NHS Tayside

# Precision Medicine

## PD-L1

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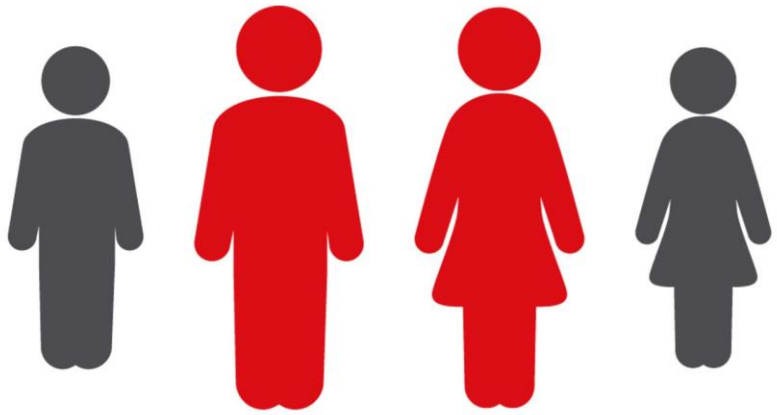
# What is cancer?

- Means different things to different people
- Hugely emotive word with massive implications

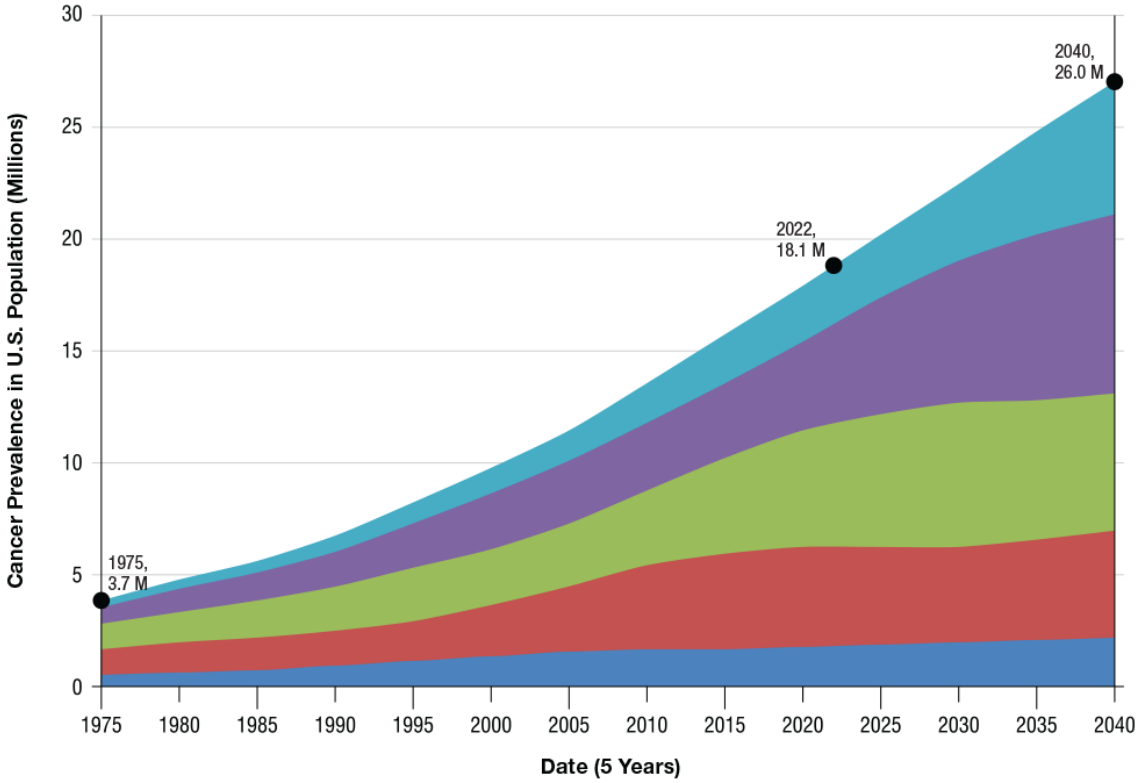

# The statistics



**1 in 2 people**

will be diagnosed with cancer in their lifetime

**Cancer Prevalence and Projections in U.S. Population from 1975–2040**





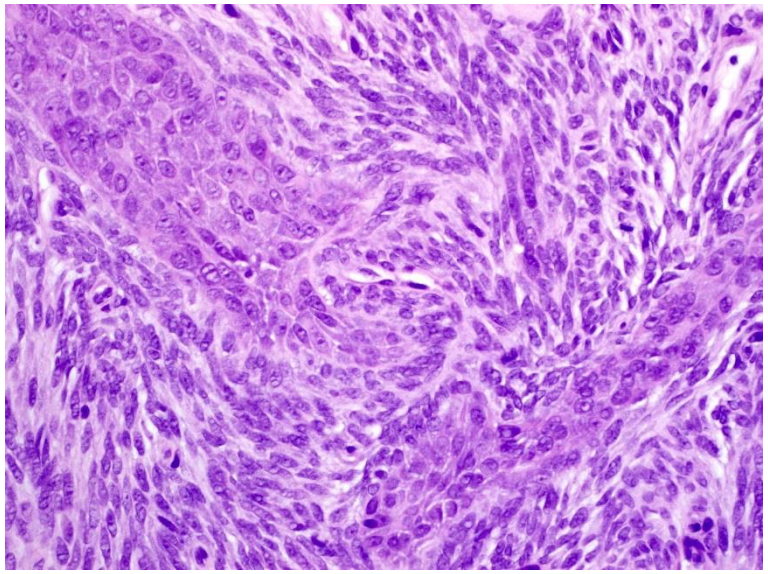
