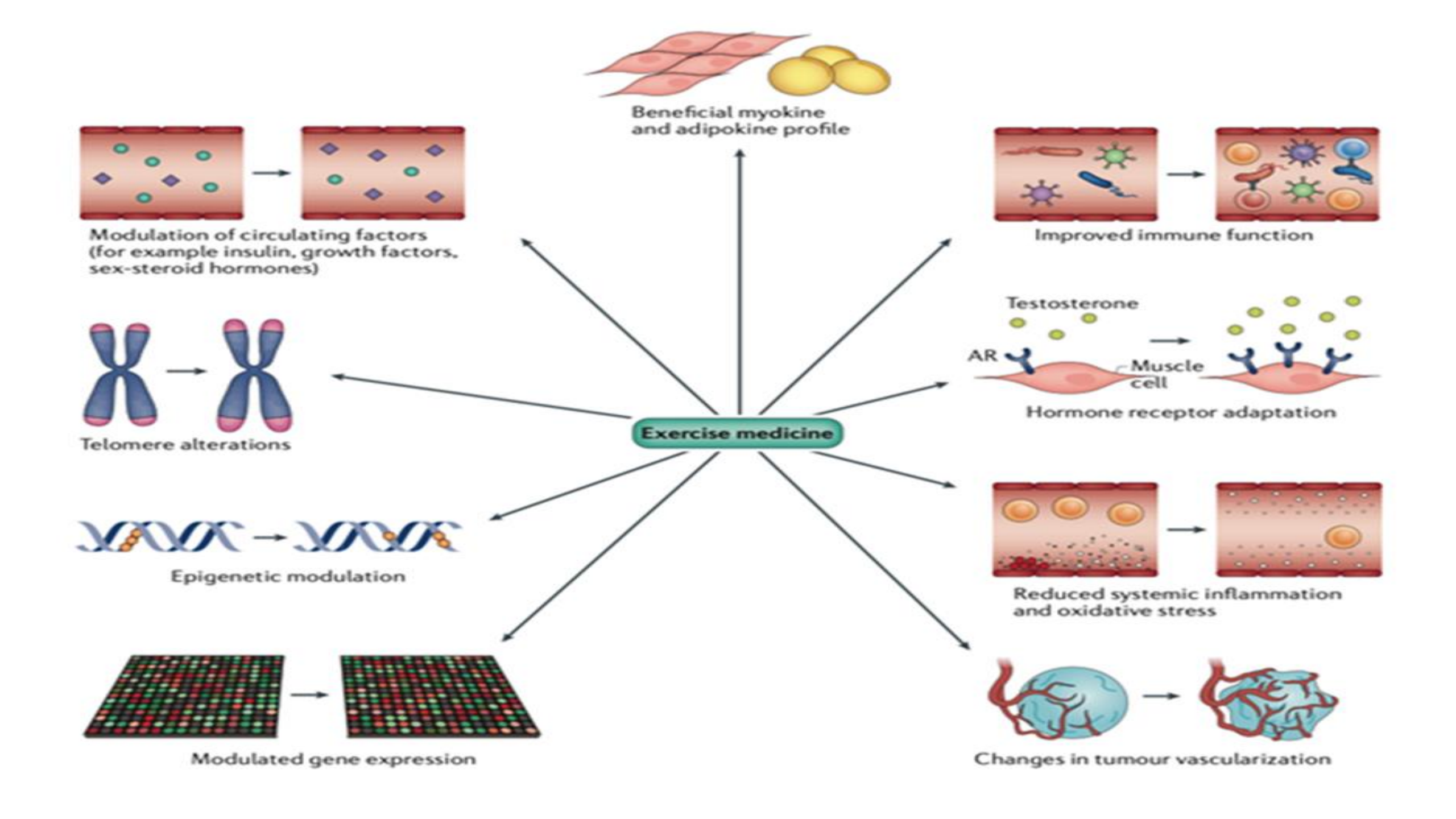
  ED – PDE5is

Bhatia N Cardiovascular Effects of Androgen Deprivation Therapy for the Treatment of Prostate Cancer ABCDE Steps to Reduce Cardiovascular Disease in Patients With Prostate Cancer Circulation 2016 133 (5) 537-541

Androgen deprivation therapy (ADT) has proven to be highly successful in slowing the progression of prostate cancer by either preventing testosterone production or blocking androgen receptors, so depriving cancerous cells of the signalling they require for growth and proliferation.

