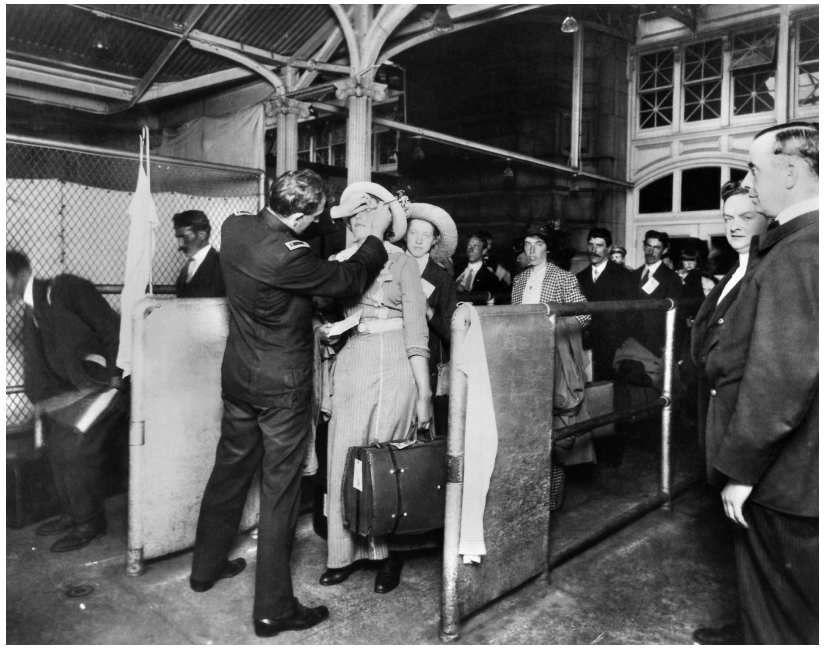
Screening. When it useful, when is it not?

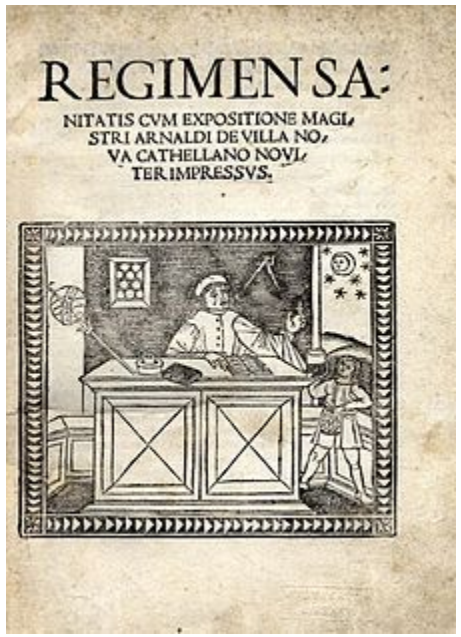


Christopher Whitty

Gresham College 2021

Screening.

- Curative medicine has historically depended on people with symptoms coming forward for diagnosis.
- Alongside that a long tradition of preventing disease through diet, sanitation, exercise.
- Screening lies between these two.



Regimen sanitatis Salernitanum, 1480

Scuola Medica Salernitana, from Avicenna's Canons.

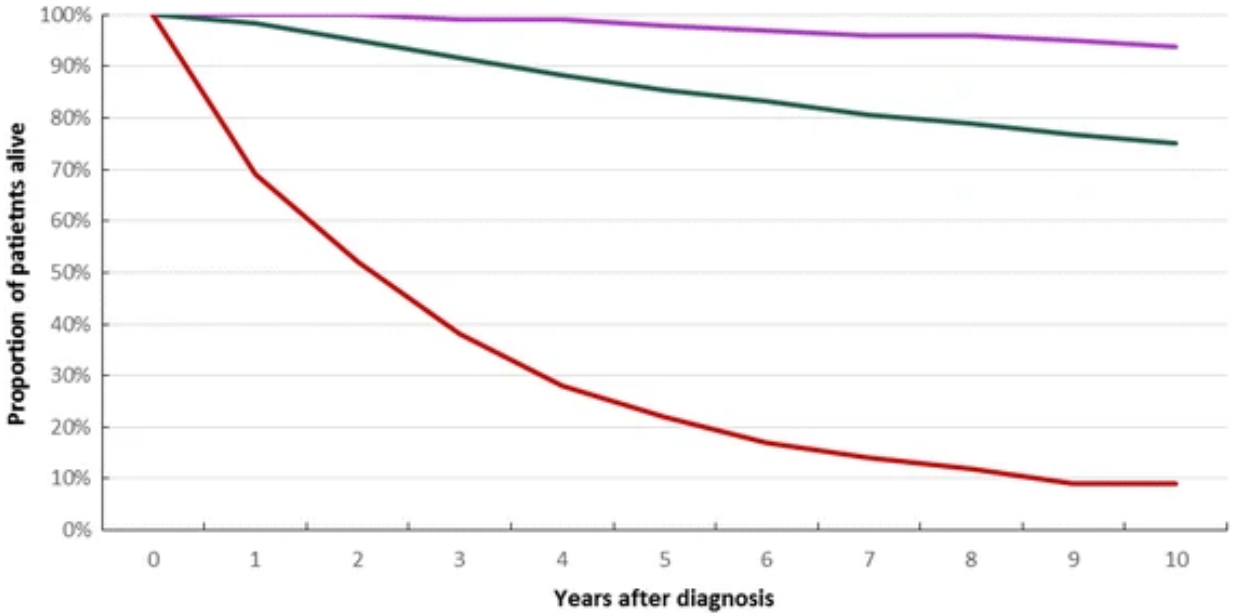
Many diseases have a much better outlook if identified early.

- Most cancers, including:
- breast
- prostate
- lung
- bowel cancer.

- Many genetic diseases.

- Predisposing factors for disease.

10 year survival for early, advanced and metastatic breast cancer.



Vondeling G et al *BMC Cancer* 2018. Dutch data.

5 year net survival by stage at diagnosis. (CRUK, rounded data)

	Stage 1	**Stage 2**	**Stage 3**	**Stage 4**
Breast cancer*	98%	90%	71%	28%
Prostate cancer	100%	100%	96%	48%
Lung cancer	57%	34%	13%	3%
Bowel cancer*	92%	84%	65%	10%

For most diseases screening is currently not a good idea.

To be an exception:

- Serious disease;
- Which we can diagnose reliably

and safely (and cheaply);

- And prevent or treat effectively

and safely relative to risk

- Which is reasonably common;
- With a sufficiently long time from flash-to-bang you can intervene.

Wiki

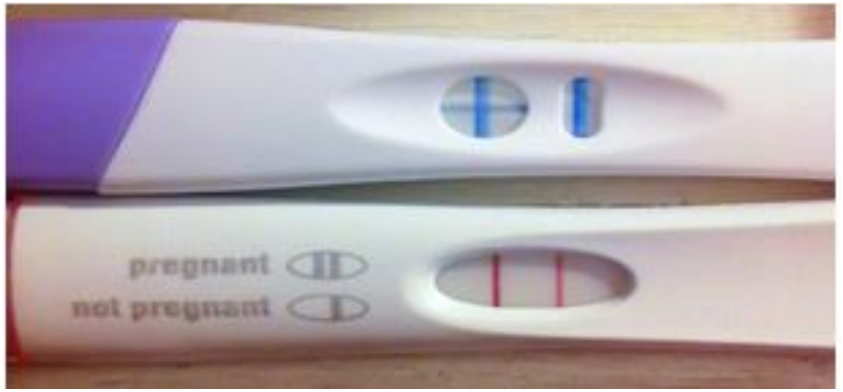
For the diagnostic step in screening the practical question is what is the risk of a false positive or false negative test.

- A false positive result means you will have a procedure or treatment which you do not need.
- A false negative result means you will be incorrectly reassured.

	Have disease	No disease
Test positive	True positive	False positive
Test negative	False negative	True negative

Diagnose reliably… sensitivity and specificity of test or screening tool.

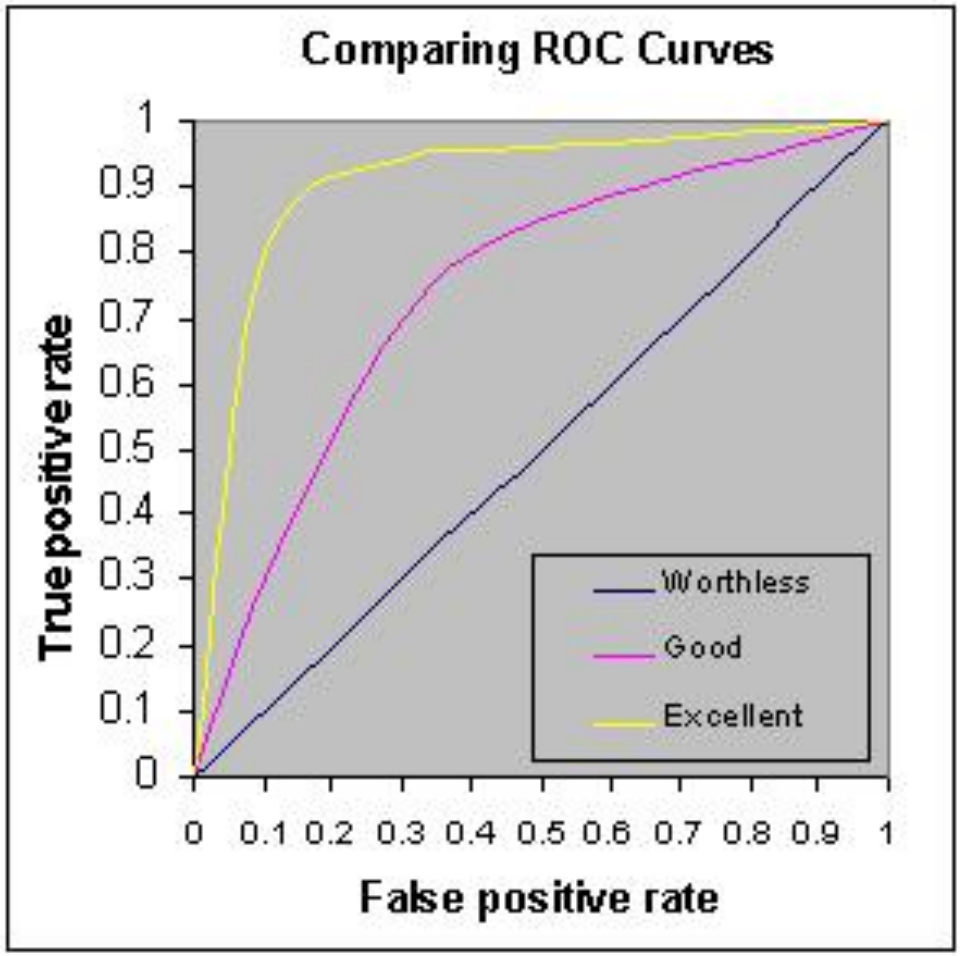
- Sensitivity: percentage of true positives the test detects.
- E.g.- ECG is around 50% sensitive for ischaemic heart disease with chest pain.
- Specificity: percentage of true negatives the test detects.
- MRI is about 80% specific for diagnosing multiple sclerosis.
- Very few tests have both 100% sensitivity and specificity. Some come close.



There is generally a tradeoff between sensitivity and specificity.

- For most tests, if you make them more sensitive they become less specific.
- Improving the test reduces the tradeoff.

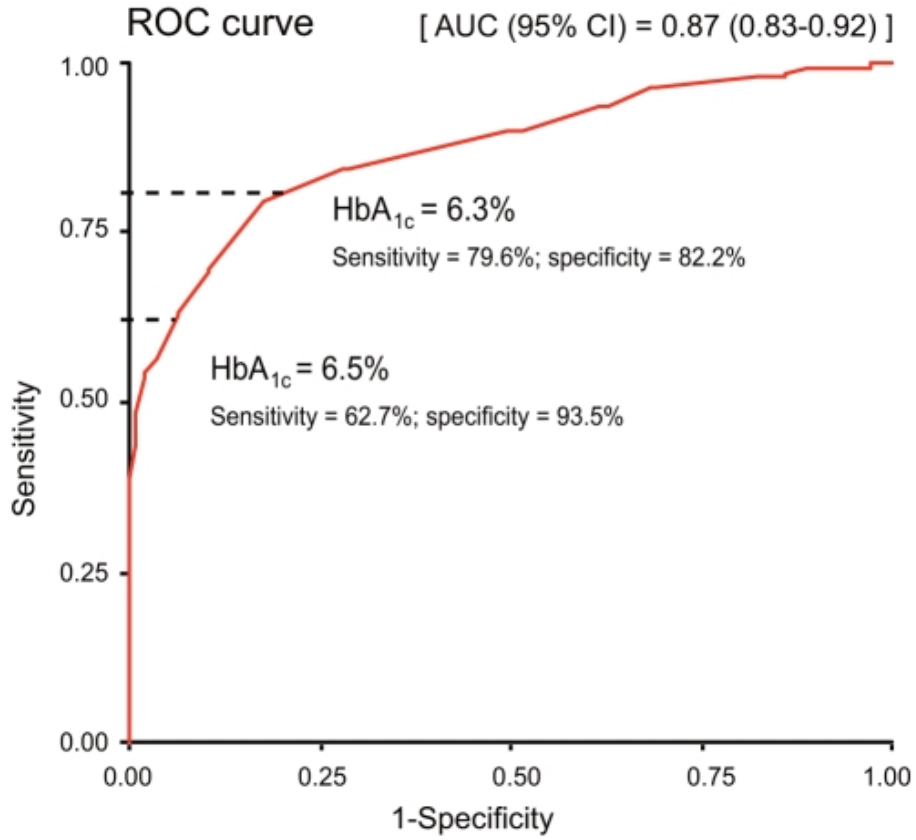
- What is more important? Not missing a true case, or not diagnosing false positives?
- Depends on the clinical situation.