**REFERENCES**

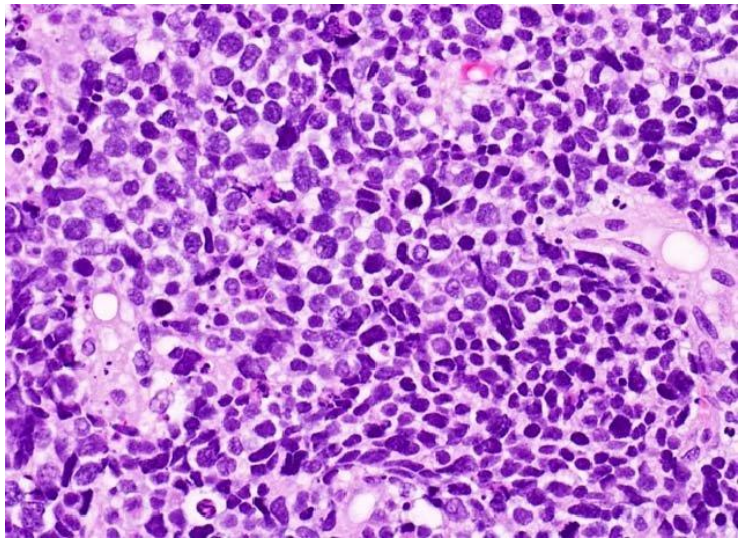
Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "Silver Tsunami": Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. Cancer Epidemiol Biomarkers Prev. 2016 Jul;25(7):1029-36.

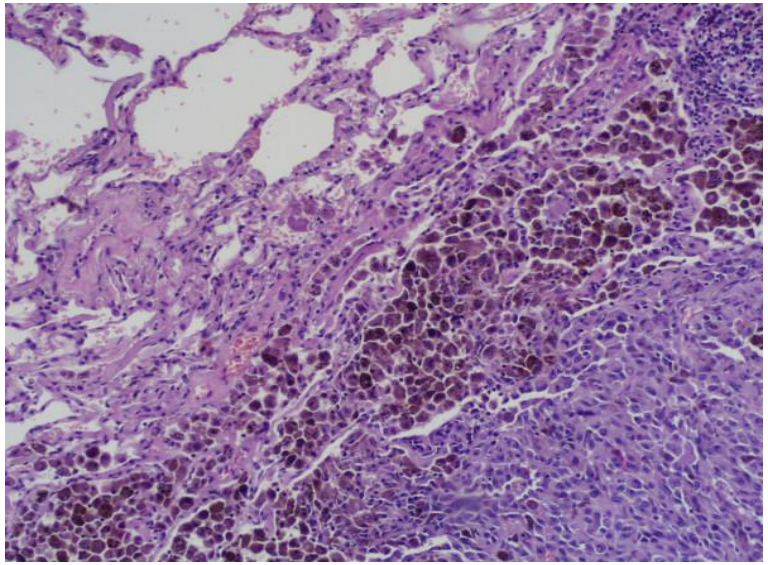
Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, Kramer J and Siegel RL. Cancer Treatment and Survivorship Statistics. CA A Cancer J Clin. 2022.