However, the toxicities of ADT have been extensively documented and range from rapid onset of metabolic and cardiovascular disease to loss of muscle and bone mass. Addressing this problem has been a focus of exercise medicine research in prostate cancer, as it was recognised more than a decade ago that targeted exercise has a high potential to ameliorate most if not all ADT side-effects

Galvão DA, Spry NA, Taaffe DR, et al.Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int 2008;102:44–7


Beneficial myokine and adipokine profile
Modulation of circulating factors (for example insulin, growth factors, sex-steroid hormones)
Improved immune function
Testosterone
AR
Muscle cell
Hormone receptor adaptation
Telomere alterations
Exercise medicine
Epigenetic modulation
Reduced systemic inflammation and oxidative stress
Modulated gene expression
Changes in tumour vascularization

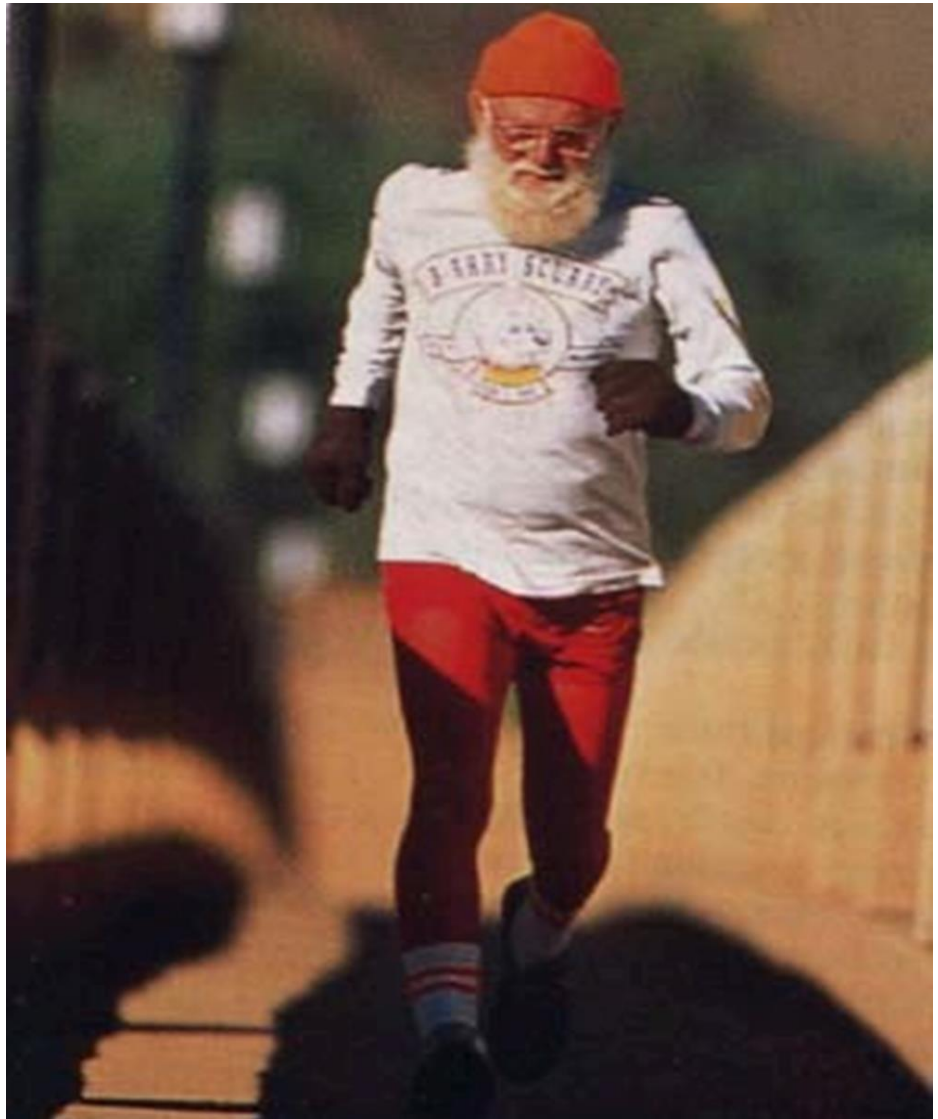
Results: **Prostate Cancer-specific mortality**