An example: screening for diabetes.

- HbA1c is a standard screening tool for diabetes.
- If you set the cutoff at 6.3%, sensitivity 80%, specificity 82%.
- Miss 20%, and overdiagnose 18%.

- If you set the cutoff at 6.5% sensitivity 63%, specificity 94%.
- Miss 37% people, overdiagnose 6%.



Wang et al 2018 (Chinese population, against OTT)

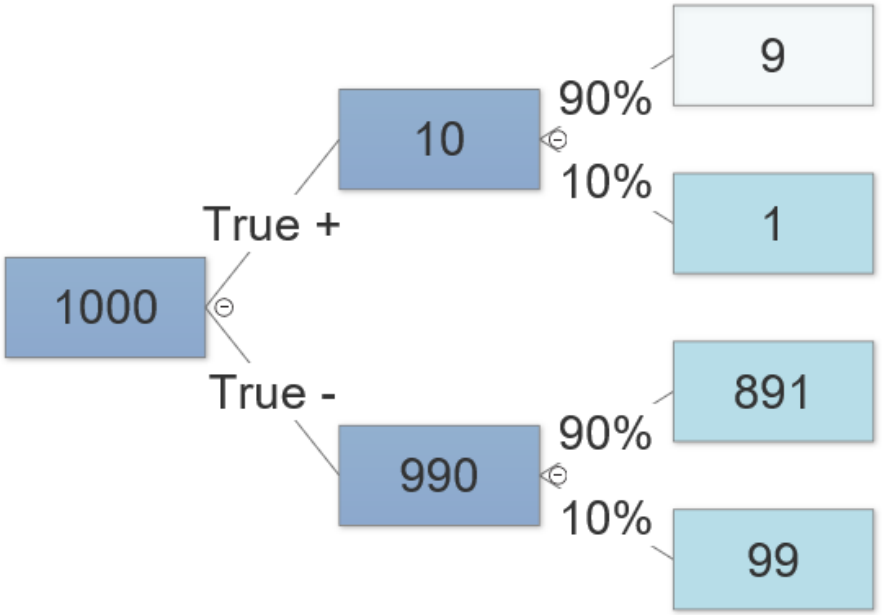
Bayesian statistics- the importance of prior probability.

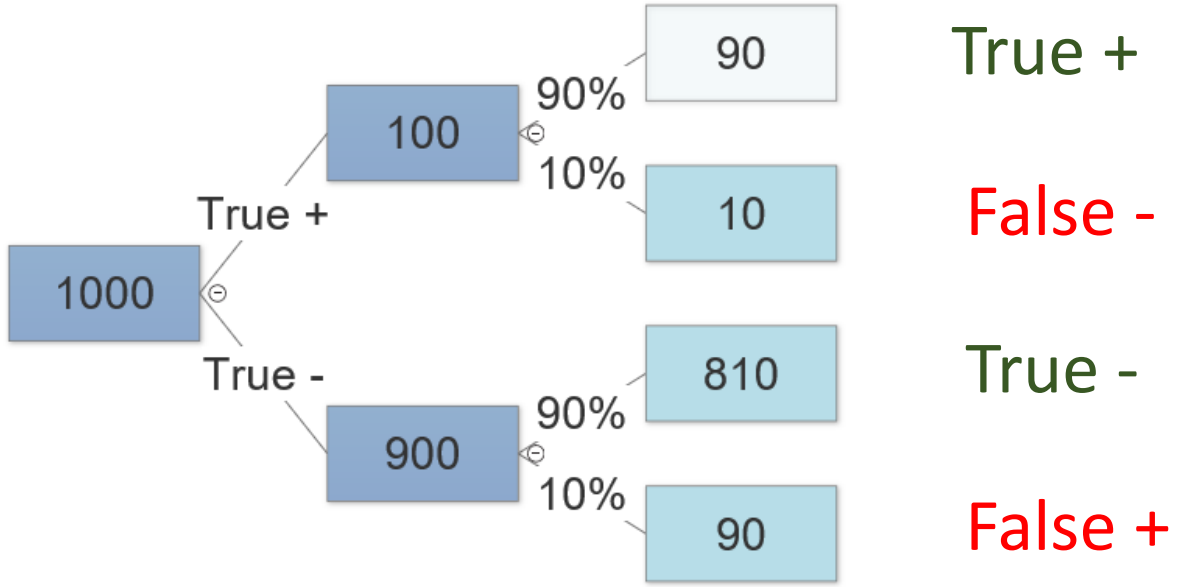
- The mathematical proof that if you ask a silly question, you get a silly answer.
- If it is unlikely before the test, it is still unlikely even if the test is positive (unless the test 100% specific).
- Pre-test probability very important- as important as how good the test is.

Rev Thomas Bayes FRS 1701-1761.
Tunbridge Wells. Prob. not a real likeness.

Sensitivity 90% and specificity 90%.

Positive predictive value (PPV), negative predictive value (NPV).



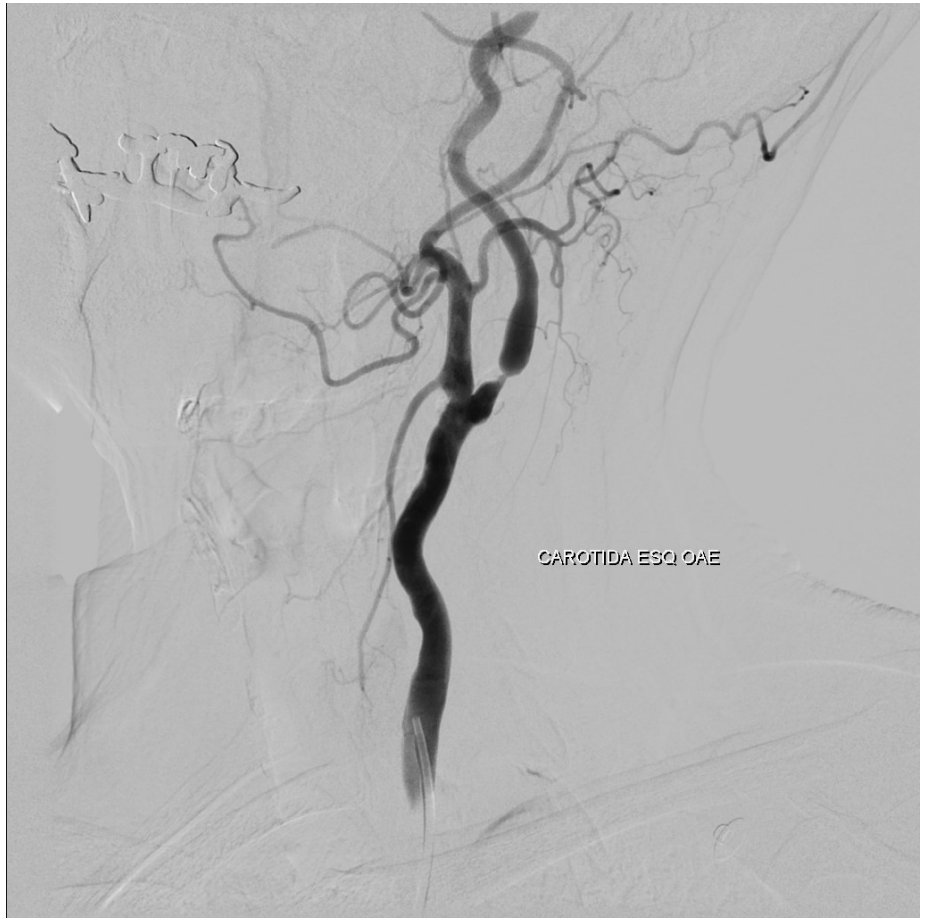


Prevalence 1%,
PPV 8% (9/108), NPV>99%

Prevalence 10%,
PPV 50% (90/180), NPV 99%

Many treatments, and some diagnostic tests, can do harm.

- All of medicine is a risk of treatment v risk of no treatment judgement.
- If you treat someone with no benefit from treatment (false positive) you only get the risk of treatment.
- An example carotid stenosis surgery to reduce stroke.



Dr Bruno Di Muzio, Radiopaedia.org

Medicalisation of otherwise healthy people.

- As a minimum turns a previously healthy person into a ‘medical case’ to be followed up.

- Often causes worry.
- And sometimes overtreatment.

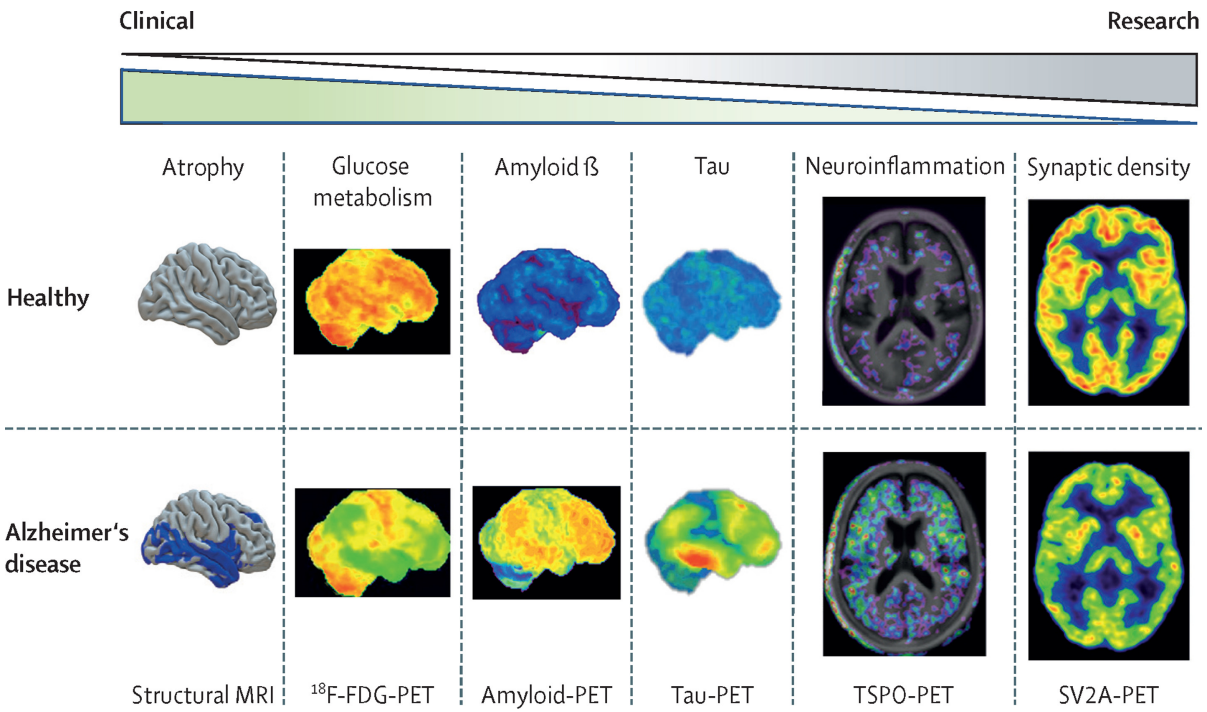
- And in the case of infectious diseases can cause stigma.

NIH/Wiki

Whether screening is a good idea for a disease is not static.

- Changes to the sensitivity, specificity, safety (and cost) of the test.
- Changes to the effectiveness, safety (and cost) of prevention or early treatment.
- Changes in epidemiology of the disease.

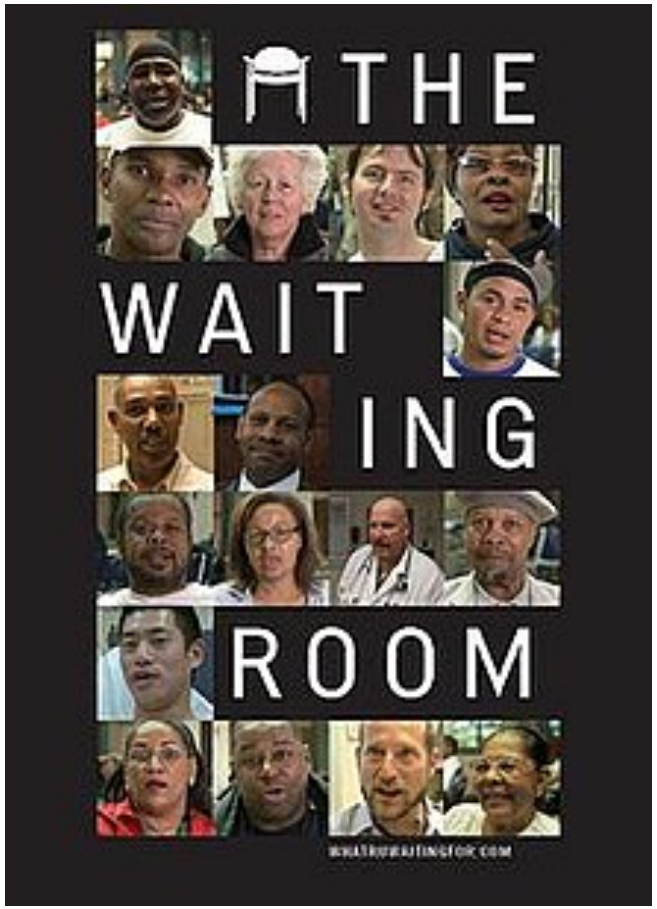
- Should we screen for pre-symptomatic Alzheimer's?