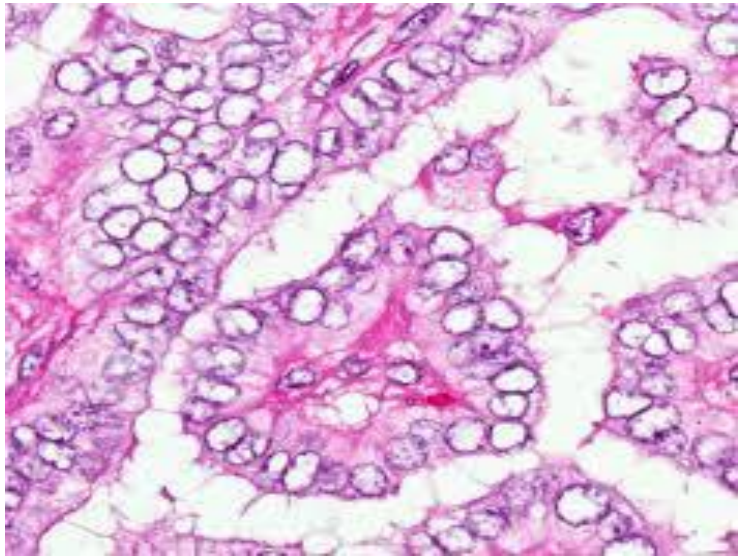
# But.....

- Its not all the same
- 5 year survival
- Small cell lung cancer – 4%
- Papillary carcinoma of thyroid – 99%



