

# Lifestyle and prostate cancer

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# Declaration of interests

- MK has received funding for research, lecturing, advice and conference attendance from the pharmaceutical industry.
- Member of the Prostate Cancer Risk Management Scientific Advisory Group
- Member NPCA National Prostate Cancer Audit group

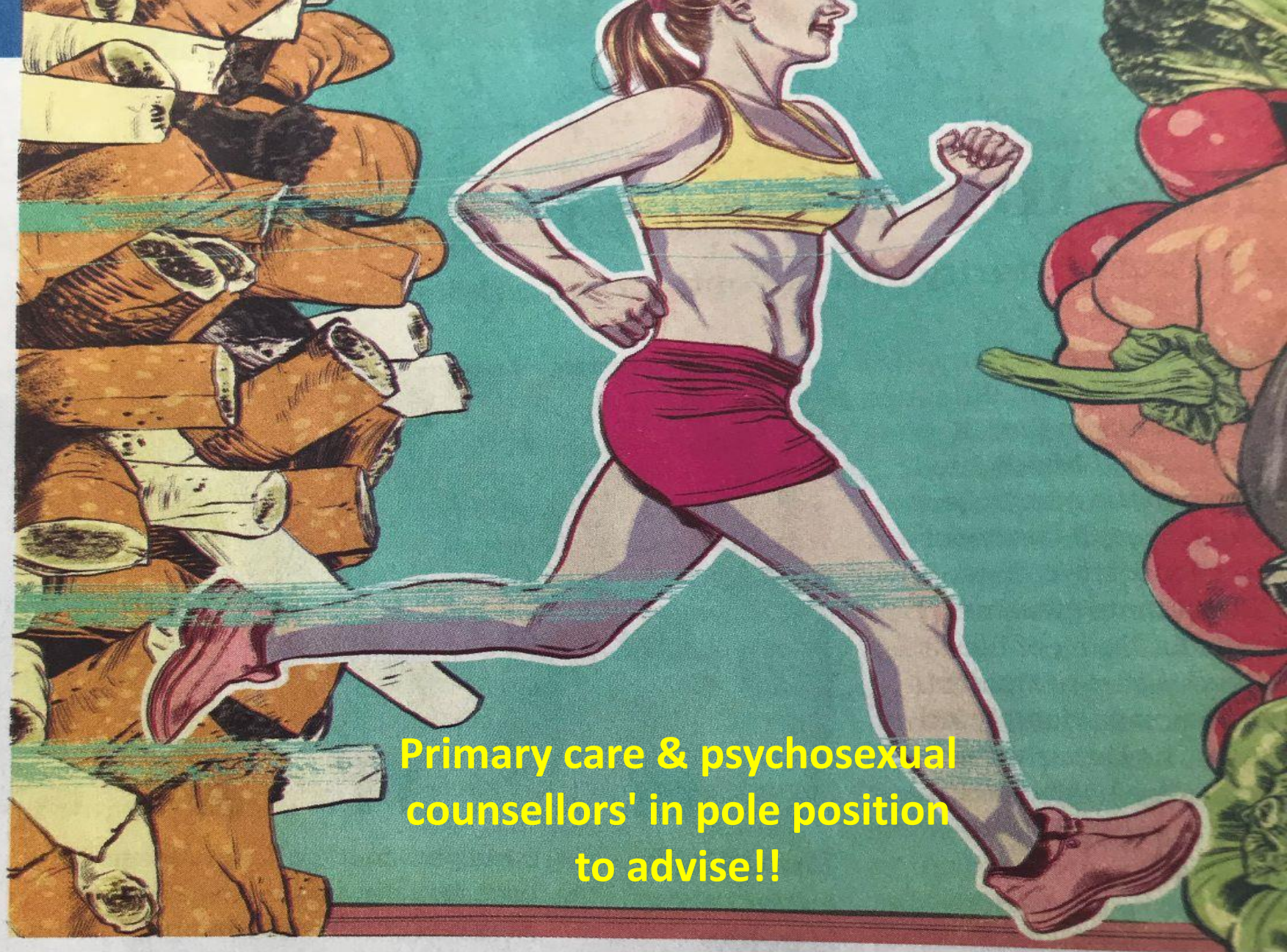


## CHRONIC DISEASE

# Is lifestyle medicine emerging as a new medical specialty?

The approach is on the rise in medical education.