Chételat G et al *Lancet Neurology* 2020

Risk stratification.

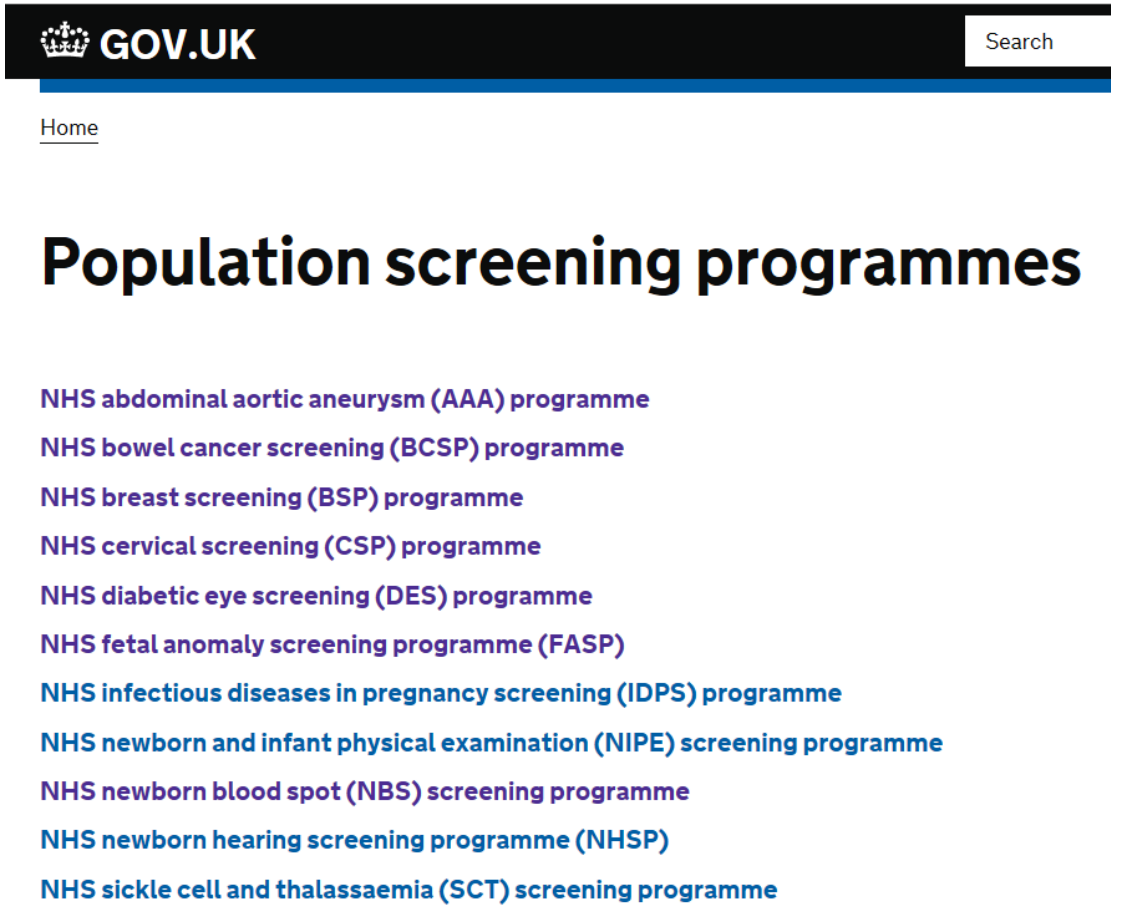
- The key to most screening is risk-stratification.
- The higher the pre-test probability the more accurate the screening.
- The greater the disease risk the greater the justification of side effects of treatment.
- Age, gender, ethnicity.
- But also smoking, SES, occupation etc.



Documentary *The Waiting Room*.

Current UK national screening.

- Some antenatal. Major fetal abnormalities.
- Immediately postnatal- genetic abnormalities where treatment prevents lifelong ill health.
- National screening in adults.
- Screening in high-risk groups.
- ‘Health checks’ and other opportunistic GP screens.



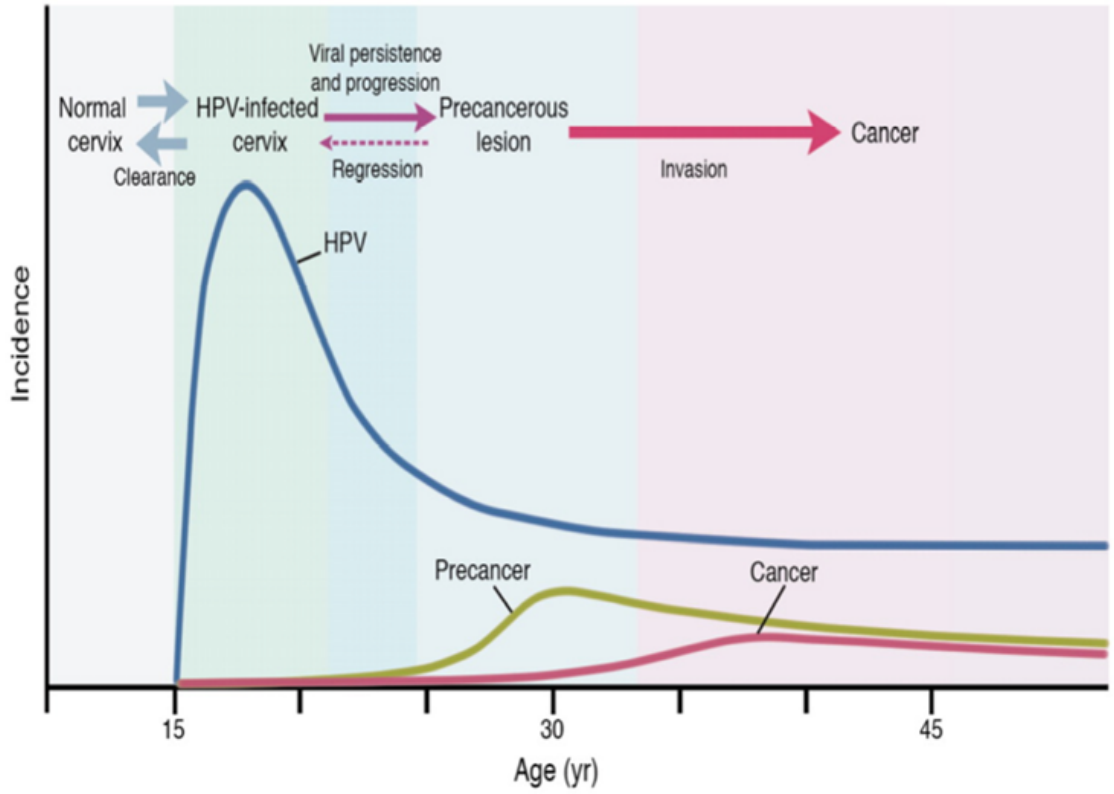
It is often said that screening prevents disease.

- Actually many screening programmes are to prevent *progression* of disease.
- 4 general national screening programmes in adults:
- Cervical screening
- Breast screening
- Bowel screening
- Aortic aneurysm

Cervical screening.

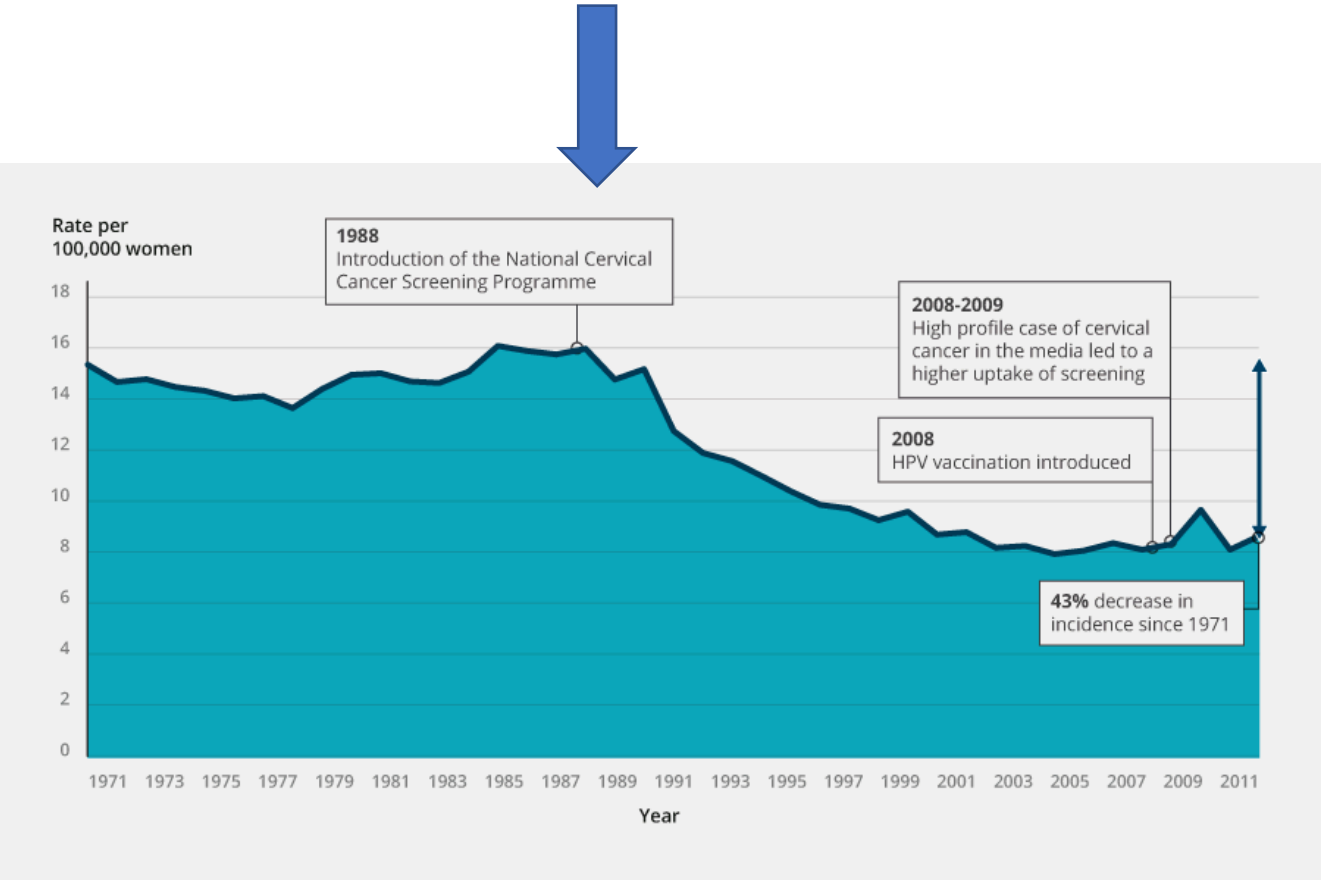
- Over 3000 cervical cancer cases a year in UK. Commonest cancer of young women.

- Women aged 25 to 49 are offered screening every 3 years; those aged 50 to 64 are offered screening every 5 years.



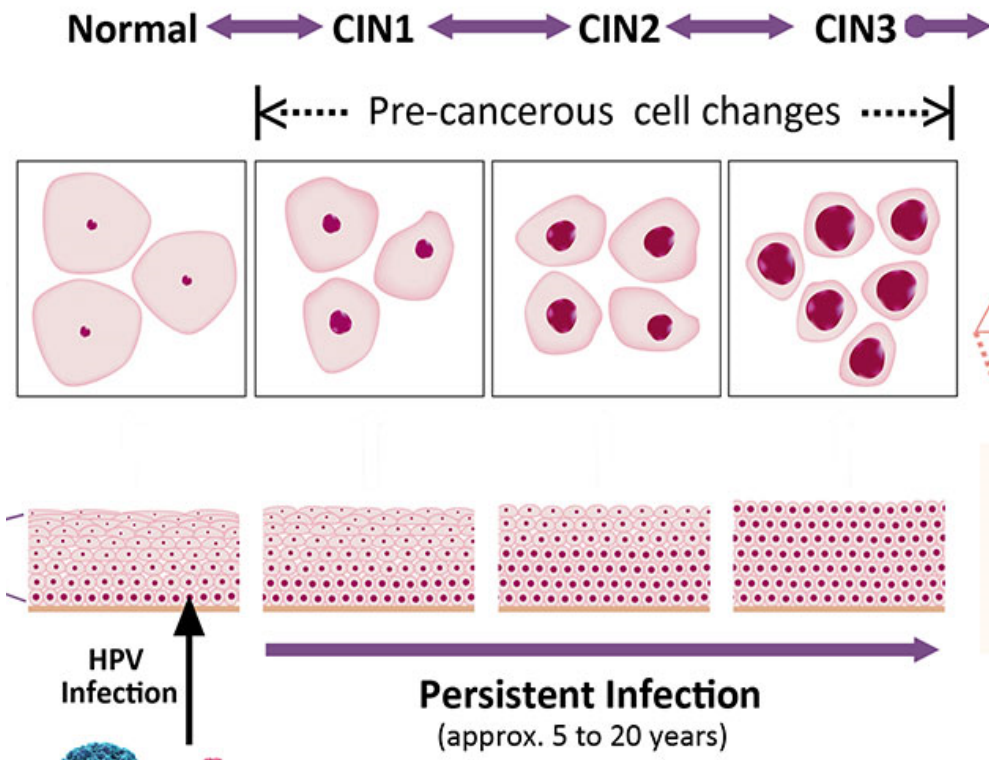
Screening of women in UK 1988.