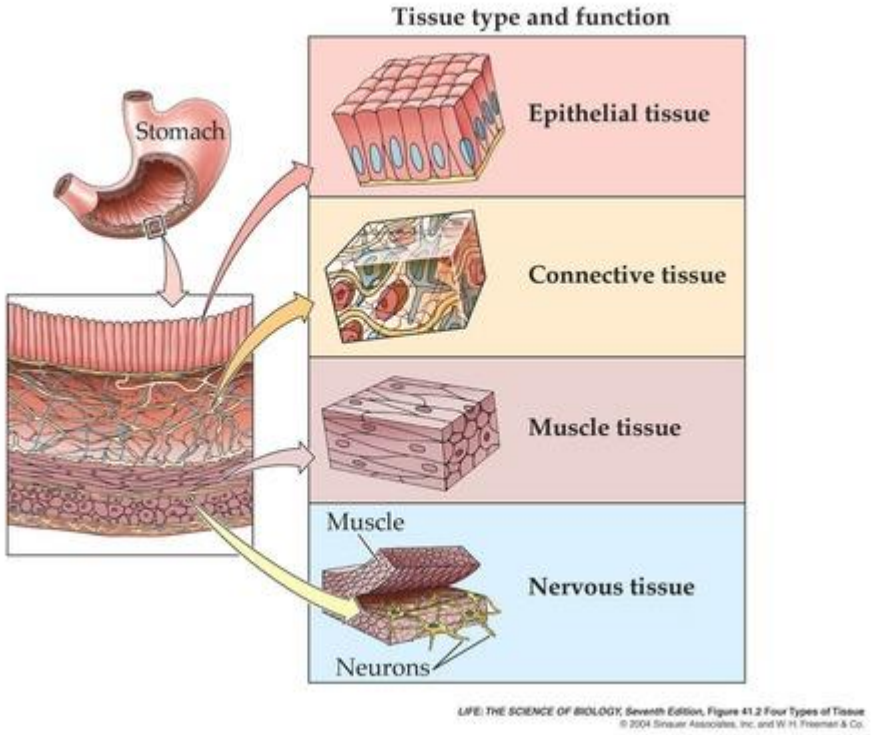


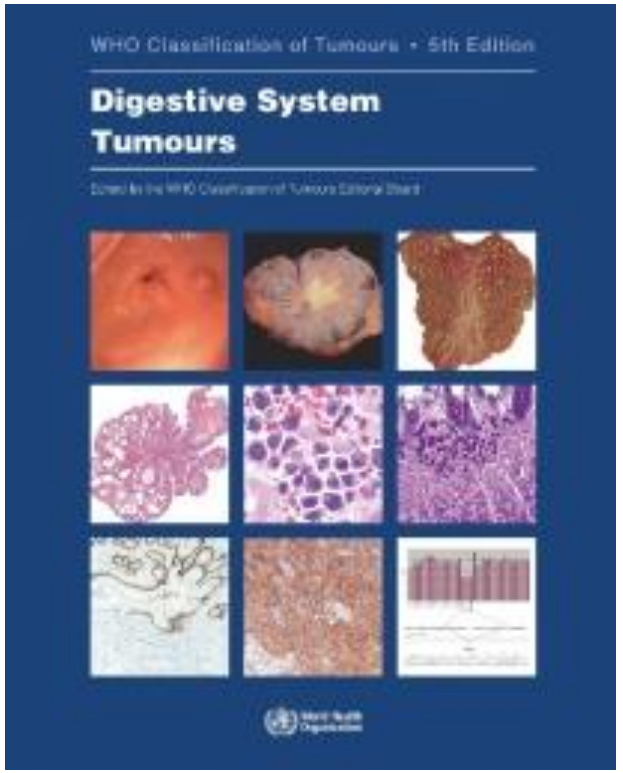




# Classifications

- Organ of origin
- Cell of origin

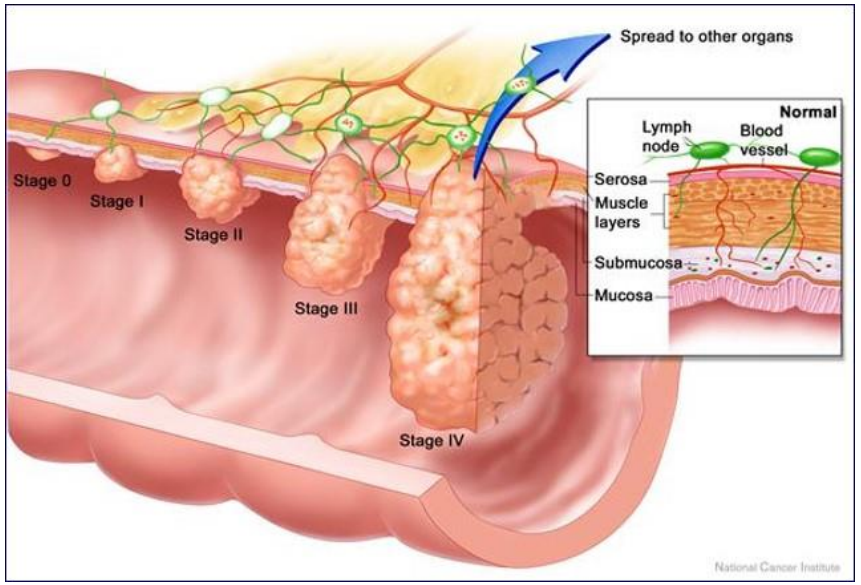


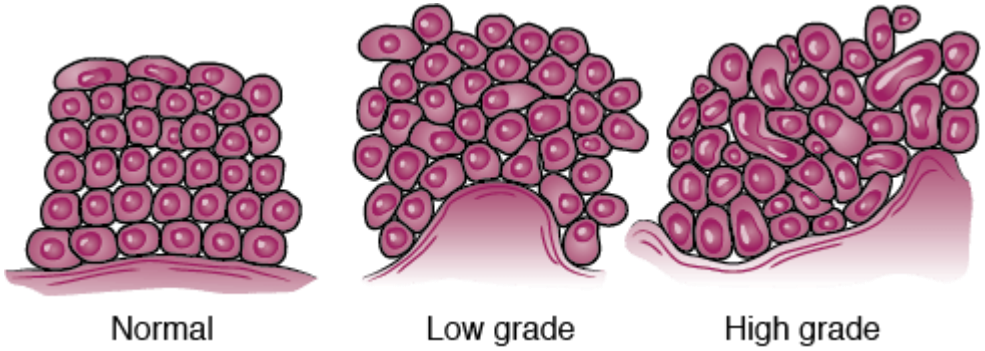
# Classifications

- Stage – how far has it spread

Often size based criteria or on invasion through different layers of tissue




- Grade – how nasty are the cells themselves
- Grade and stage not mutually exclusive
- Low grade ovarian can spread far
- High grade laryngeal SCC can present early



# Twins

- Same classification of tumour don’t always behave the same
- Some good prognosis patients do badly and some with poor prognosis get the miracle cure
- The doctor told me I only had months to live