**Anna Sayburn** asks if it can help reduce chronic disease without putting blame on patients for their conditions



**Primary care & psychosexual counsellors' in pole position to advise!!**

**L**ifestyle medicine's adherents talk

about nutrition. "You've got to get to the people who need it most. They're

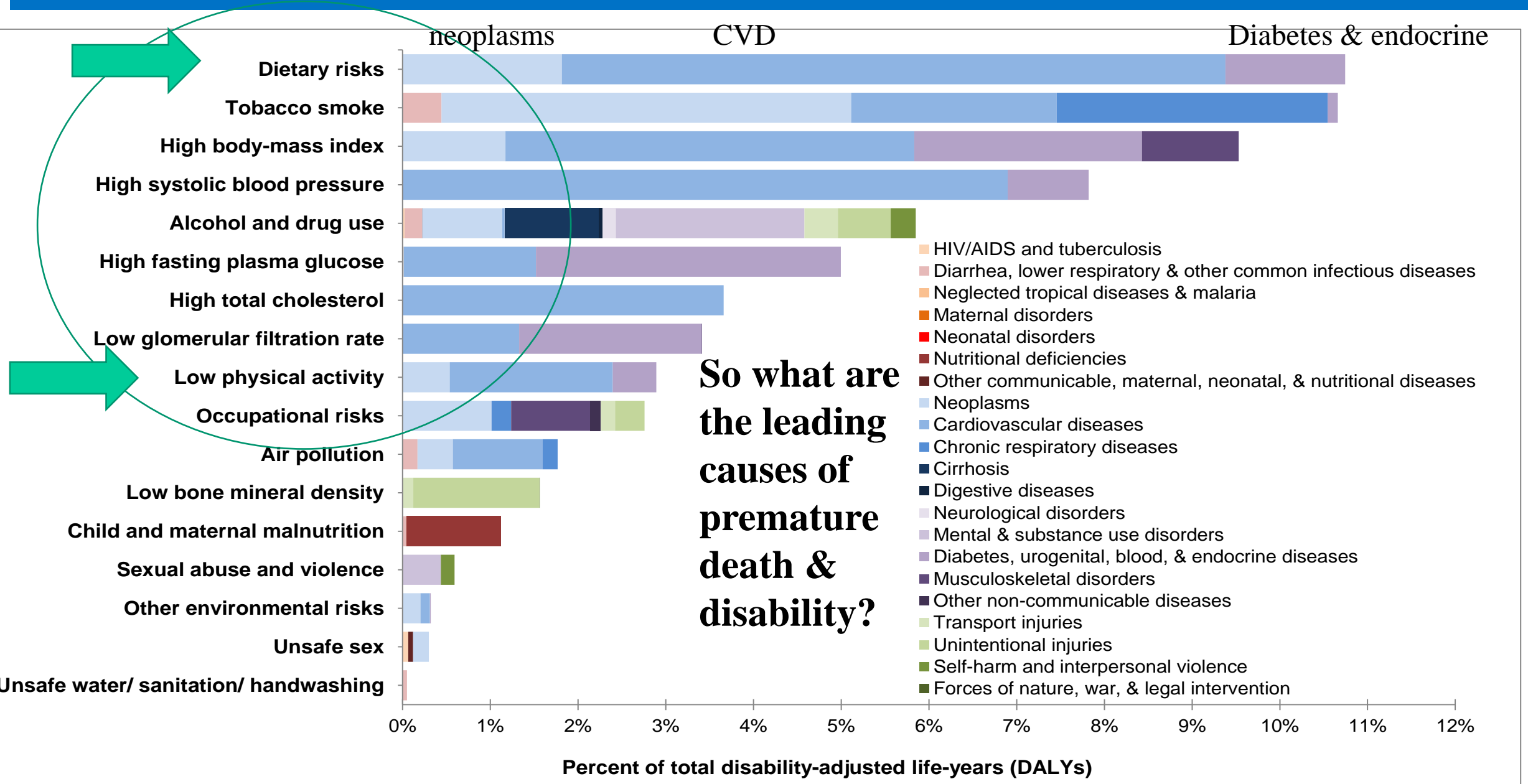
**Demand for education**

In August, 40 healthcare



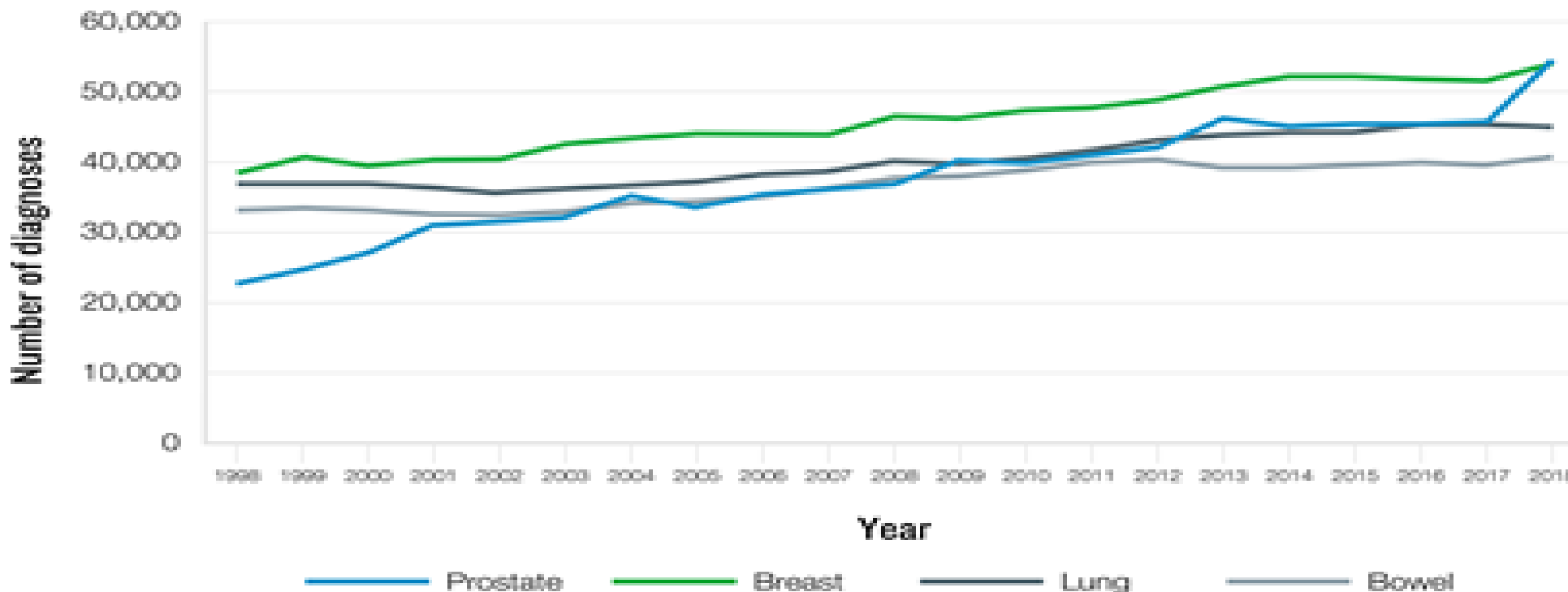
# Global Burden of Disease Study 2013 Leading causes of premature death and disability in England

Expressed as a percentage of disability-adjusted life-years



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.**

### UK most commonly diagnosed cancers\*



\*excluding Wales data

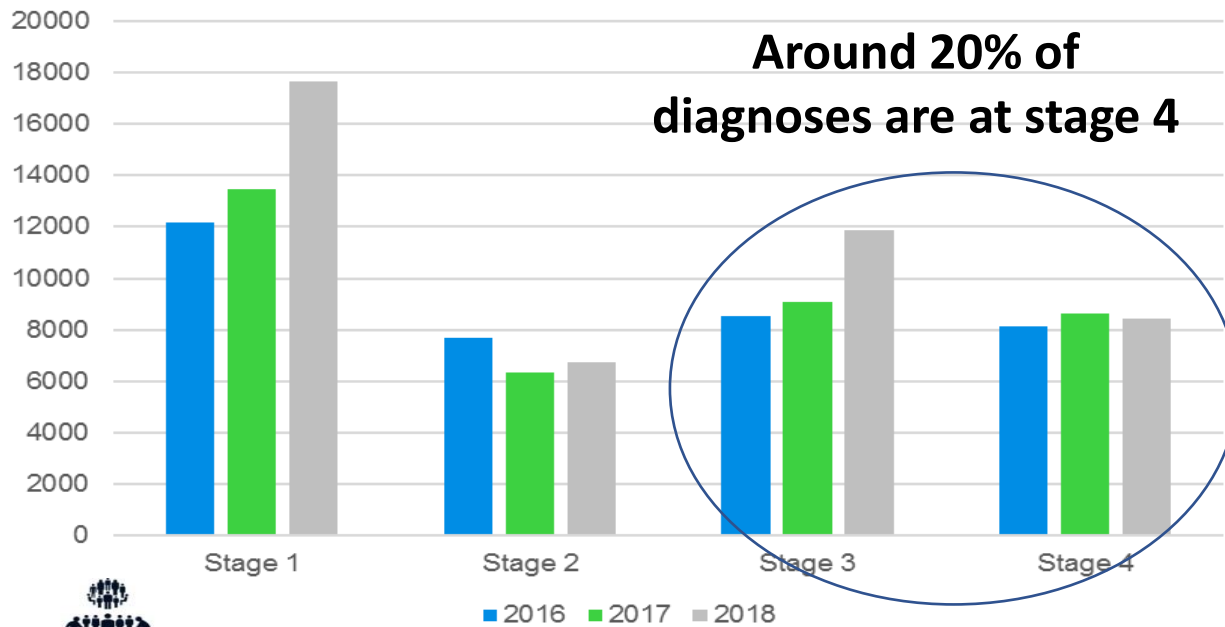
[https://prostatecanceruk.org/about-us/news-and-views/2020/6/most-common-cancer-in-uk?utm\\_source=Adestra&utm\\_medium=email&utm\\_content=header&utm\\_campaign=Men%20Utd%20-%20June%204%20-%20most%20common%20story](https://prostatecanceruk.org/about-us/news-and-views/2020/6/most-common-cancer-in-uk?utm_source=Adestra&utm_medium=email&utm_content=header&utm_campaign=Men%20Utd%20-%20June%204%20-%20most%20common%20story)

# Why is this a priority?

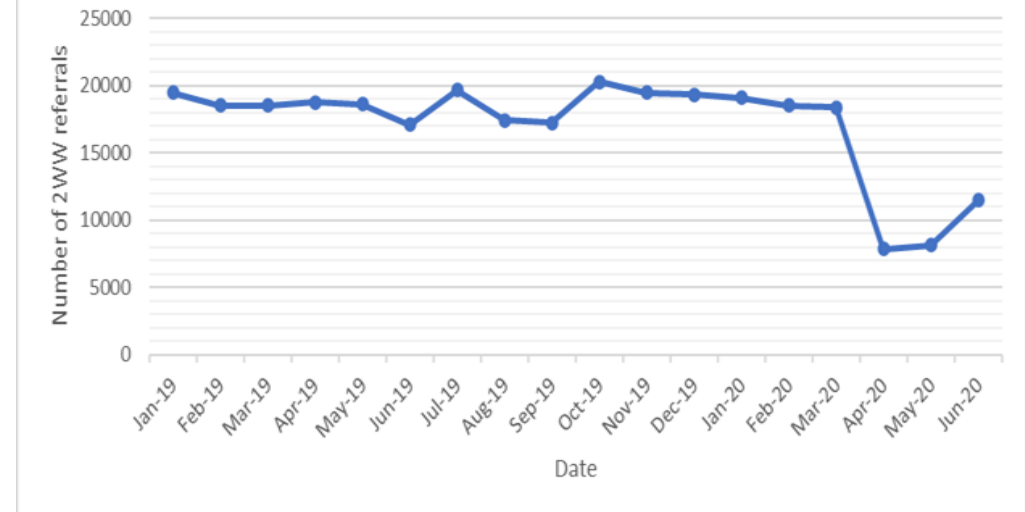
Too many men are diagnosed late

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

Prostate Cancer Diagnoses by stage



Two week wait referral data 2017 - present (England)