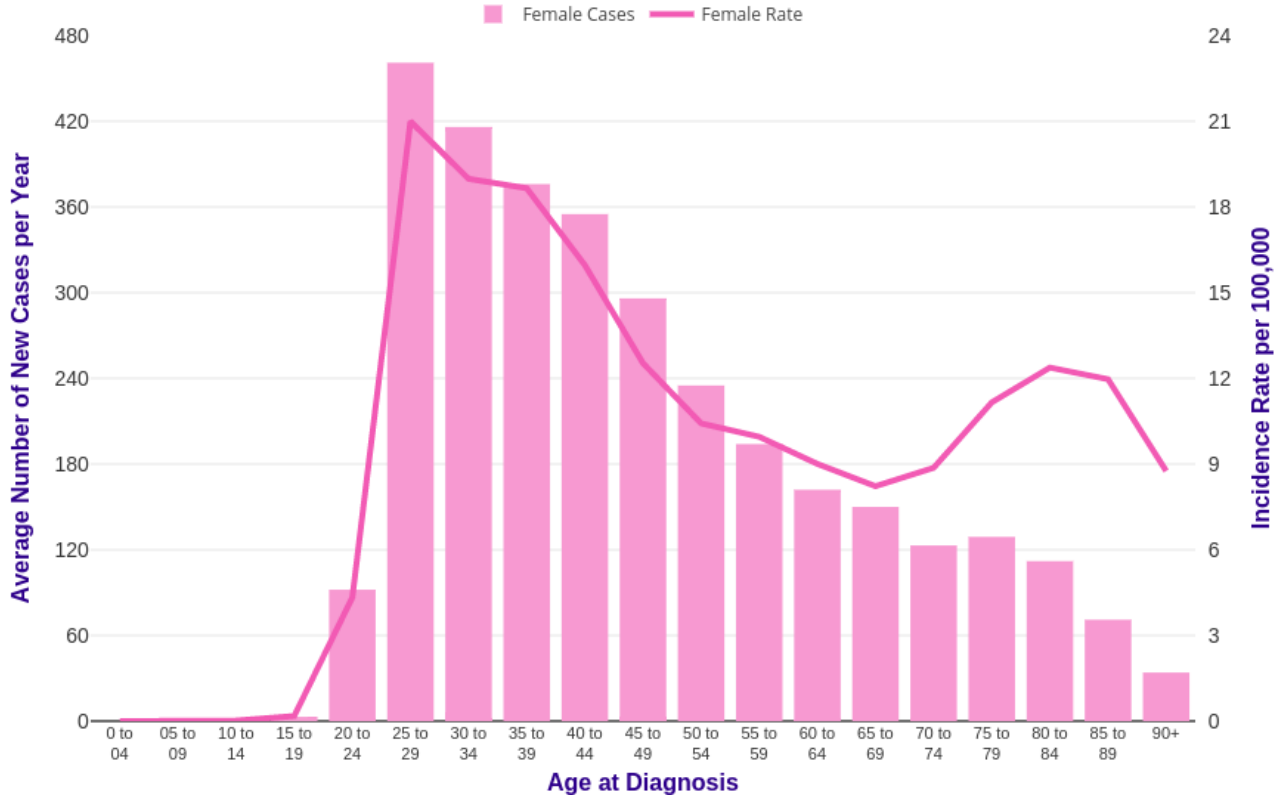
- Has led to a substantial reduction in cervical cancer- 30-40% in UK (ONS).
- Saves at least 2000 lives a year in the UK.
- New primary HPV DNA tests from last year (UK) improve accuracy. Around 20% less cancer possible.



Rate/100,000 women since 1970

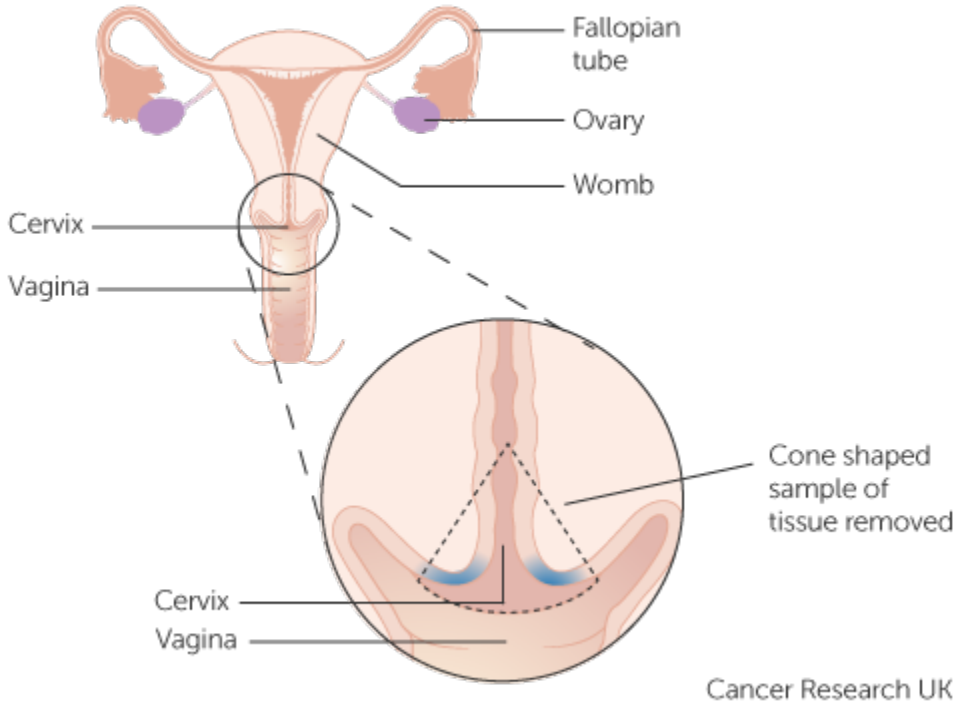
Unlike most cancers HPV decreases with age. There is a clear, and fairly easily diagnosable pre-cancerous state. UK data.





What are the downsides? It's a balance of risk and benefit.

- The less advanced the cells the less invasive the treatment.
- The less advanced the cells, the less certainty they will progress.
- Early identification leads to over-treatment with relatively low-risk procedures.
- Later identification higher risk and some unnecessary adverse outcomes but more will progress.
- Late identification- surgery- e.g. hysterectomy.
- Very late- it has spread. Major treatment.

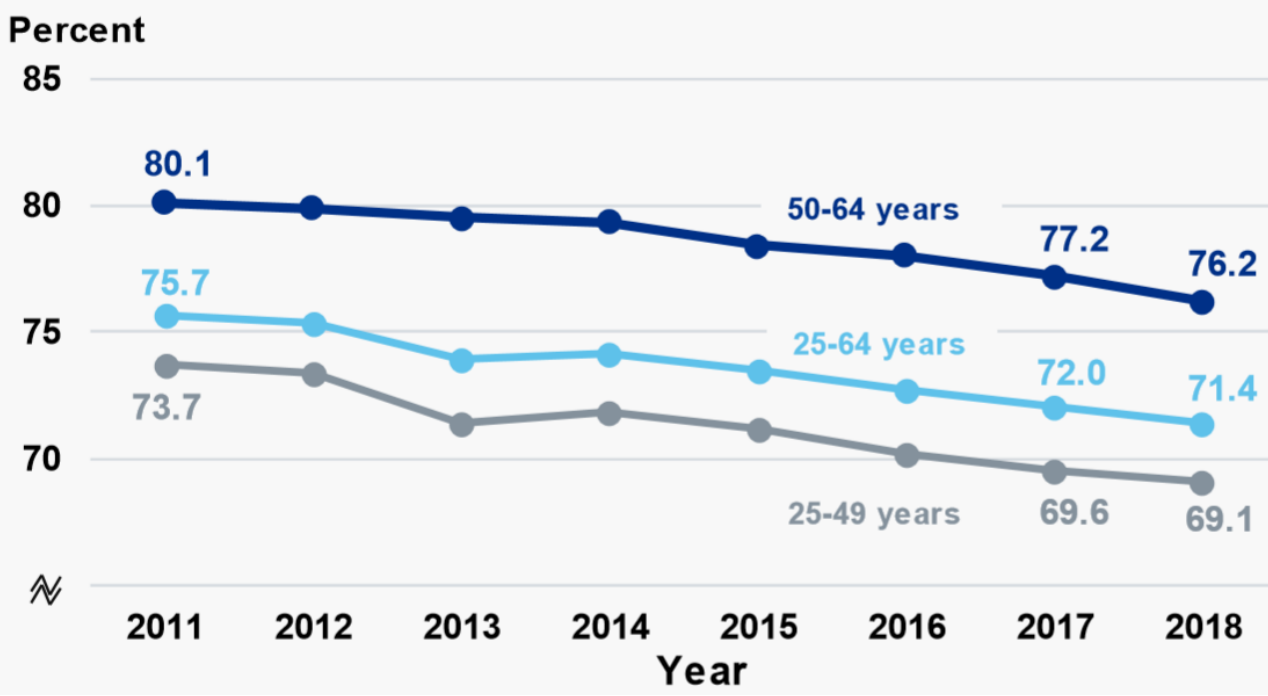


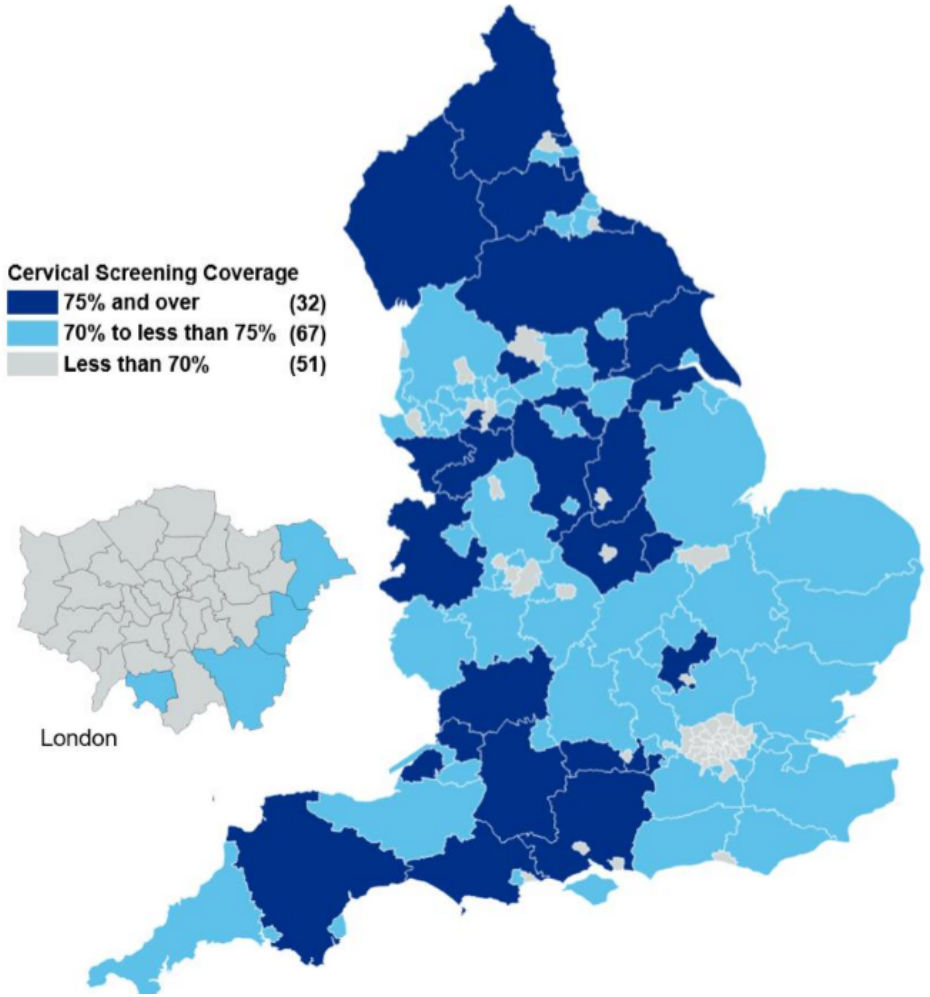
Both the test, and the epidemiology are changing.

- HPV16 and 18 responsible for 50-70%.
- Vaccines are over 95% effective against these if before sexually active.
- UK coverage of girls 89%. Likely to reduce cervical cancer by 50% or more.
- New vaccine covering HPV 31, 33 and 45 will extend protection.

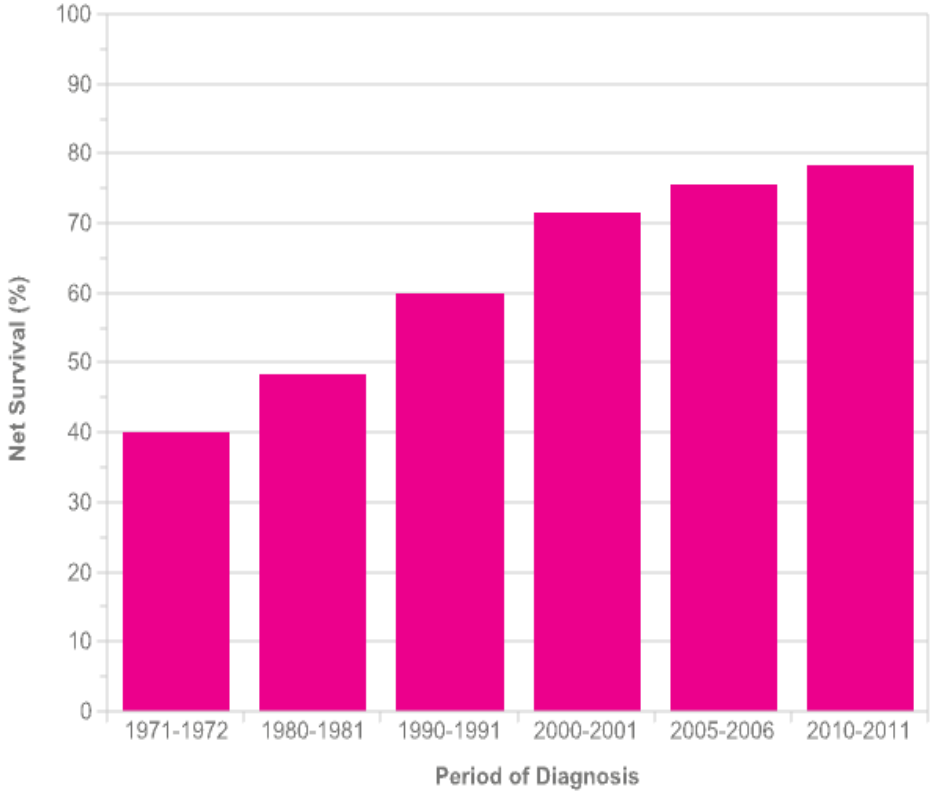
- Move over to HPV DNA testing. Will reduce overtreatment.