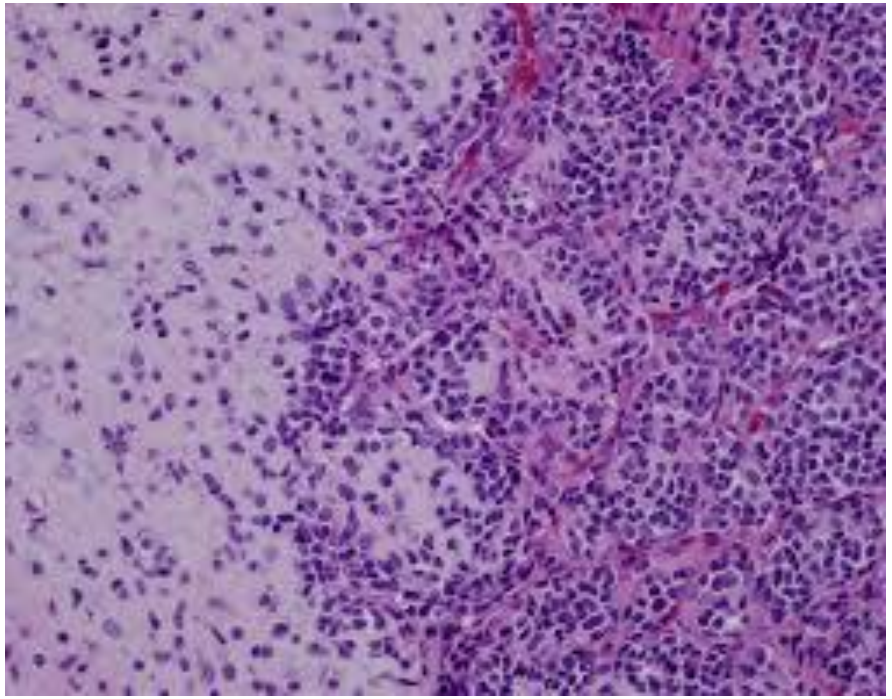
# Why

- People are different
- People’s tumours are different

- The genetic information (including faults) in one tumour is not the same as another. There are commonalities but not always
- p53 is the most commonly mutated gene in solid cancers. Still only around 50% of all
- APC mutation in colorectal cancer is present in 80%

# Tumour heterogeneity

- Small cell lung cancer
- >20 000 mutations
- Carcinogenesis isn’t a binary process
- Not all small cell cancers are therefore the same
- Even within the same tumour there were will be significant variation



# Precision medicine

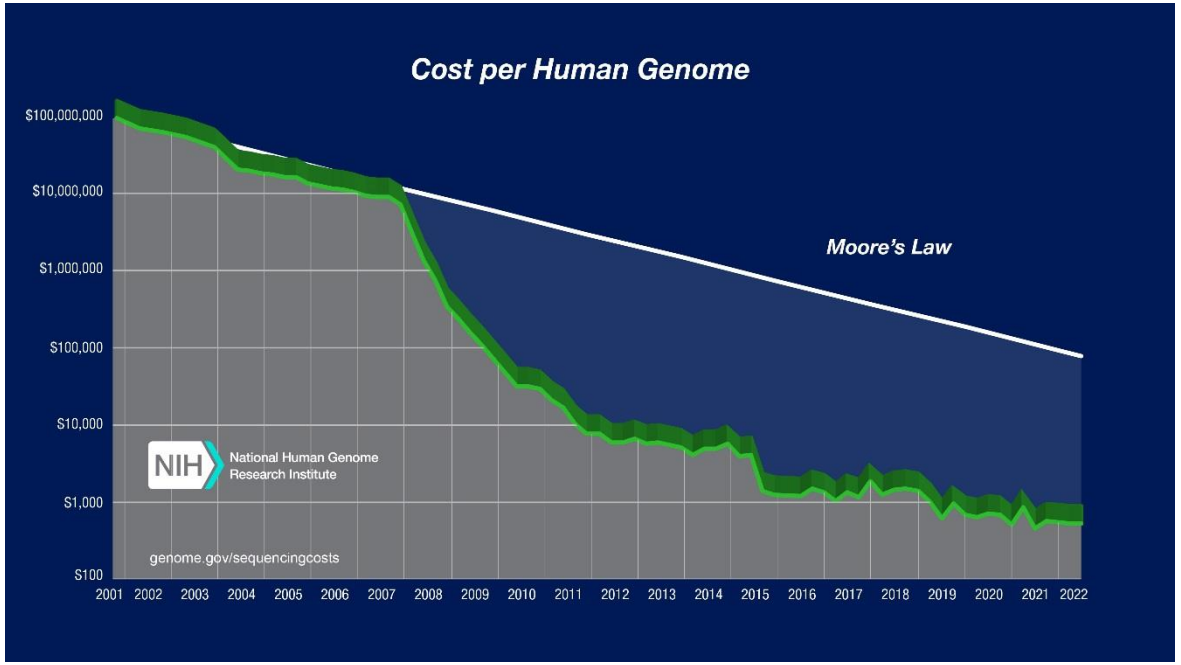
- Maximising information about a tumour's mutations to specifically tailor therapy to specific cancer cells
- Not a one size fits all