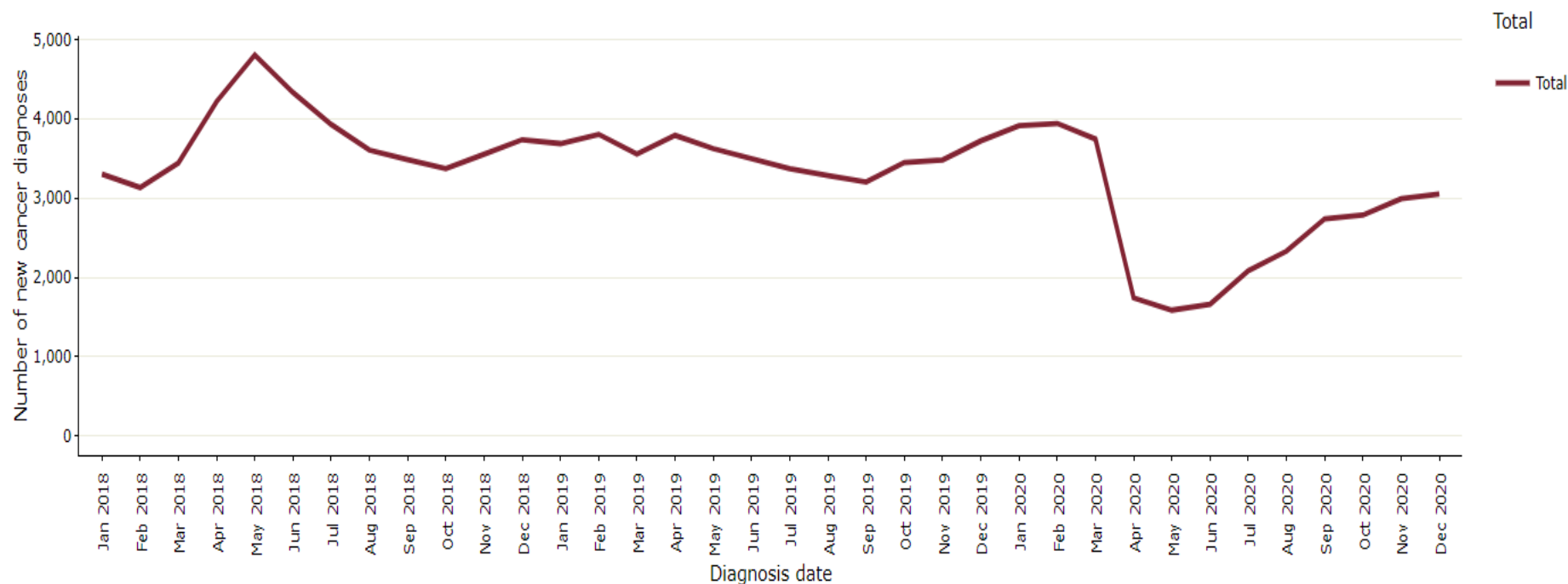


# 10,000 fewer diagnoses of prostate cancer

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

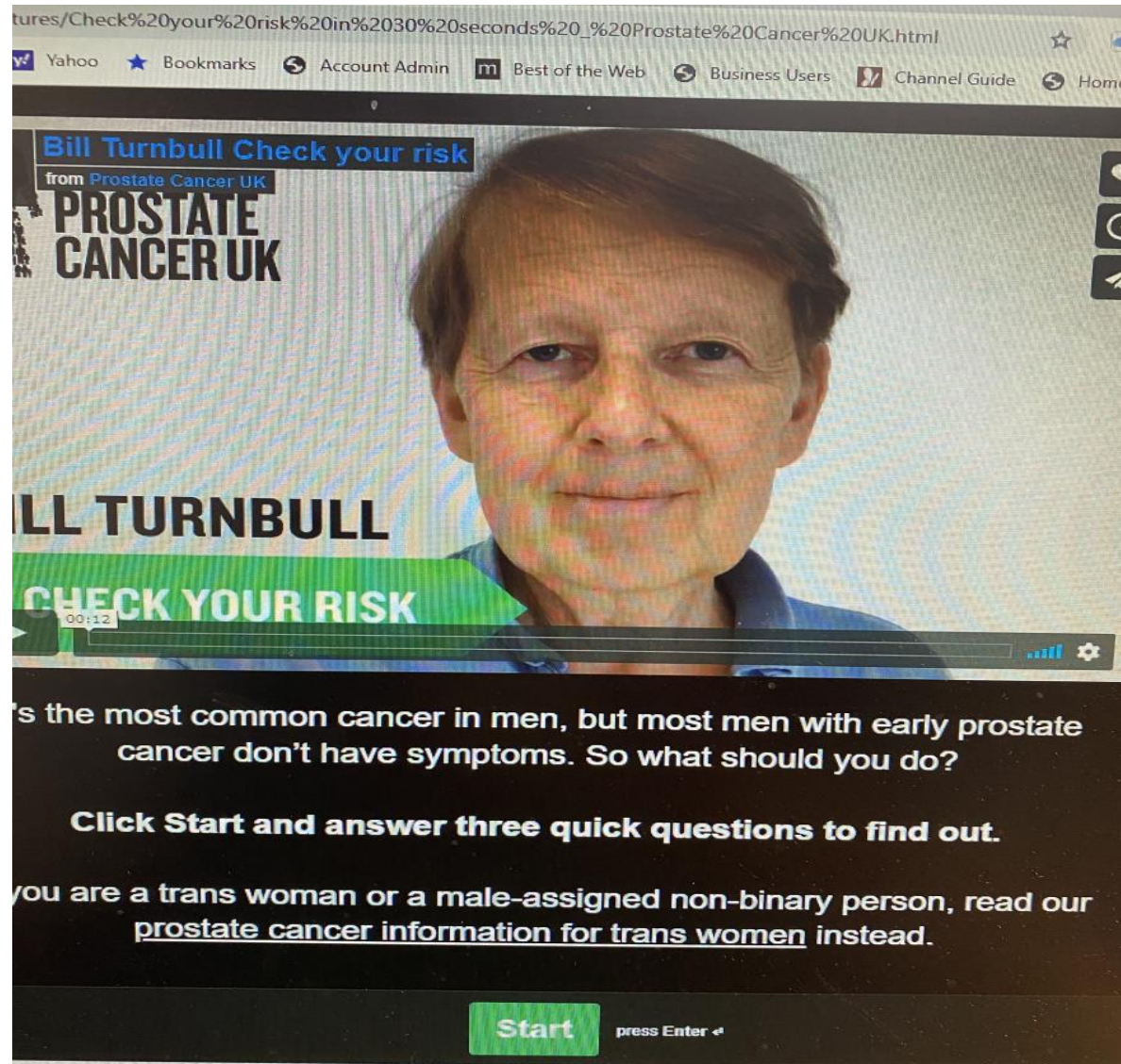
New cancer diagnoses, England, January 2018 to December 2020

Cancer group: Prostate



This work has been produced by The National Disease Registration Service.

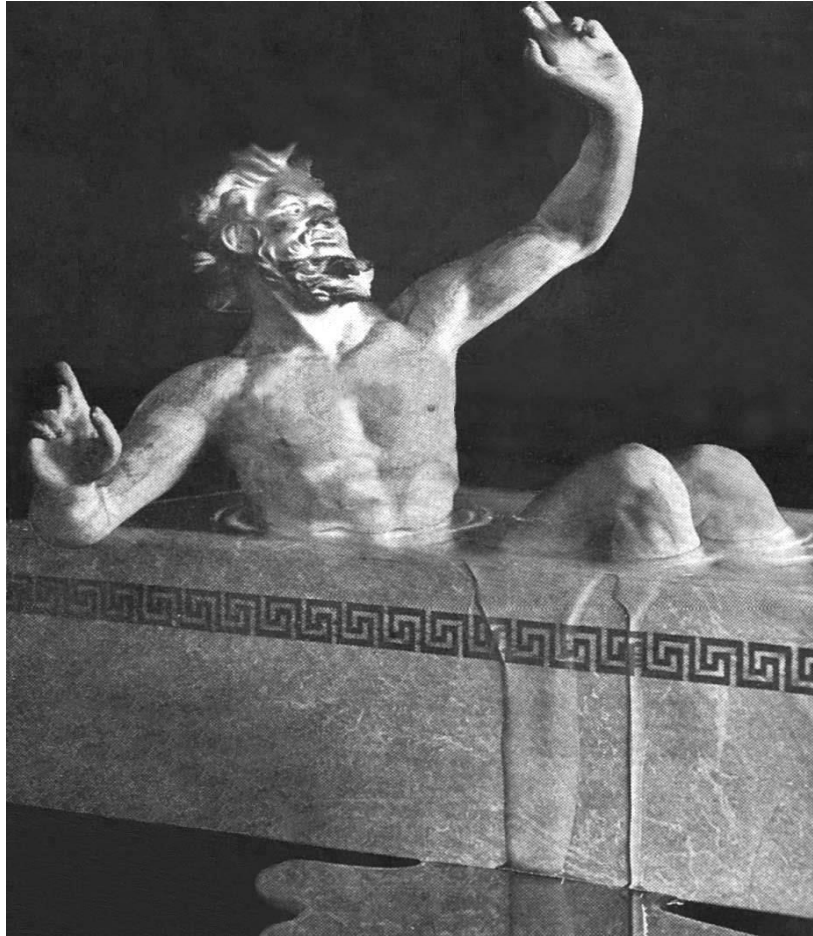
<https://prostatecanceruk.org/risk-checker>



The screenshot shows a video player interface. At the top, the browser address bar displays the URL: `tures/Check%20your%20risk%20in%2030%20seconds%20_%20Prostate%20Cancer%20UK.html`. Below the address bar, there are navigation icons for Yahoo, Bookmarks, Account Admin, Best of the Web, Business Users, Channel Guide, and Home. The video content features a man with short brown hair, wearing a blue shirt, looking directly at the camera. Text overlays on the video include "Bill Turnbull Check your risk" in blue, "from Prostate Cancer UK" in small black text, and "PROSTATE CANCER UK" in large, bold, black letters. A green arrow graphic with the text "CHECK YOUR RISK" points towards the right. Below the video player, there is a black text box with white text that reads: "It's the most common cancer in men, but most men with early prostate cancer don't have symptoms. So what should you do?" followed by "Click Start and answer three quick questions to find out." and "If you are a trans woman or a male-assigned non-binary person, read our [prostate cancer information for trans women](#) instead." At the bottom of the page, there is a green "Start" button with the text "press Enter" next to it.