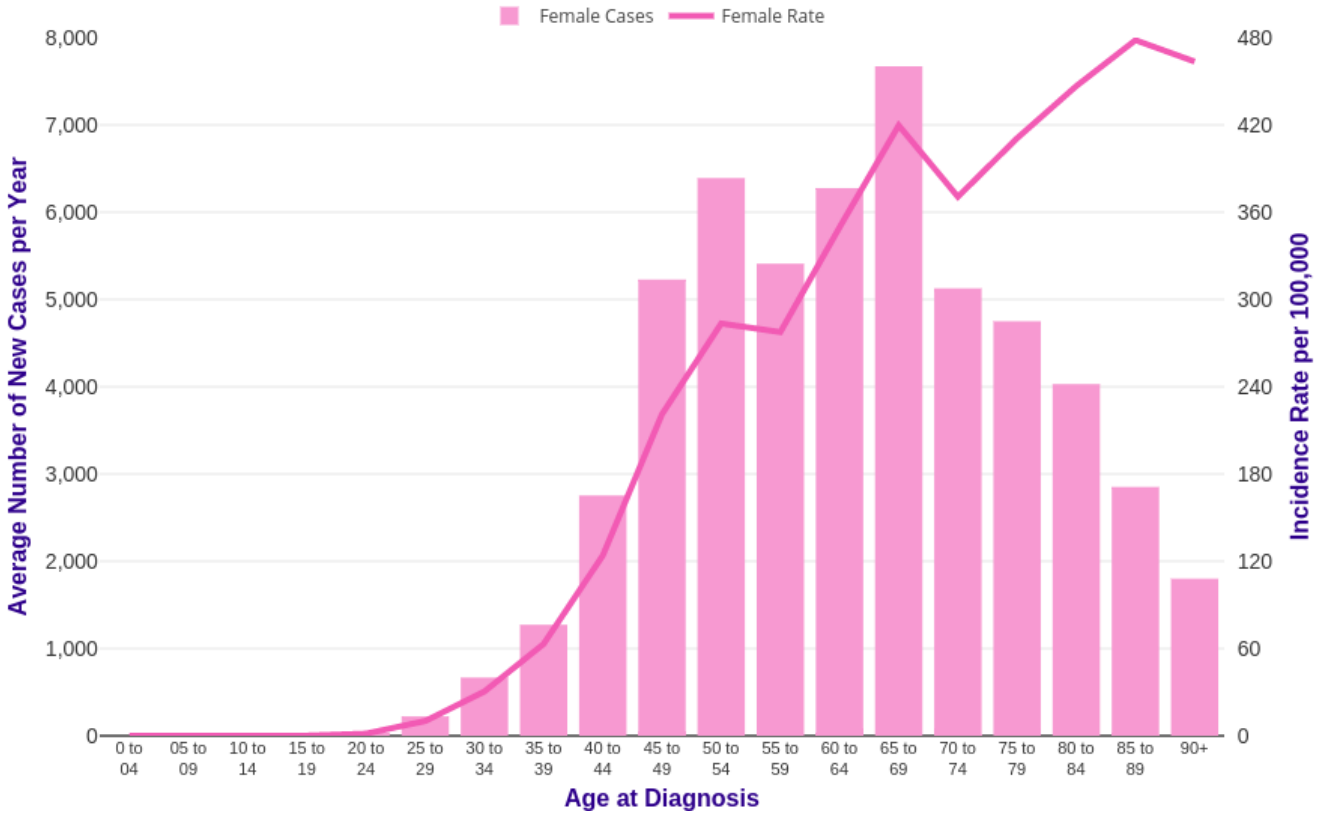
Cervical screening rates are declining in England. London has a particular problem. *NHS Digital*





11,500 breast cancer deaths a year UK, 55,000 cases. 10-year survival over time (L), age profile (R).

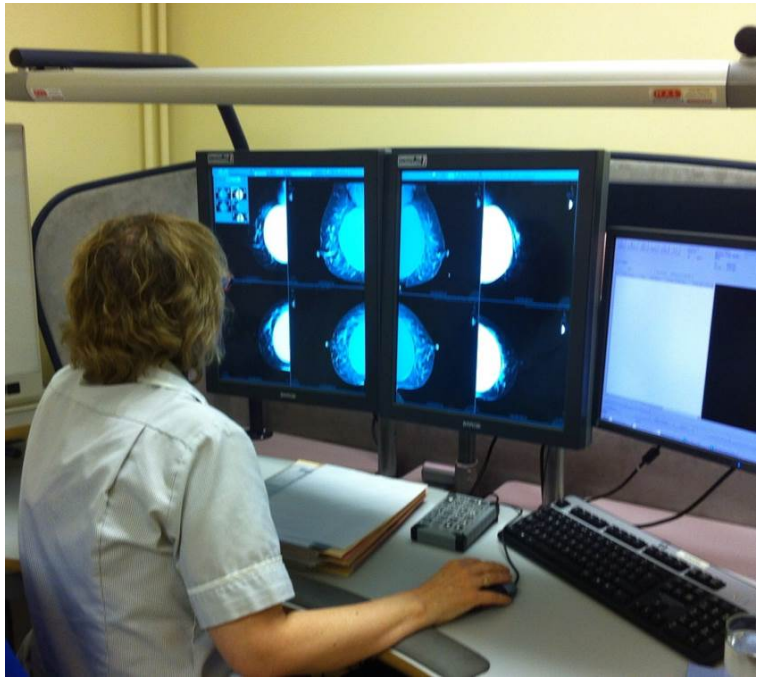




CRUK

Breast screening.

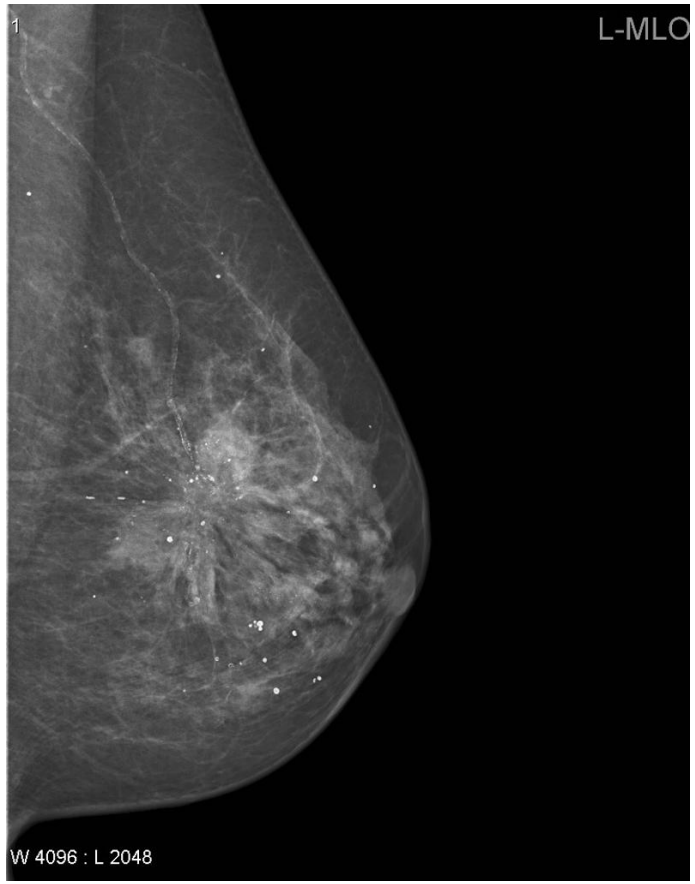
- Benefit of breast screening catching early cancers.
- Risks: overdiagnosis, over-treatment, worry.
- In current breast cancer screening benefits thought greater than risks in those aged over 47 (NICE).
- Women screened 50-70 every 3 years.
- In England breast cancer detected in around 8 per 1000 women screened.
- Around 1.5 million screens pa, estimate 1,300 lives saved.



PHE.

Imaging for breast cancer: mammogram, MRI, ultrasound.

- Mammography remains the best screening modality.
- MRI more sensitive but can lead to more unnecessary procedures. Better in dense breasts.
- Ultrasound useful for suspicious areas, lumps that do not show up, or to guide biopsy.



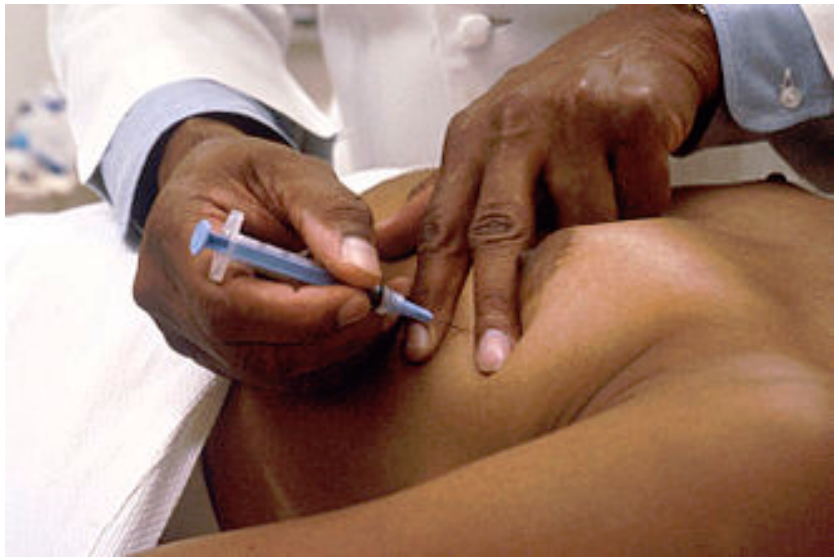
Courtesy Dr Henry Knipe, Radiopaedia.org

Some numbers: meta-analyses of trials of breast screening 40-70.

Meyers et al JAMA 2015; CRUK data.

At 13 years:

- RR of reduced mortality from screening 0.8 for UK data.
- RR 0.82 Canadian, RR 0.81 Cochrane.
- So a relatively consistent 20% reduction breast cancer mortality.
- For every 10,000 UK women aged 50 years invited to screening for the next 20 years, 43 deaths from breast cancer would be prevented and 129 cases of breast cancer overdiagnosed.



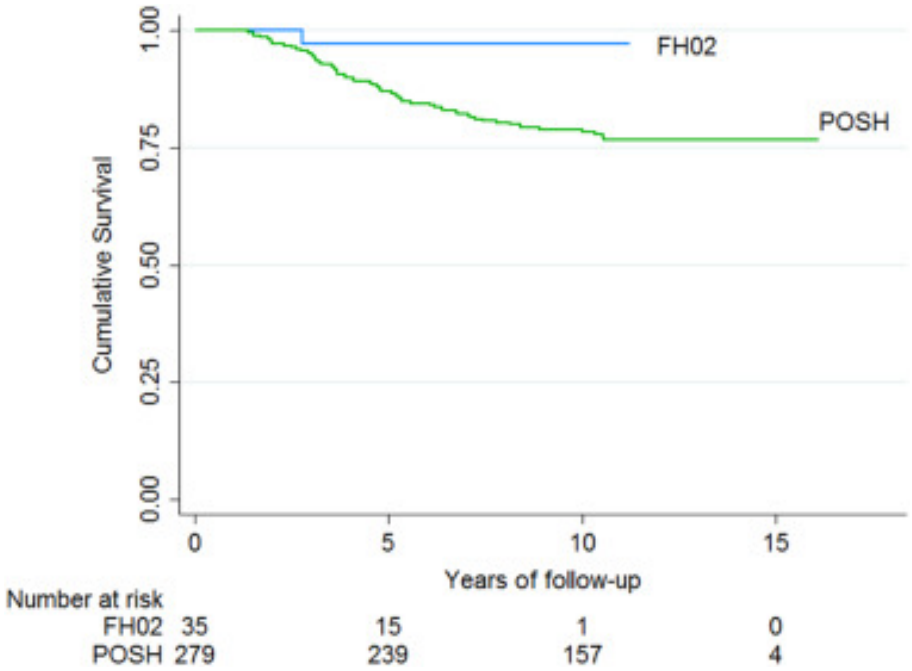
FNA. NCI

Age extension studies for those under 50 and over 70.