# History lessons

- First cancer description – Edwin Smith Papyrus. (3000bce)
- Microscope – see and name tissue types. (1600s)
- Surgery – anaesthesia meant we could operate. (1840s)
- WW2 – mustard gas as chemotherapy agent
- Franklin, Watson and Crick – DNA (1953)
- Venter – human genome project (2003)

# Genomic sequencing

- Took Venter *et al.* years
- Can now be done in a morning



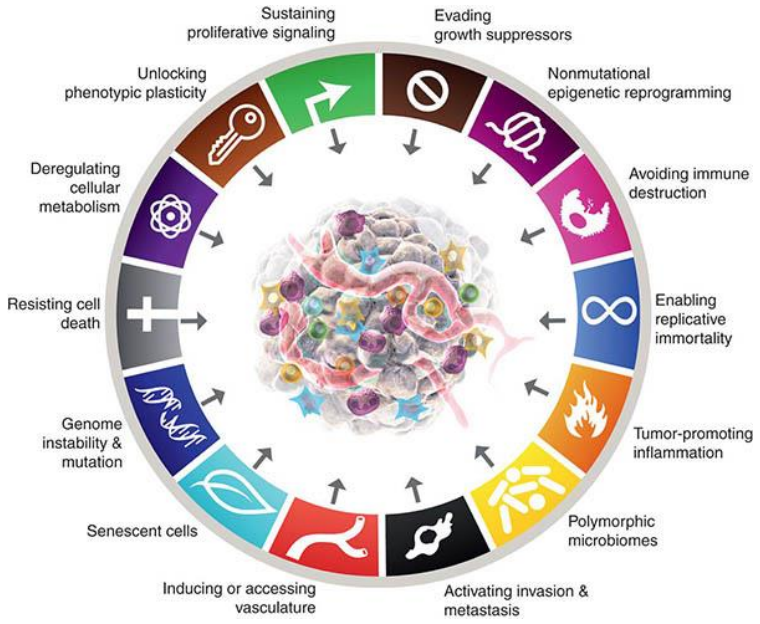
# We can now tell a lot about a cancer

- Anatomical site
- Morphology – cell of origin
- Stage and grade
- Information from genetics and ICC
- There are 100,000 genes in the human genome

- That's a LOT of information

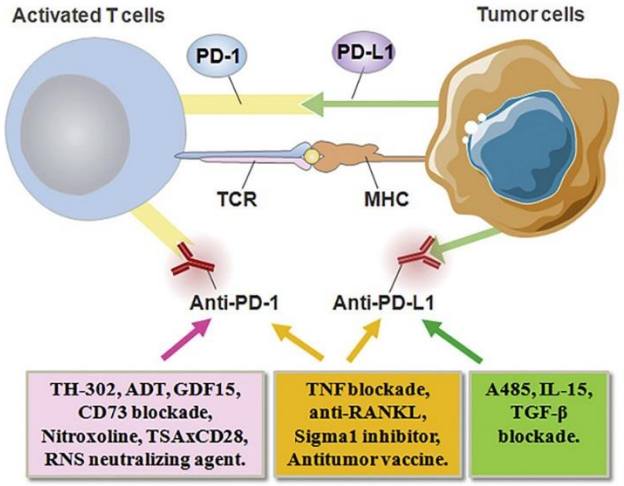
# PD-L1- one of the hallmarks of cancer

- Cancer cells develop lots and lots of different mutations
- “Succesful” cancers have to be able to do certain things
- Mainly dividing over and over again and not dying
- Invade tissue
- Metastasise