# PSA



**P**ractitioner

**S**hould

**A**ssist

- 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., Rapi E., Verkoijen 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

# 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



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

**Conclusions**

- TRUS-biopsy has poor attributes for a diagnostic test
- MP-MRI prior to TRUS-biopsy can identify at least one quarter of men presenting with an elevated PSA who might safely avoid prostate biopsies
- MP-MRI followed by biopsy can reduce the over-diagnosis of clinically insignificant prostate cancer
- MP-MRI can identify over 90% of men with clinically significant prostate cancers

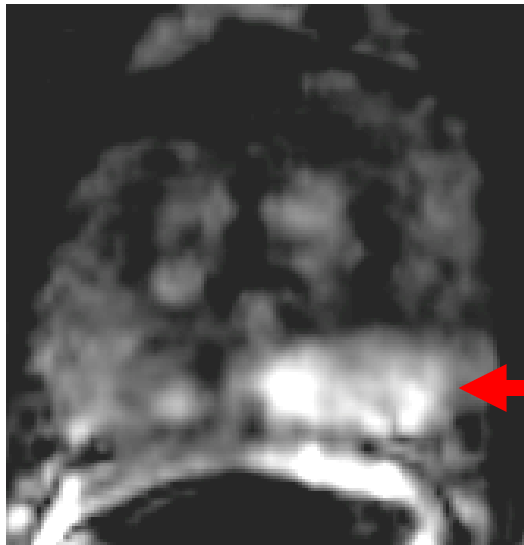
ASCO ANNUAL MEETING '16 Presented by: Hashim U. Ahmed PROMIS Prostate MRI Imaging Study