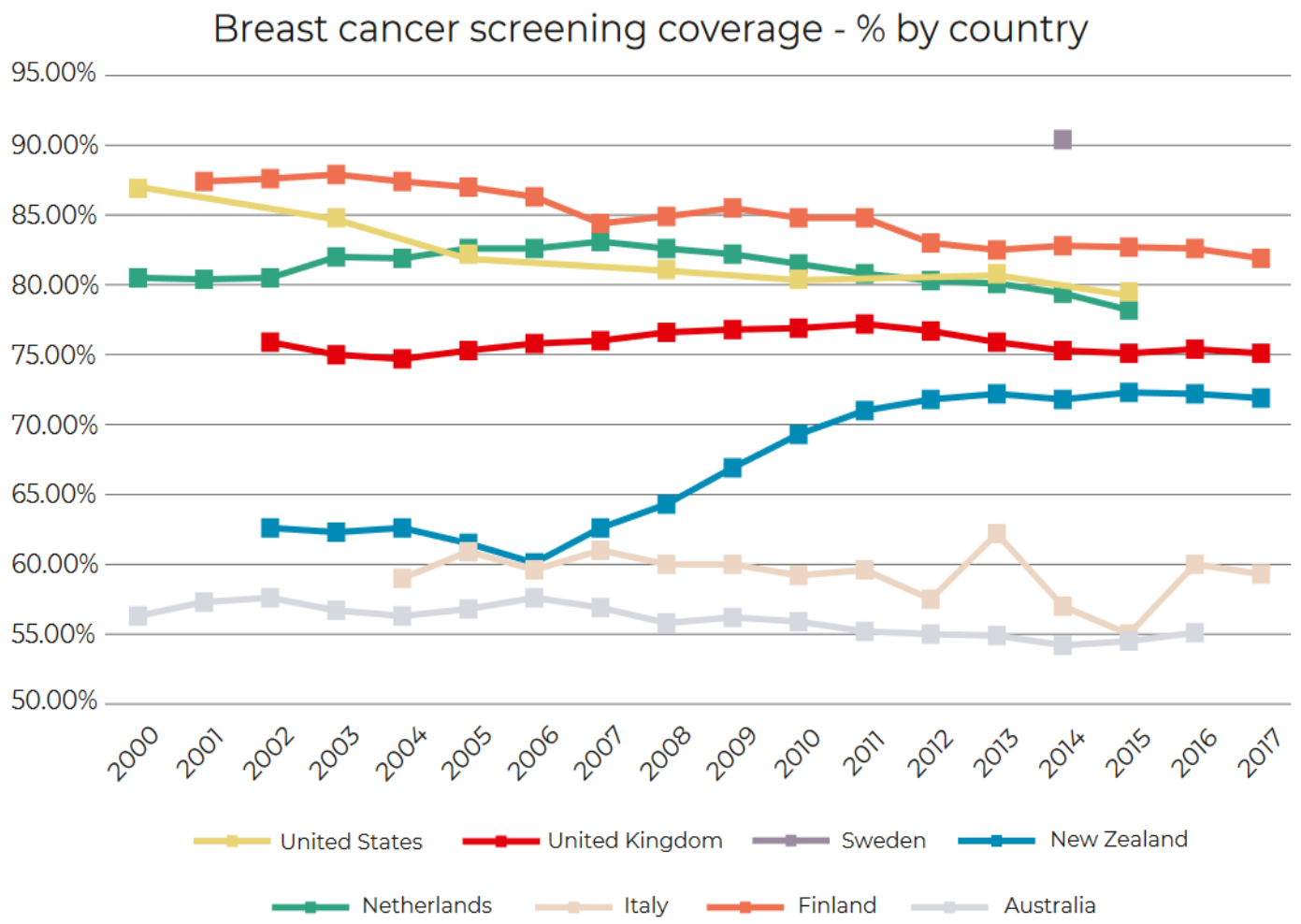
FH02 study, Evans et al E-Lancet. NIHR.

- Agex study: women 47-50 and 70-73 being enrolled. Large trial.

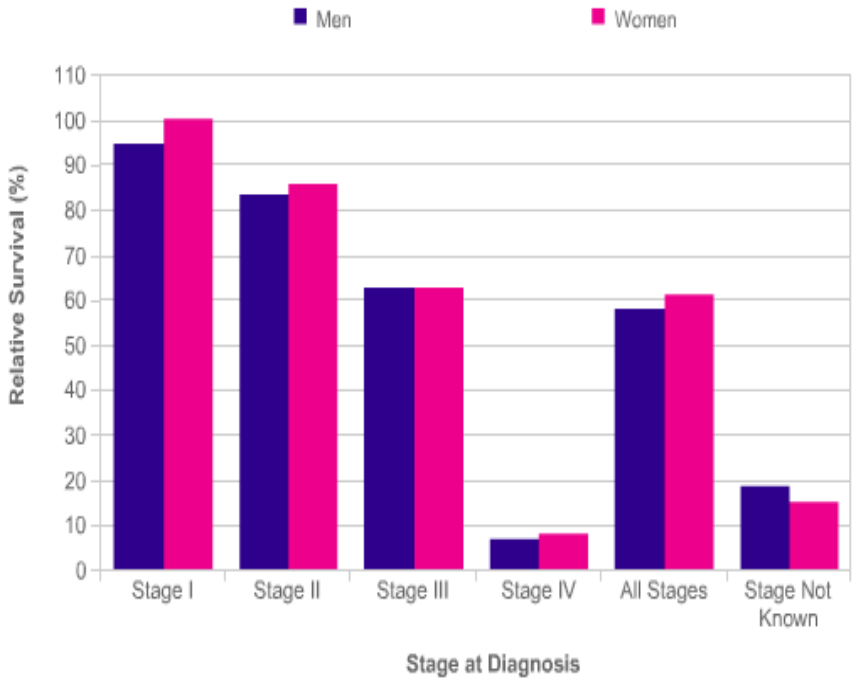
- FH02 study in high-risk women 35-39 with 1st degree relative Dx with cancer <40 years, bilat cancer <50 etc.
- Detects breast cancer at an early stage.
- Better survival than a control cohort (but not a trial).
- Only around 50% picked up by genetic testing in a small sub-sample.



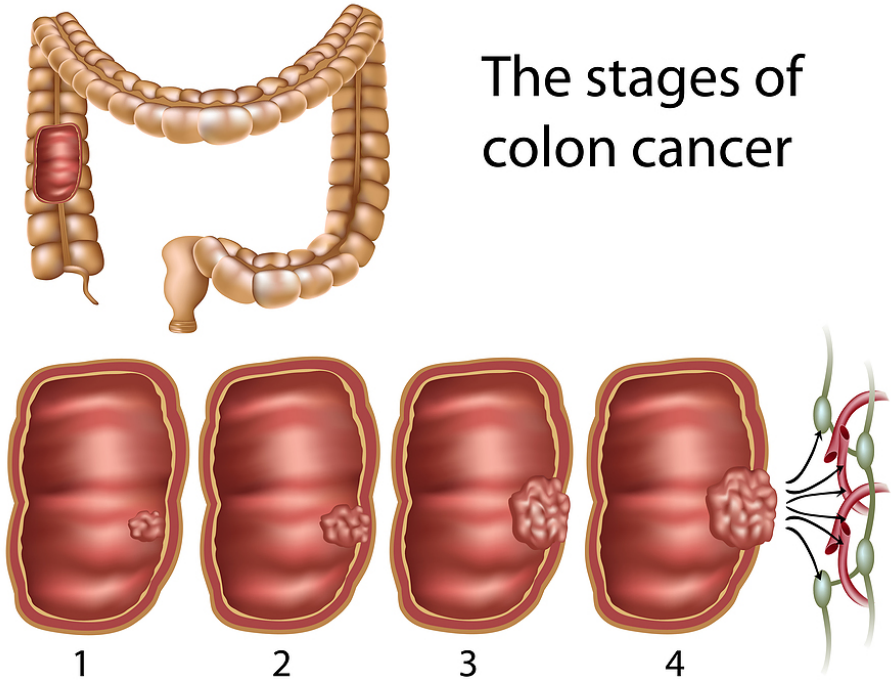
Breast screening coverage by country (L). *(Richards Review, 2019).*



Early diagnosis is key to good outcome in bowel cancer.



Anglia Cancer Network and CRUK.
5 year relative survival.

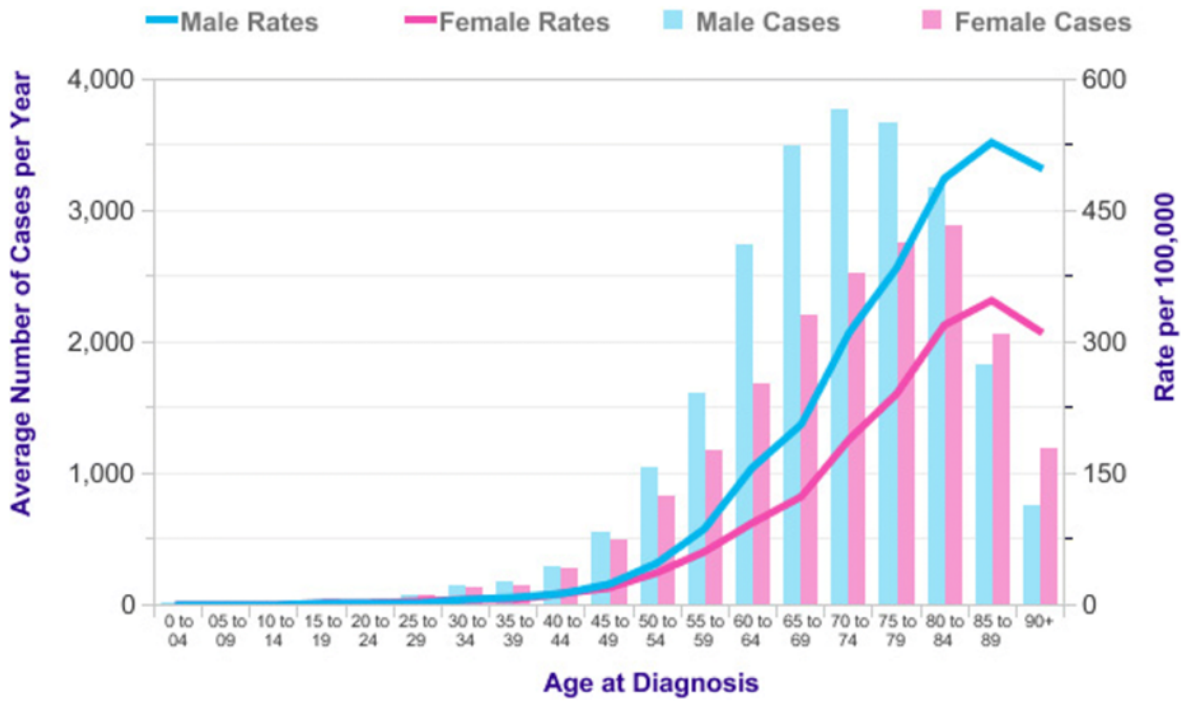


The Colorectal Institute.

Bowel cancer screening.

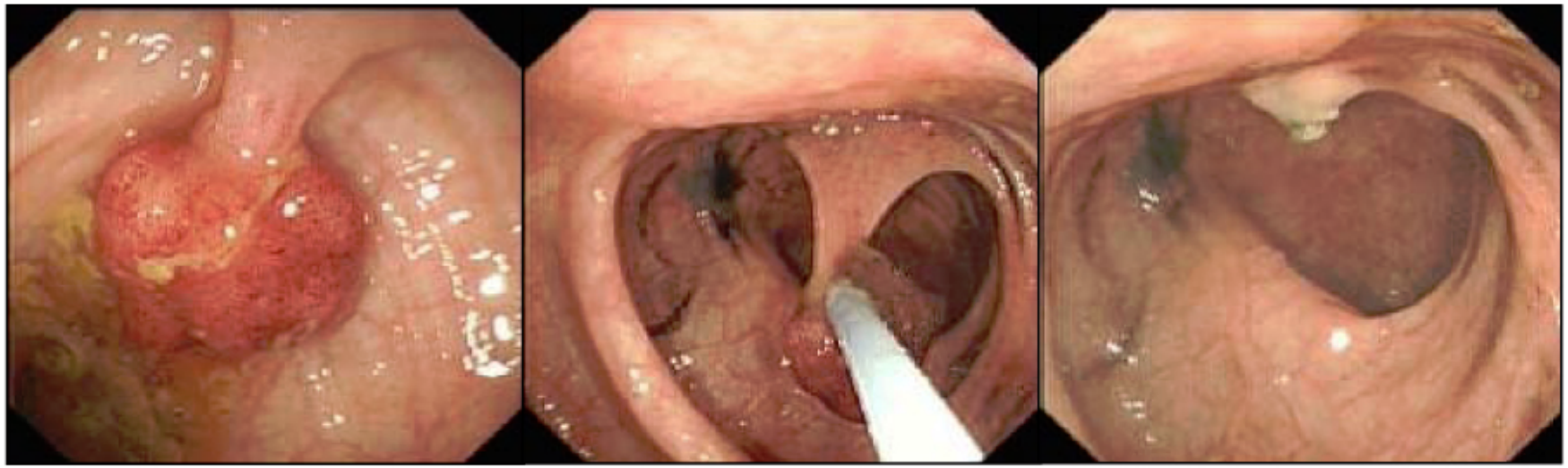
- Was Bowel-scope at 55 and/or
- FOB faecal testing every 2 years from 60-74 (and after by request). Done at home.

- Move to FIT testing- more sensitive and only 1 sample rather than 3.
- If positive colonoscopy.