- **Statistically significantly lower mortality rates found in men who:**

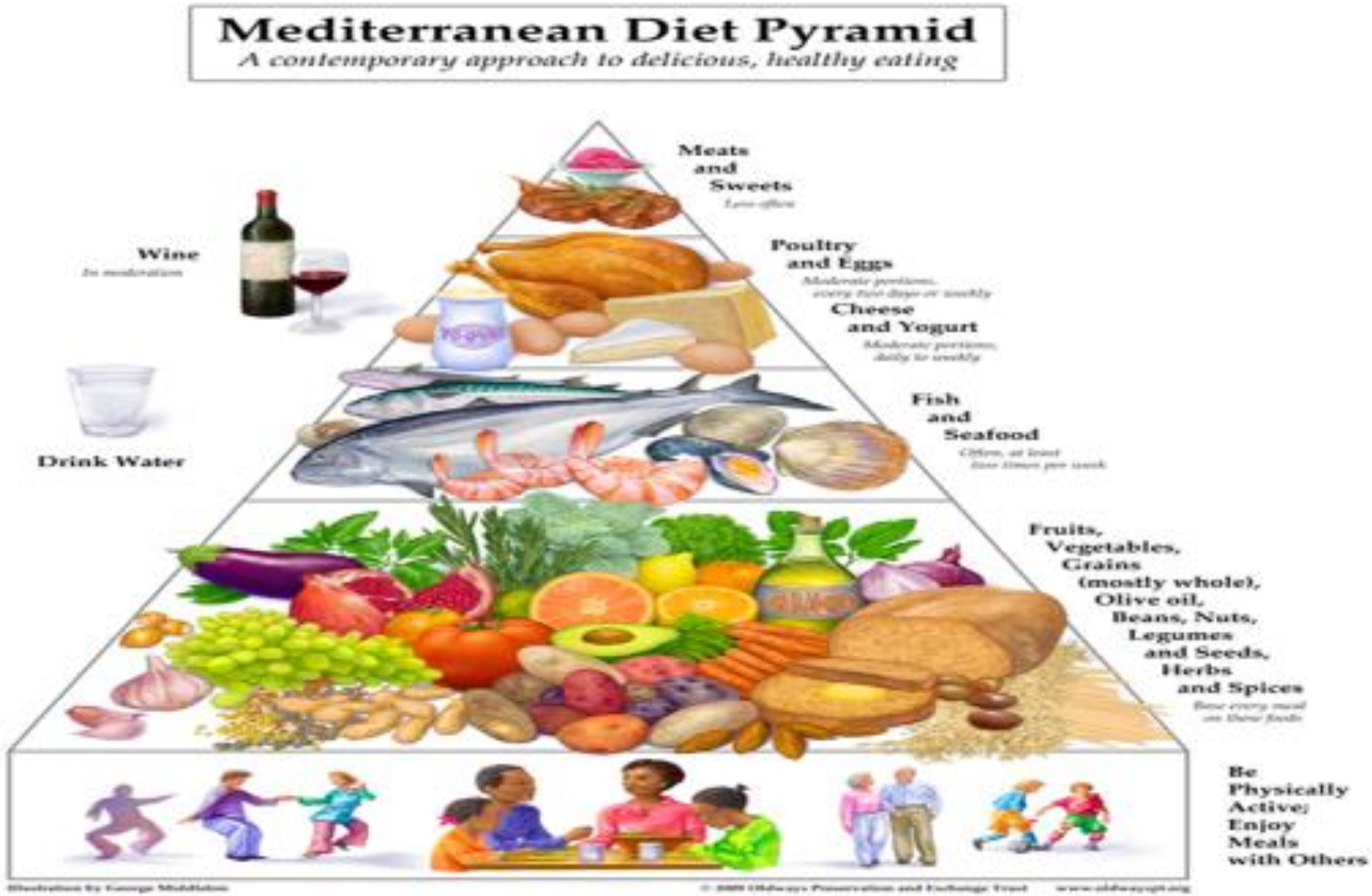
- walked/cycled ≥20 min/day (**HR 0.61**; 95% CI, 0.43-0.87

or

- exercised ≥1 hr/wk (**HR 0.68**; 95% CI, 0.48-0.94)



Bonn SE et al. Cancer Epidemiol Biomarkers Prev 2015;24(1):57-64.


Mediterranean Diet Pyramid
A contemporary approach to delicious, healthy eating
Meats and Sweets
Poultry and Eggs
Cheese and Yogurt
Fish and Seafood
Fruits, Vegetables, Grains (mostly whole), Olive oil, Beans, Nuts, Legumes and Seeds, Herbs and Spices
Wine
Drink Water
Be Physically Active; Enjoy Meals with Others

Try to follow these ABCD steps, knowing what the patient's blood pressure is, **do they smoke, what their cholesterol is, do they have metabolic syndrome or diabetes, and whether they exercise.**

And **these are steps that we can all intervene on, for all of our patients, but particularly our cancer survivors**.