# Tailoring Nerve Sparing Based on MRI (1)

-

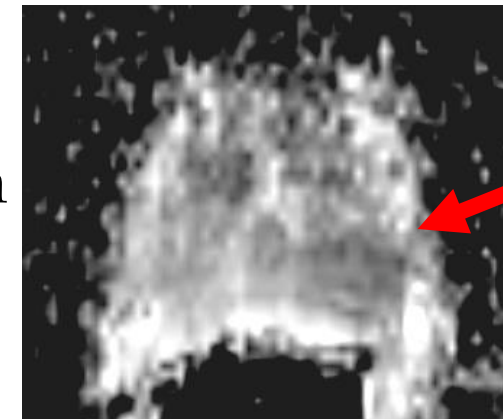


T2 weighted image  
Irregular capsule



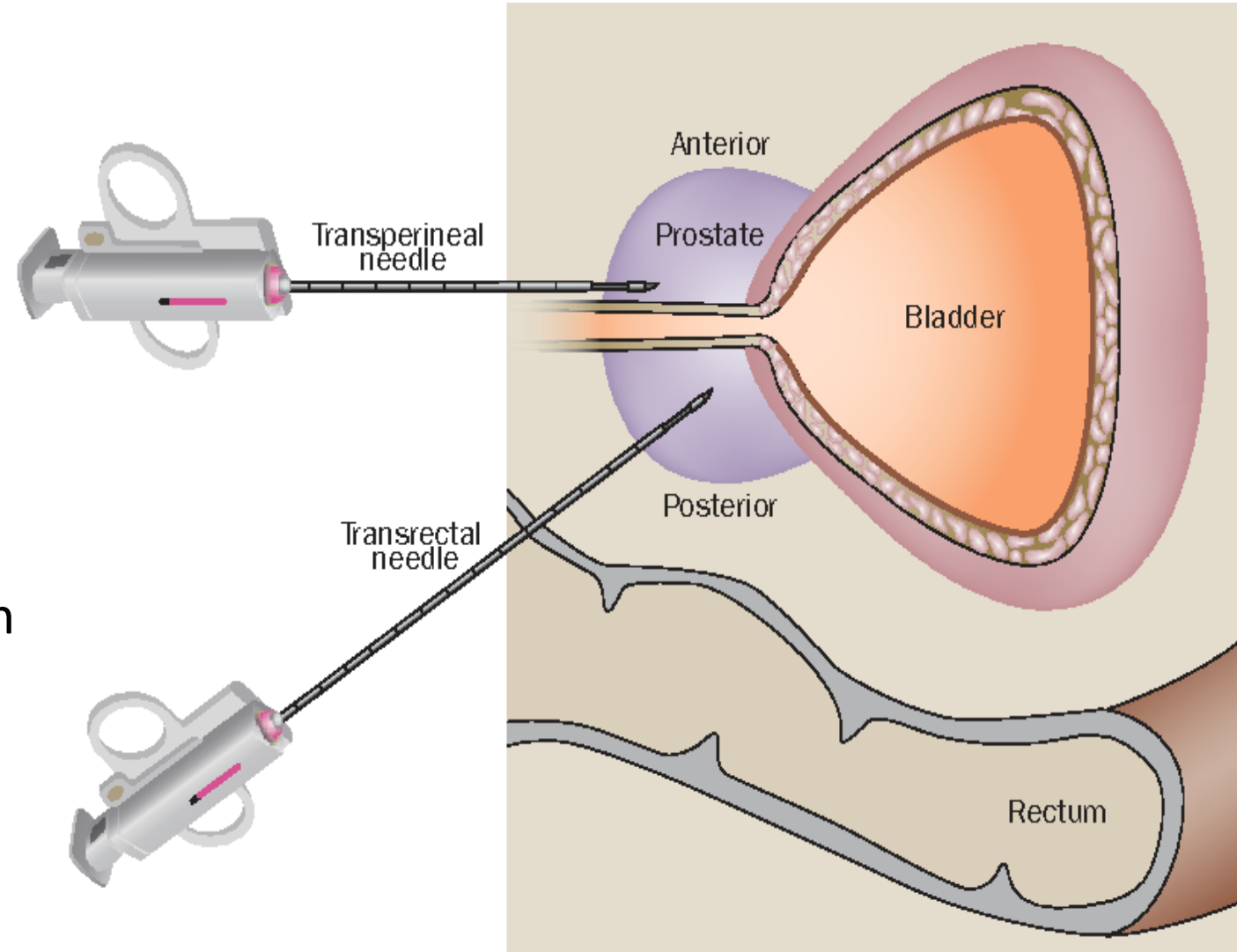
Perfusion

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

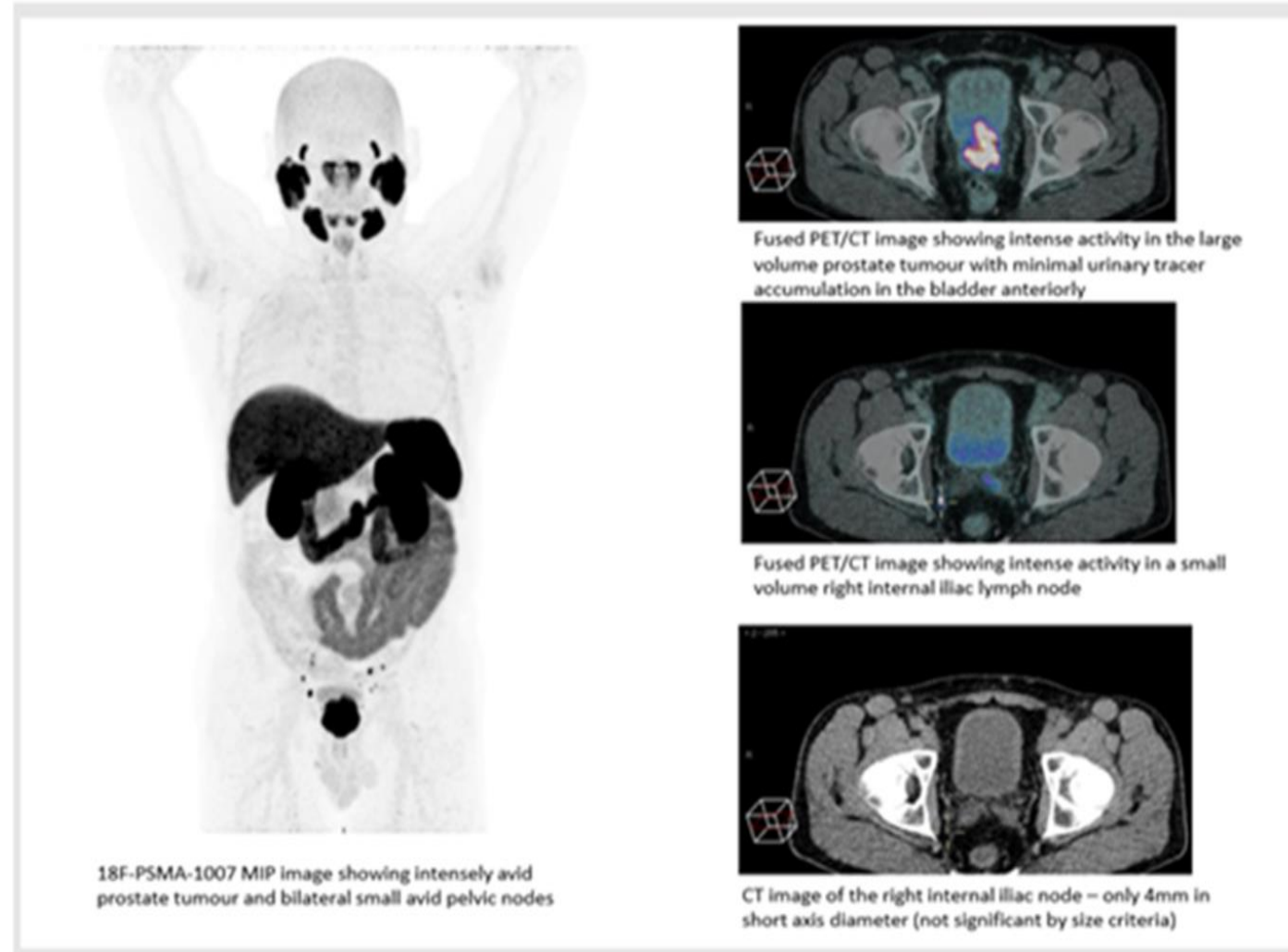
Surgery

Robotic radical prostatectomy

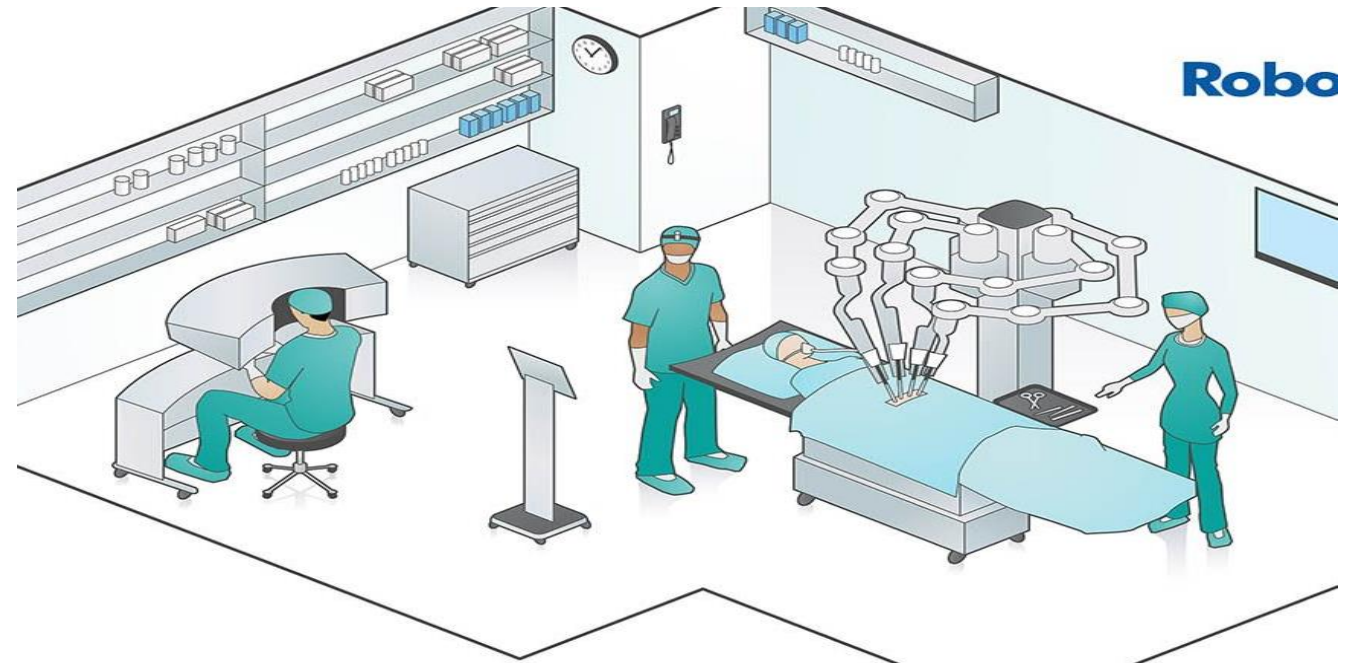
Principle is to kill the cancer with minimal damage to important surrounding tissues-

**Balance between functional and oncological benefits**

## PSMA PET Scan



- 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%



# Oncological outcome surgery vs radiotherapy are the same

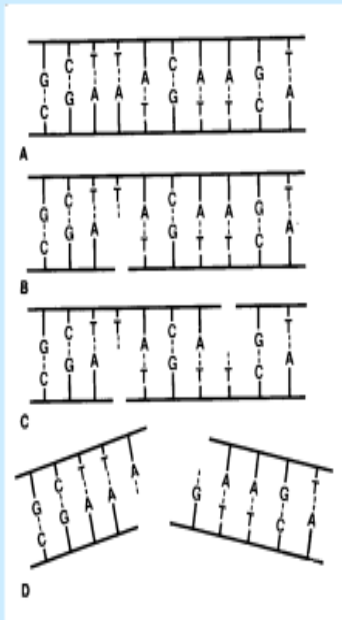
- Need to be fit for surgery
- Previous abdominal surgery
- Bowel disease
- Pre-existing LUTs
- If you have radiotherapy and it fails- results of surgery are poor
- If surgery fails, salvage radiotherapy is often successful
  
- Young fit people tend to go for surgery
- Older less fit people tend to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





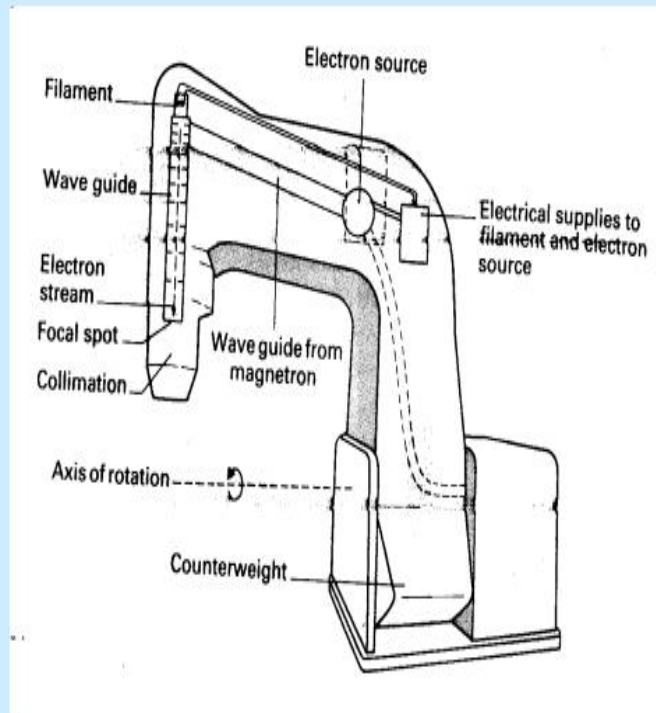
# RADIOTHERAPY

## 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

## Image-guided RT (IGRT)

- Fiducial markers
- Cone-beam imaging
- Tomotherapy

## High dose rate (HDR) brachytherapy boost

## Cyberknife and Proton Beam under investigation

## Intensity-modulated RT (IMRT)

- Optimised form of 3D-CRT
- Dose distribution shaped more precisely to target than 3D-CRT to spare organs at risk

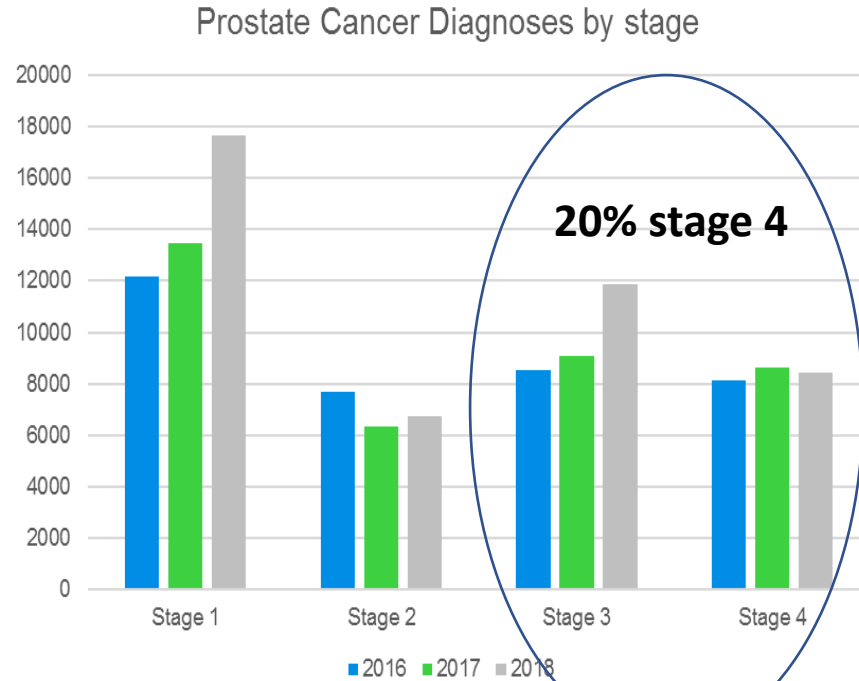
## Hypofractionation

## Combined RT and ADT

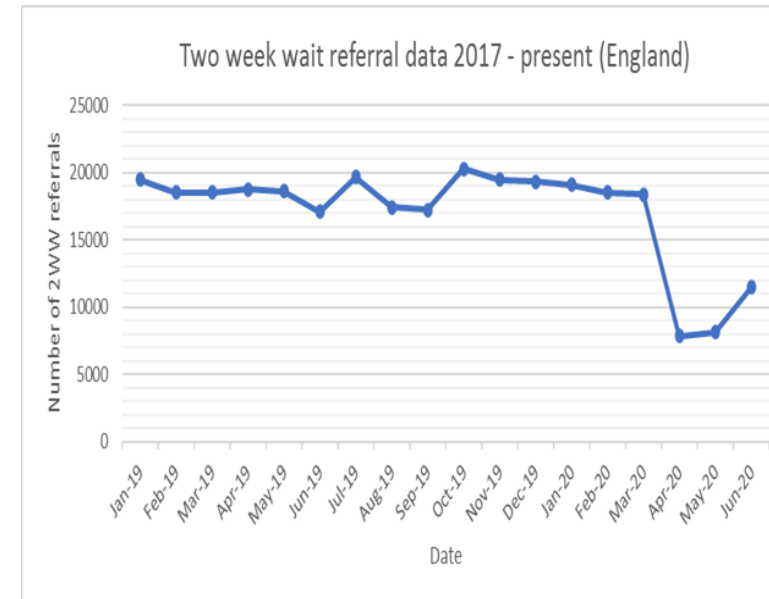
- Can delay progression and improve overall survival
- Concomitant and adjuvant ADT mandatory for RT of high-risk PCa<sup>1</sup>

# Hormone therapy?

Too many men are diagnosed late



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



**PROSTATE  
CANCER UK**

# 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 complexity of treatments

## Prostate Cancer UK's Best Practice Pathway – Prostate cancer: Treatment by risk stratification

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

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.