Colorectal cancer by age, UK. White et al 2018

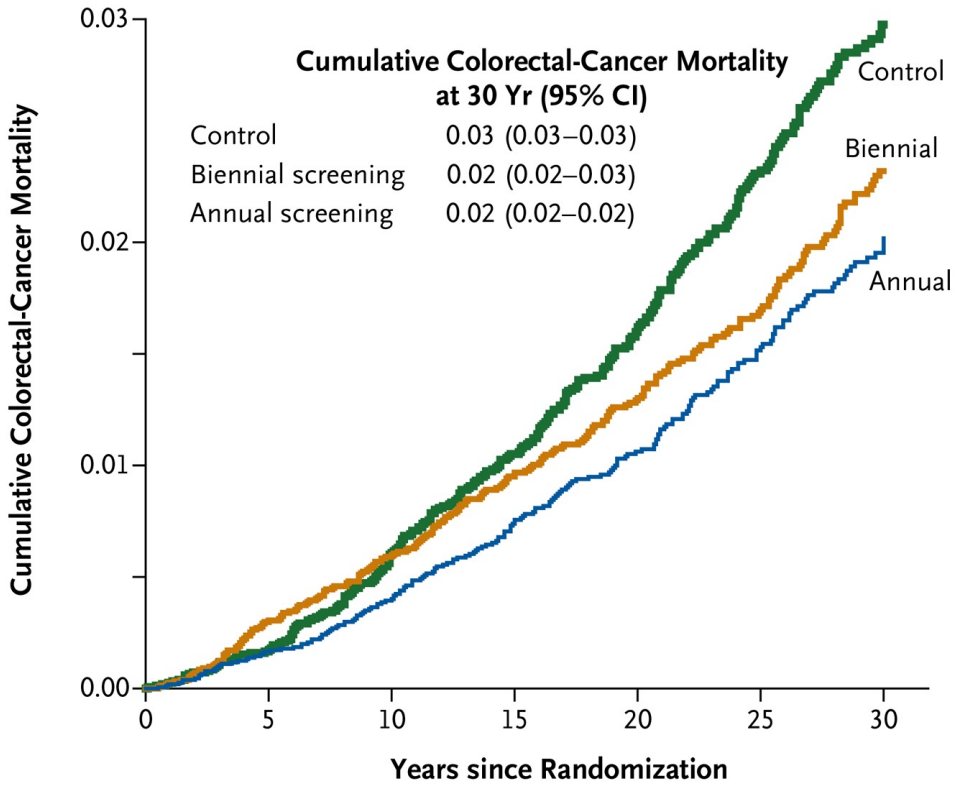
Colonoscopy allows both detection and treatment in early disease.



Gilo1969 Wikimedia commons

Bowel screening trials.

- FIT (faecal immunochemical test) for blood in stool. Currently age 60-74. Uses antibodies that specifically recognise human haemoglobin.
- Uptake around 67% in England.
- Nottingham trial randomised 152,850 individuals FOB. At 19.5 years there was a 13% reduction in colorectal cancer deaths. *Scholefield et al Gut 2011.*
- US study (R) 46,551 randomised. RR with biennial FOB screening 0.78. *Shaukat et al NEJM 2013.*

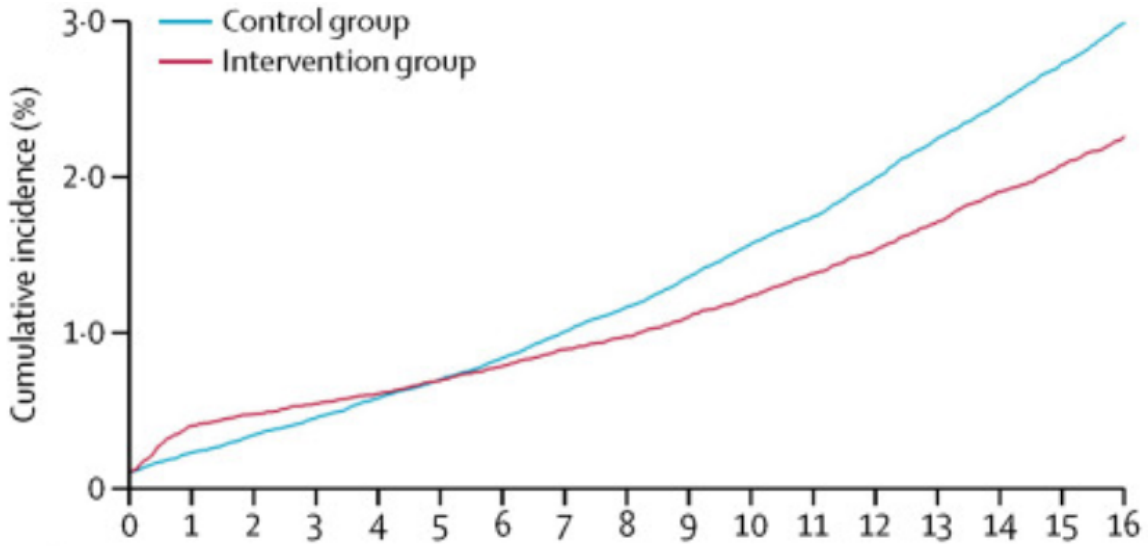


Trial of UK bowel-scope; 170 034 people, 17 years follow-up.

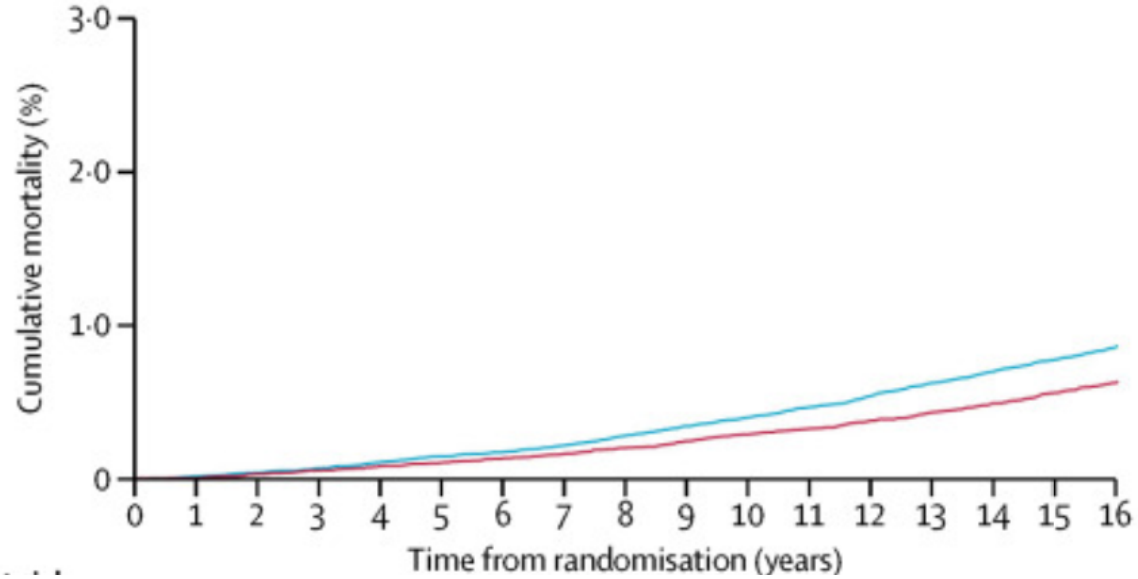
Atkins et al, *Lancet* 2017. NIHR funding.

Randomised to invitation for single screening or not at 55.

HR 27% reduction colorectal cancer incidence.

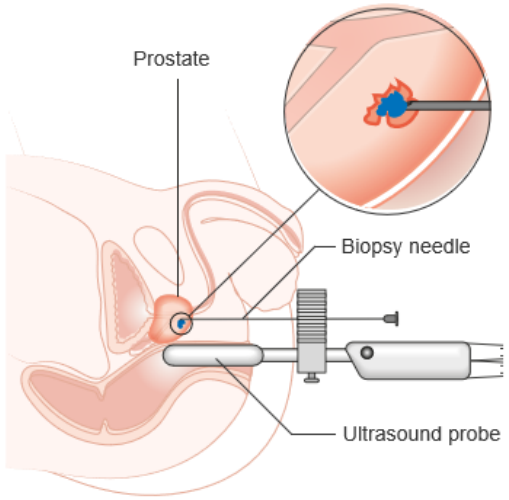


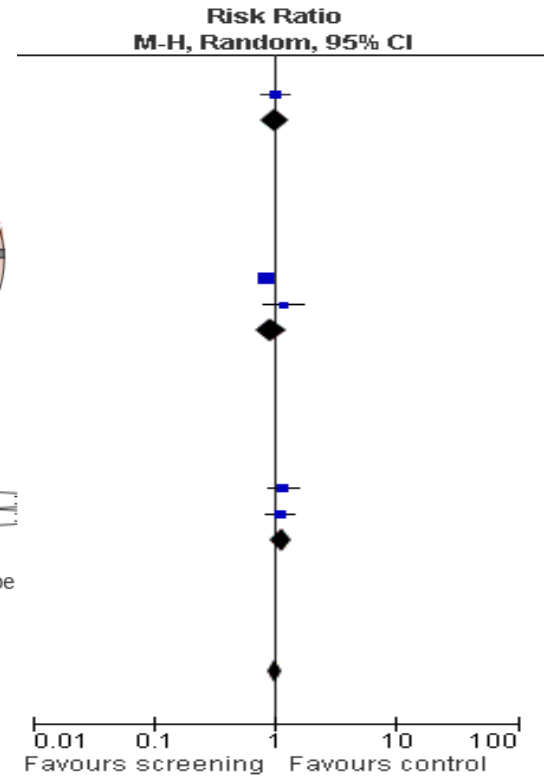
30% reduction colorectal cancer mortality.



Screening trials when impact is uncertain: example of prostate cancer.

- Current prostate cancer screening is with PSA blood test.
- Systematic review of 341,342 men in trials found relative risk 1 (no difference).
- Screening not currently worthwhile.
- Stage 2 is not particularly pleasant.