Risk stratification	Additional treatment combinations	Active surveillance	Surgery (prostatectomy)	Radiotherapy			Hormone therapy				Chemotherapy		Radium-223	
				External beam intensity modulated	Brachytherapy		Androgen deprivation therapy		Anti-androgen	Abiraterone	Enzalutamide	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-naïve	LHRHa and anti-androgen			●*			●	●	●	●		●		
Metastatic castrate-resistant										●	●	●	●	●

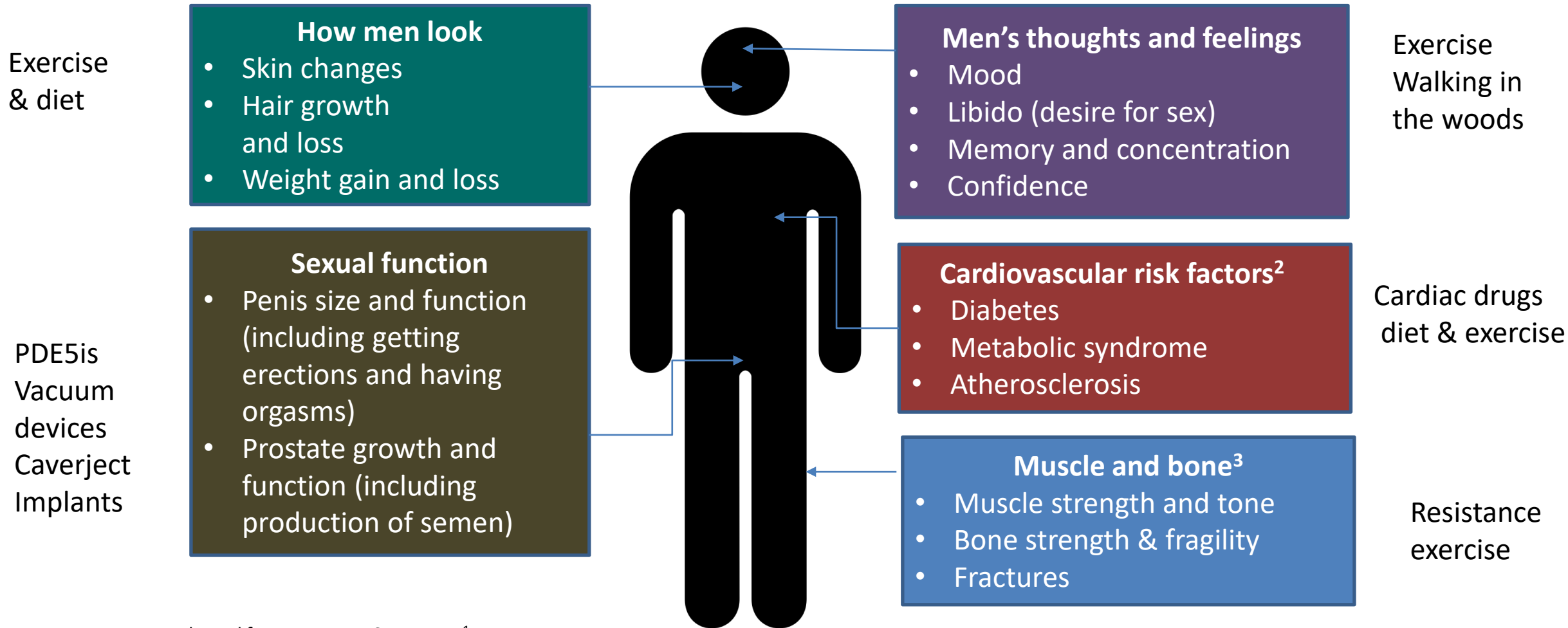
● Treatment choice   ● Optimal treatment supported by evidence   ● Optimal treatment combination supported by evidence   □ Not appropriate

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

## 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**

# ADT can impact men's health and QoL<sup>1</sup>



Adapted from: Prostate Cancer UK.<sup>1</sup>

# What you don't see: Loss of bone mineral density (BMD)

- Patients with non-metastatic PCa who receive ADT have been reported to experience significant cumulative loss of BMD of  $3.3 \pm 0.7\%$  in the lumbar spine<sup>1</sup>
- Compared with a 13% risk of fracture for healthy men, men with PCa >50 years of age have a 21–37% increase in risk of fracture<sup>2</sup>
- Consider assessing fracture risk for men on ADT (*NICE prostate guidance 2019*)<sup>3</sup>





# What you don't see: Cardiovascular health

Potential increased cardiovascular and metabolic risk with ADT as an adjuvant treatment<sup>1</sup>

- Men with prostate cancer may be at higher cardiac risk because of shared risk factors, including older age, obesity and low levels of physical activity that are associated with cardiovascular disease (CVD), diabetes and prostate cancer<sup>1-4</sup>
  - ADT has also been associated with an increased risk of diabetes and CVD
- **CVD is a leading cause of death in men living with and beyond prostate cancer<sup>5</sup>**



# Secondary prevention to reduce the risk of cardiovascular side effects?

- Important to assess comorbidities, lipid profile, blood pressure and identify 10-year predicted cardiovascular disease risk
- ESC-ICOS guideline in cardio-oncology
  - Statins (in patients at high risk for cancer therapy-related cardiac dysfunction [CTRD])
  - ACE inhibitors plus other BP lowering therapies (in patients at high risk for CTRD)
  - Refer men at high risk or who have ADT cardiac side effects to cardio-oncology
  - Aspirin + other antiplatelet therapies
  - Lifestyle intervention

ACE=angiotensin converting enzyme; ADT=androgen deprivation therapy; BP=blood pressure; ESC=European Society of Cardiology; ICOS=International Cardio-Oncology Society.

1. Lyon A, et al. *European Heart Journal*. 2022;00:1–133.

# Exercise is an important way to mitigate the cardiovascular and metabolic risks of ADT

- Resistance training and increasing physical activity can improve physical functioning and reduce fatigue in men recommended 2x a week for 12 weeks (*NICE prostate guidance 2019*)<sup>1</sup>
- In the RADAR study (N=100), 6 months of supervised exercise resulted in improved cardiorespiratory fitness, lower-body physical function, self-reported physical functioning and mental health, and muscle strength compared with standard public health recommendations on physical activity<sup>2</sup>
- True NTH exercise and diet study (N=116) of community pharmacy intervention in men with prostate cancer post-treatment. Moderate to vigorous physical activity scores increased on average by 34 minutes (95% CI 6 to 62, P=0.018) over 3 months<sup>3</sup>

# Dietary considerations

- ADT often leads to weight gain<sup>1</sup>
  - Dietary advice should emphasise Mediterranean diet with vegetables, fruits, lean protein, and whole grains<sup>\*,2</sup>
- Bone health: calcium-rich foods
  - Adequate daily calcium intake (700–1200 mg) and vitamin D 800 IU through diet, sunlight exposure and supplementation if needed<sup>3</sup>
  - Systematic review and meta-analysis of randomised-controlled trials comparing the effects of exercise and dietary interventions alone or in combination on anthropometric measures of adult cancer patients and survivors:<sup>2</sup>
    - Diet alone (mean difference [MD] -2.25kg, 95% CrI -3.43 to -0.91kg) not as effective as combination strategies (MD -2.52kg, 95% CrI -3.54 to -1.62kg) but were associated with more weight loss compared to standard care
    - All dietary interventions achieved a similar magnitude of weight loss (MD range from -2.03kg to -2.52kg)



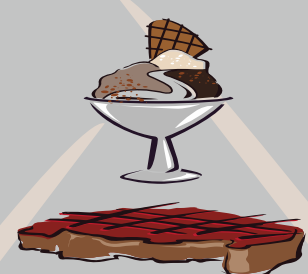
Wine  
*In moderation*



Drink Water



Meats and Sweets  
*Eat less often*



Poultry, Cheese,  
and Yogurt  
*Eat moderate portions,  
daily to weekly*



Fish, Seafood and Eggs  
*Eat often, at least two times  
per week*



Fruits, Vegetables,  
Grains (mostly  
whole), Olive oil,  
Beans, Nuts,  
Legumes and  
Seeds, Herbs  
and Spices  
*Base every  
meal on  
these foods*



Be physically active;  
enjoy meals with others

# Multidisciplinary effort: Proactive Approach

## communicate effectively with both men and primary care

- Early assessment of cardiovascular and bone health risk factors
- Consider multi-morbidity of patients in light of many potential complications of ADT
- Discuss healthy diet to maintain or lose weight
- Assess physical activity and discuss maintaining muscle strength during ADT, i.e., resistance training (e.g. sports, yoga, tai chi) to improve bone mineral density, muscle and CV fitness
- Prostate cancer diagnosis is a teachable moment to improve health and be proactively involved in prostate cancer treatment
- Inform GP and primary care team of ADT and screening for potential CVD and bone health risks

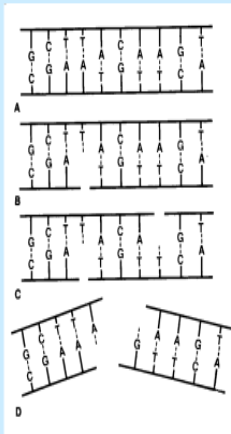
## Surgical patients do not need ADT



# RADIOTHERAPY

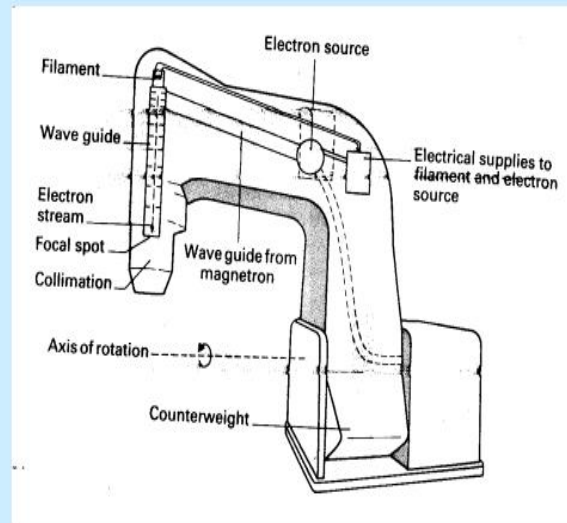
Combined RT and ADT can delay progression and improve overall survival  
Concomitant and adjuvant ADT mandatory for RT of high-risk PCa

## DNA Strand Breaks



- Major biological target is DNA.
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- Double strand breaks are lethal lesions that lead to cell death

## Isocentrically mounted Linear Accelerator



# Can medical therapy reduce the risk of cardiovascular side effects?

- Yes, in non-cancer patients
- So reasonable to presume that it does...
  - Statins
  - ACE inhibitors, plus other BP lowering therapies
  - SGLT2 inhibition
  - GLP1agonist
  - Aspirin + other antiplatelet therapies
  - Not to forget lifestyle!

## Can We Predict the Future?



**Perhaps better to look at the past!**

Video available from <http://www.youtube.com/watch?v=f32P-FLrNdY> [Accessed August 2012].





## “EXERCISE”



“An agent with lipid lowering, antihypertensive, positive inotropic, negative chronotropic, vasodilating, diuretic, and weight-reducing, cathartic, hypotensive, tranquilizing, hypnotic and antidepressive qualities.”



*William C. Roberts, M.D.  
Editor-in-Chief  
American Journal of Cardiology 1984;53:261*

# Can too much exercise be dangerous: what can we learn from the athlete's heart?

June 2021 Br J Cardiol 2021;28:95–7 doi:10.5837/bjc.2021.030

- Current evidence **cannot affirm** that high levels of exercise are dangerous, although there is an indication of diminishing mortality benefit and increased AF risk.
- **As with nearly everything in medicine, and life, exercise in moderation, may be the wise choice**

# Exercise

- Powerful potential for exercise to enhance chemotherapeutic and radiotherapeutic effectiveness.
  - To interfere with tumour-driven dysregulation of angiogenesis and osteogenesis
- And delay disease progression and extend survival.

Exercise medicine for advanced prostate cancer

Hart, Nicolas H.; Galvão, Daniel A.; Newton, Robert U. Author Information

Current Opinion in Supportive and Palliative Care: September 2017 - Volume 11 - Issue 3 - p 247-257

doi: 10.1097/SPC.0000000000000276

**Exercise is one of the most important ways to mitigate the cardiovascular and metabolic risks of ADT.**

For example, resistance exercise can prevent and even reverse adiposity in these patients.

In a year-long multicentre analysis of men starting ADT in the RADAR trial early initiation of exercise helped preserve body mass index, lean body mass, bone mineral density, fat mass, and cholesterol.

In contrast, the control group showed increased adiposity, sarcopenia, dyslipidaemia, and bone loss.

## Exercise is one of the most important ways to mitigate the cardiovascular and metabolic risks of ADT.

- In a single-centre study, men receiving ADT who exercised 3x weekly for 12 weeks lost an average of 2cm in waist circumference, while non-exercising controls gained an average of 0.7 cm.
- Notably, none of the exercisers developed metabolic syndrome, compared with 8% of controls

Dorff TB, Gross ME, Quinn DI, et al. Impact of resistance exercise on metabolic syndrome (MetS) parameters in men receiving androgen deprivation therapy (ADT) for prostate cancer. J Clin Oncol. 2017;35(suppl 6):abstr 223.



**“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”**



# Results: Prostate Cancer-specific mortality

- **Statistically significantly lower mortality rates found in men who:**
  - walked/cycled  $\geq 20$  min/day (**HR 0.61**; 95% CI, 0.43-0.87)
  - or
  - exercised  $\geq 1$  hr/wk (**HR 0.68**; 95% CI, 0.48-0.94)

# Advice BUT:

Four in five cancer patients said their GPs, oncologists and clinical nurse specialists did not speak to them about the importance of being physically active, according to Macmillan Cancer Support research.

1,098 cancer patients - 37% not physically active at all

September 2012



# Physical activity could reduce cancer incidence by as much as 85%



Tobacco, alcohol, and poor diet  
account for >50% of all cancer deaths

# Time to start ?



- Cohort 2205 Swedish men 50yrs in 1970-3 followed for 35yrs
- **Increased activity in middle age** is eventually followed by a **reduction in mortality**. (after 5-10yrs)
- Relative rate reduction 32% for high & 22% for medium activity
- **Reduction in mortality is equivalent to stopping smoking**  
**(0.51 0.26-0.97)**

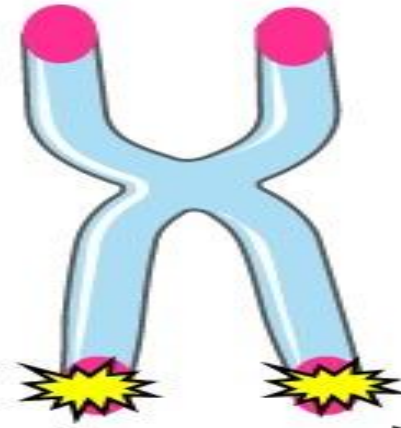
**Inflammation & Oxidative Stress**



reduction in oxidative stress.



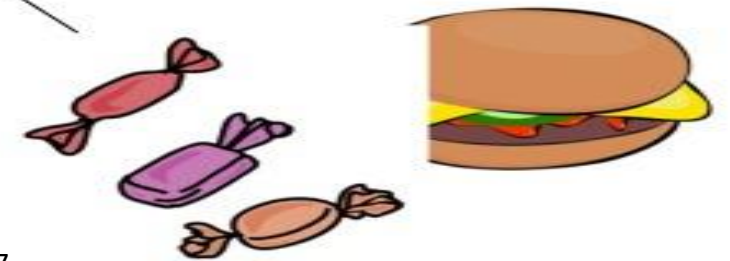
antioxidants that neutralize free radicals



**Potential influence of physical activity and nutrition on telomere health.**



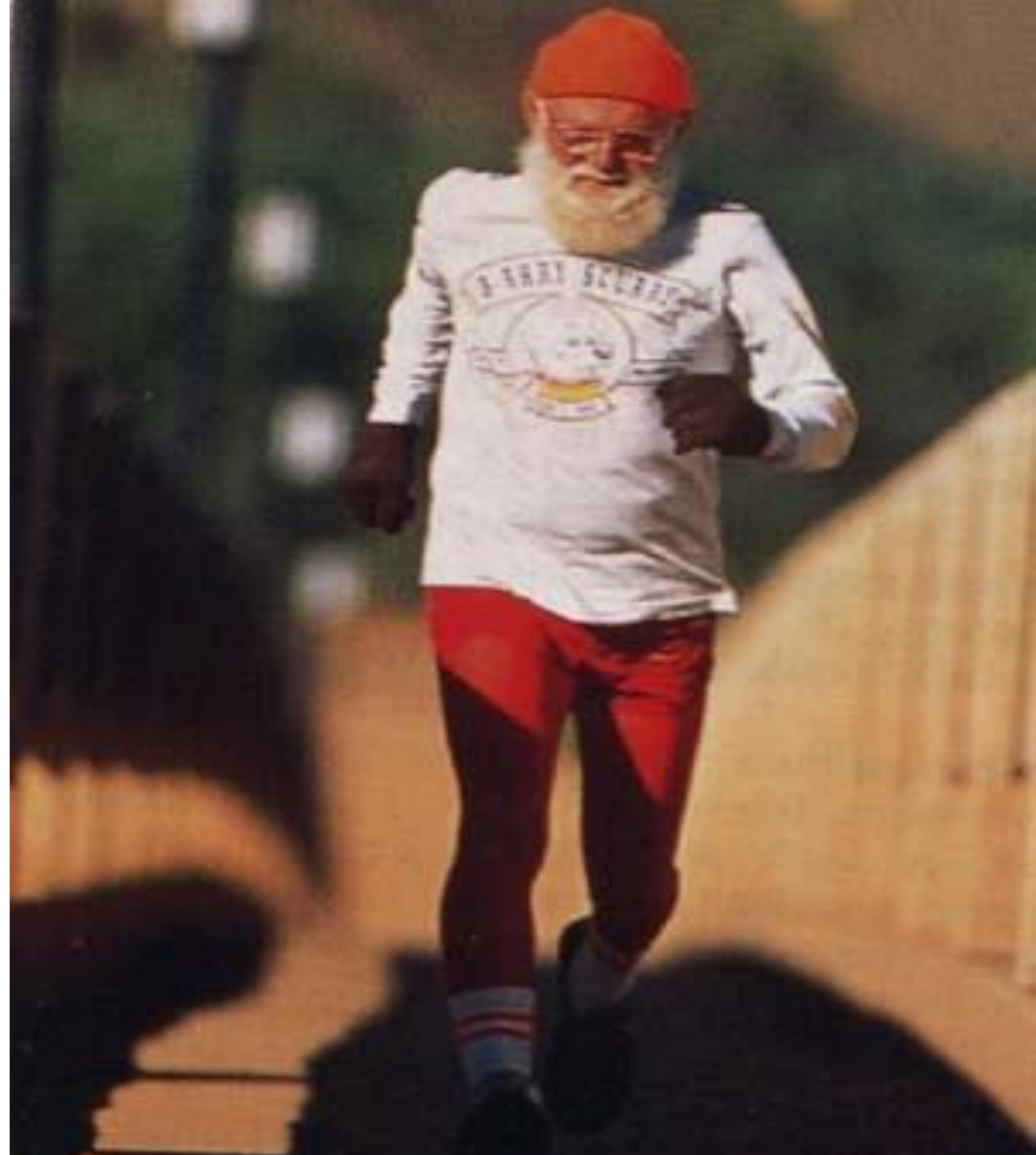
Balan E, Decottignies A, Deldicque L. Physical Activity and Nutrition: Two Promising Strategies for Telomere Maintenance?. *Nutrients*. 2018;10(12):1942. Published 2018 Dec 7. doi:10.3390/nu10121942



excess free radical production

# For everyone ???

- Perhaps not!!!!
- What do you want to do?
- What do you need to do?
- What are your cardiac risk factors?
- What are your orthopedic risk factors?