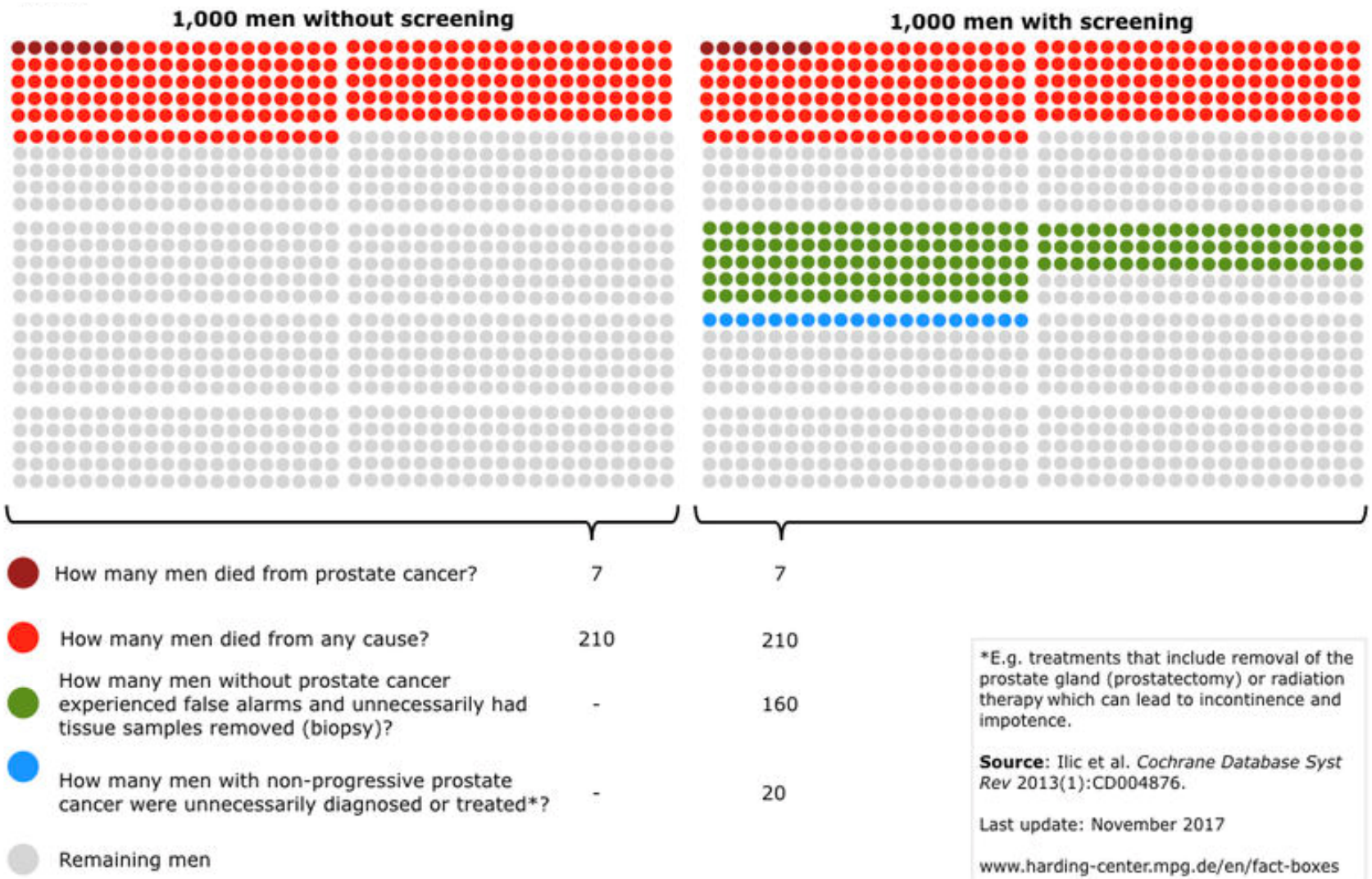




Ilic et al 2013 Cochrane

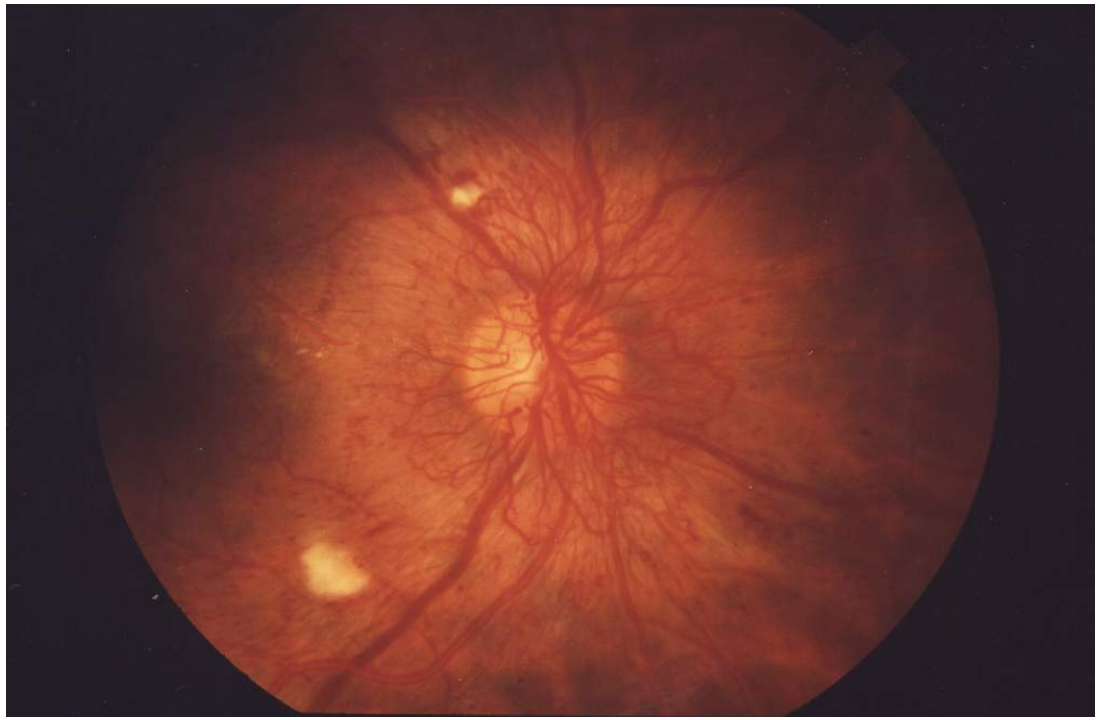
Prostate screening- a graphical representation.

Harding Centre for Risk Literacy / Cochrane.



Our ability to risk-stratify improving.

- Target some screening to very high risk groups- E.g. eye screening in those with diabetes.
- Family history of young onset cancers.



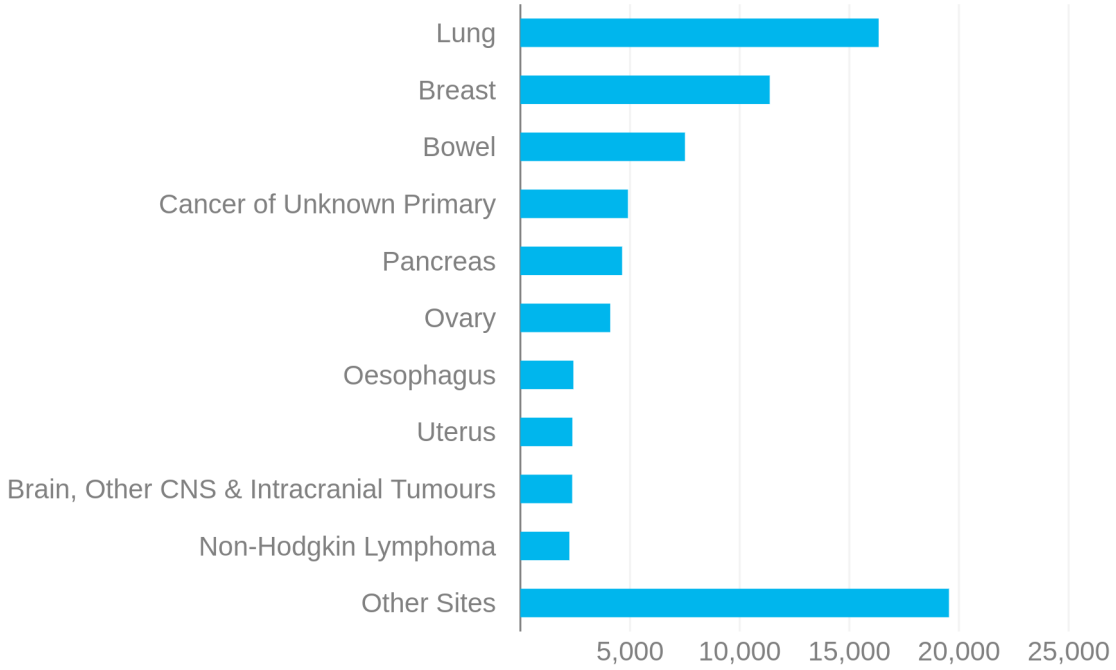
Proliferative retinopathy. NIH.

There are several diseases screening would clearly be very useful if we had better tests.

Include:

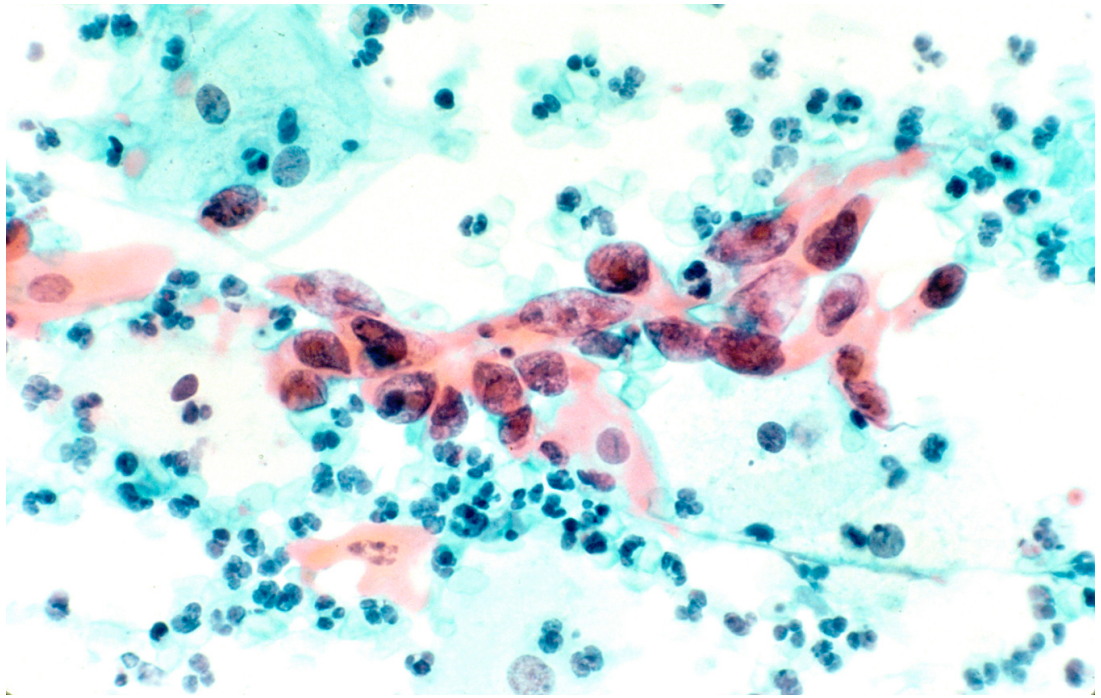
- Lung cancer
- Pancreatic cancer
- Ovarian cancer
- Oesophageal cancer

- In all of these very high mortality, usually identified in late disease.



Where is screening in adults likely to go?

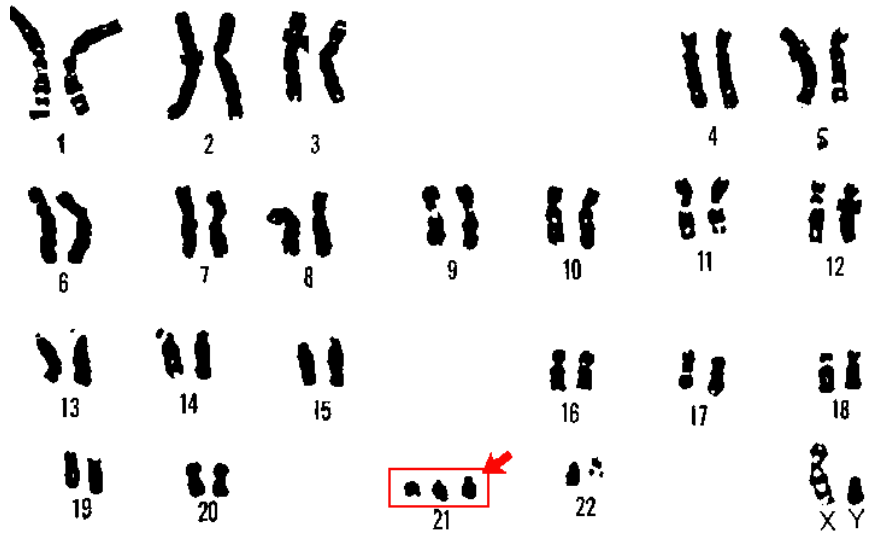
- Much better ability to risk stratify to help targeting. Genomics and other risk tools.
- For example changes in BRCA1 and 2 genes.
- AI for radiology (X-ray/CT/MRI) and histology.
- ‘Liquid biopsy’.
- Safer treatments.
- Better tests.



Cervical cancer cells. NCI.

Antenatal: Down's, Edwards' and Patau's syndrome testing.

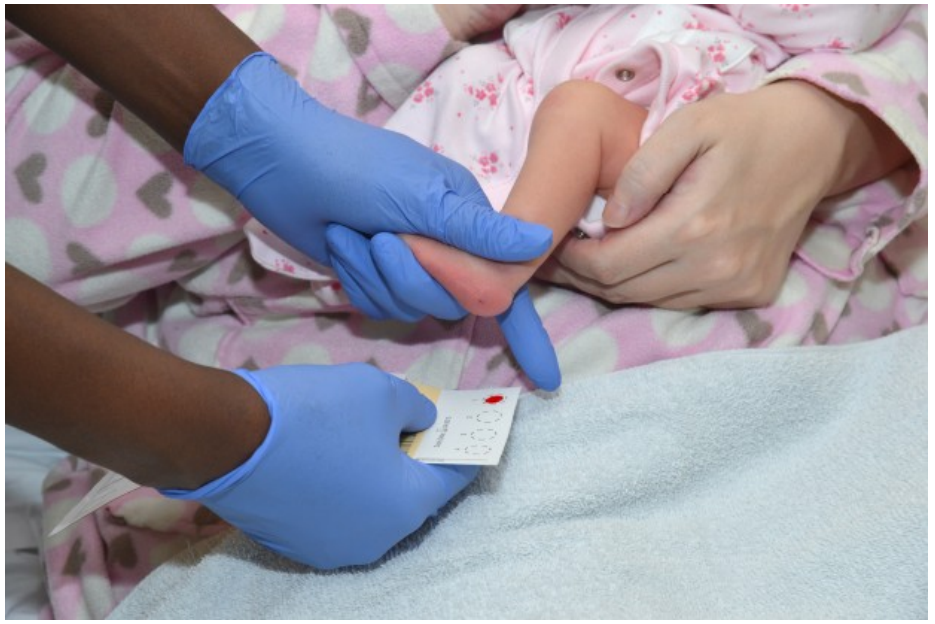
- Woman at 20 about a 1:1500 chance of a baby with Down’s (trisomy 21), at 40 its 1:100.
- Combined test- nuchal translucency and blood test- week 10-14.
- Amniocentesis or chorionic villus sampling: about 0.5 to 1 in 100 diagnostic tests miscarriage.



Newborn 9-disease blood screening at 5 days (heelprick test). High sensitivity, fairly high specificity. Needs confirmation.

- Sickle cell (1:2000)
- Cystic fibrosis (1:2500)
- Congenital hypothyroidism (1:3000)
- 6 metabolic diseases each with prevalence of between 1:10,000 and 1:150,000:

phenylketonuria (PKU); medium-chain acyl-CoA dehydrogenase deficiency (MCADD); maple syrup urine disease (MSUD); isovaleric acidaemia (IVA); glutaric aciduria type 1 (GA1); homocystinuria (pyridoxine unresponsive) (HCU).



PHE

There is a logic to identifying people with infectious diseases and treating or isolating before they pass it on.

- The practicalities of this have often proved challenging.
- It is easier to do where people remain infected and infectious for long periods of time.
- Examples are TB, and historically syphilis, trachoma, sleeping sickness.

Active v passive screening.

- Active screening- you go and find cases.
- Passive screening. You wait until they come to you, often with relevant symptoms.
- The prevalence in active screening is always lower. High risk of false positives.
- But you will miss cases.
- Active screening only sensible in populations the prevalence is reasonably high. Compare NHS active TB screening in UK 1950s and now.

Find and treat mobile unit. UCLH

Screening is very useful, under a restricted set of circumstances.

- Serious disease;
- Which we can diagnose reliably
- and safely (and cheaply);
- And prevent or treat effectively
- and safely relative to risk
- Which is reasonably common;
- With a sufficiently long time from flash-to-bang you can intervene.