- ADT often leads to weight gain, dietary advice should emphasize vegetables, fruits, lean protein, and whole grains.

Evidence supports this approach:

- In a small, single-blind, randomized controlled pilot trial of men receiving ADT for prostate cancer, a 12-week intervention consisting of improved diet and group-based cognitive behavioural therapy led to significant improvements in muscle strength, body composition, and mobility.

Focht BC, Lucas AR, Grainger E, et al. Effects of a group-mediated exercise and dietary intervention in the treatment of prostate cancer patients undergoing androgen deprivation therapy: results from the IDEA-P trial. *Ann Behav Med* 2018 Apr 19;52(5):412-428.

# Mediterranean Diet Pyramid

*A contemporary approach to delicious, healthy eating*

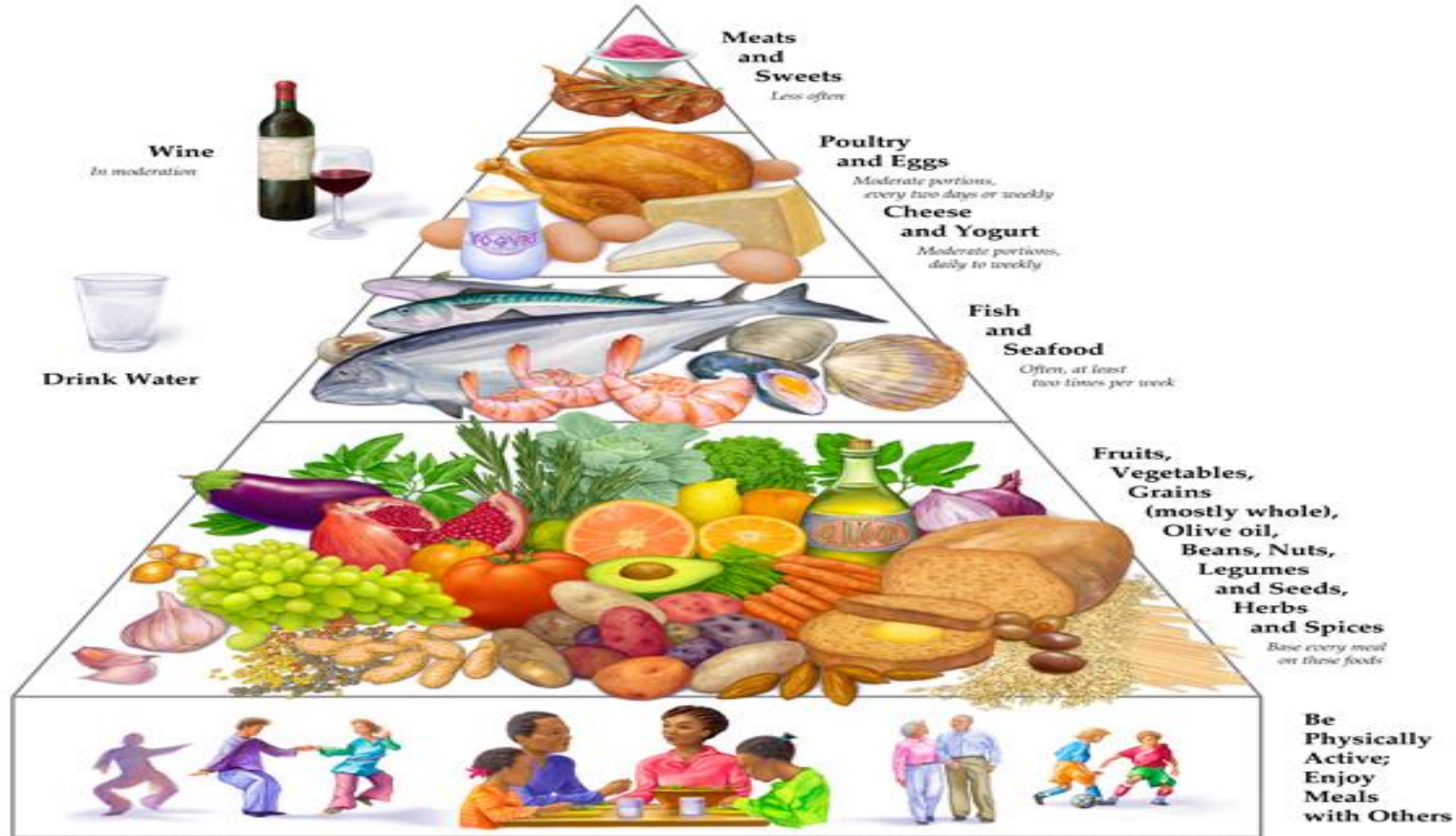


Illustration by George Middleton

© 2009 Oldways Preservation and Exchange Trust [www.oldwayspt.org](http://www.oldwayspt.org)

## Multidisciplinary effort: Proactive Approach to maintain body form

- Early consultation with dietician
- Discuss healthy diet to maintain or lose weight
- Snacking strategies
- Recommend daily calcium and vit D intake
  
- Step counter
- Physical therapist or personal trainer
- Aerobic exercise routines
- Resistance exercises



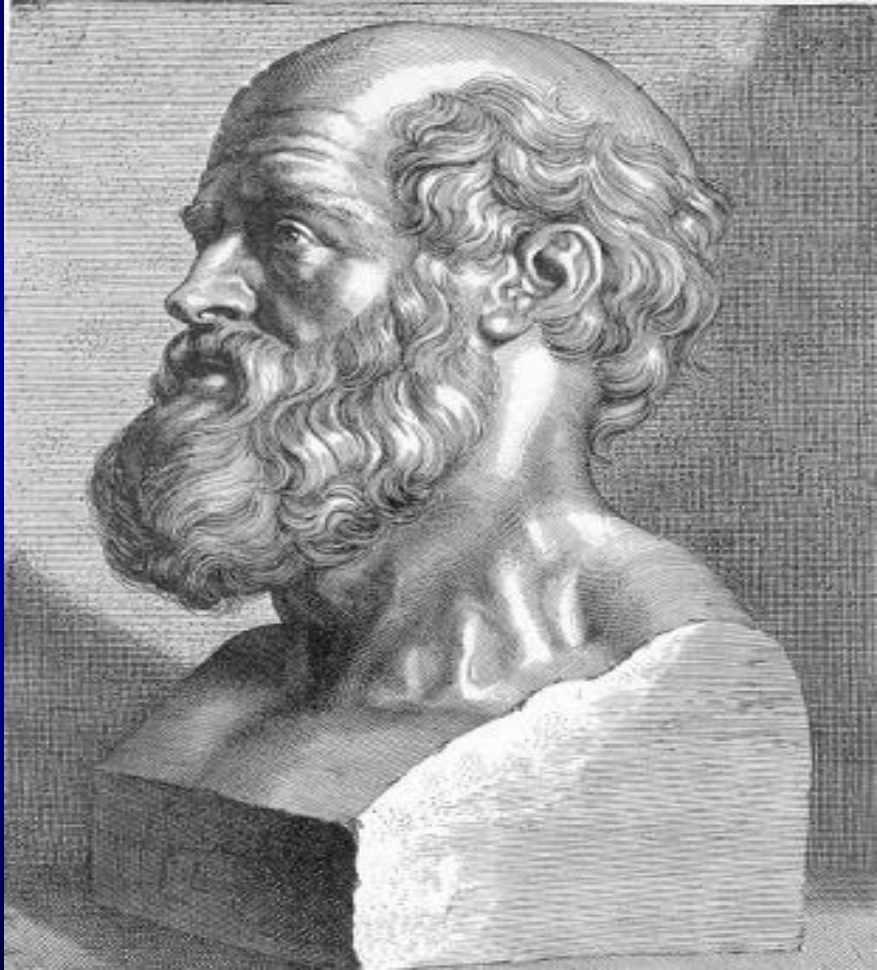
# ABCDE approach

- **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

Try to follow these ABCD steps, knowing your numbers: **blood pressure, do you smoke, what is your cholesterol, do you know your glucose level or diabetes control, and do you exercise.**

**These are steps that we can all intervene on, particularly cancer survivors.**

## 'Prescription for Prevention'



- **Hippocrates, the Father of Medicine, said nearly 2,400 years ago,**
  - "If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health."