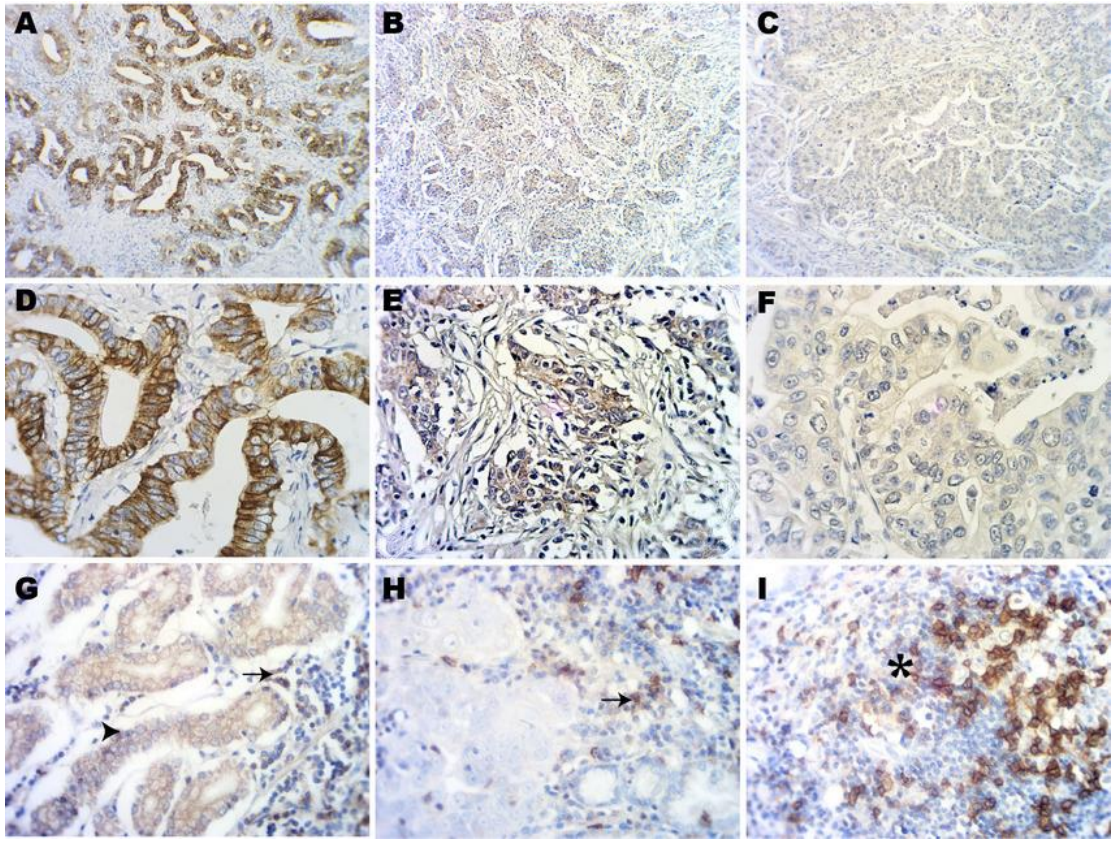
# PD-L1 – staying alive

- One mechanism that cancer cells die is actually through our own immune system
- These are mutated cells. If mutated enough they may appear “foreign” and trigger an immune response
- Main pathway is through T cells and PD-1, PD-L1 interactions
- Some “clever” cancers over express PD-L1 so reacting T cells are told to die
- PD – programmed death



# PD-L1

- If a tumour expresses PD-L1 it is blocking the patient's own immune response
- We can quantify it and if there is lots of expression we can give a drug to block it. Immune cell and tumour expression
- Pembrolizumab, Nivolumab …….lots of abs



# PD-L1

- Currently in use in lung, bladder, oesophagogastric, breast and skin cancers.
- New licenses and indications regularly
- Soon to be used in colorectal cancers
- Some require testing others don’t. In melanoma it is a licensed treatment (3rd line) regardless of scoring
- Varying testing methods – tumour proportion and combined score of tumour and immune cell positivity

# Any good?

Dostarlimab – cured

Gastric Cancer – Trial data is…

……complicated

Implications for us are……

……complicated

# PD-L1 and pathology

- Immunohistochemical test
- Range of antibodies
- Paired diagnostics
- Trial data and licenses are all predicated on use of matching platforms and antibodies for each drug
- Pembrolizumab – 22C3 on Dako
- Nivolumab – 28.8 on Dako
- Other antibodies are available……..

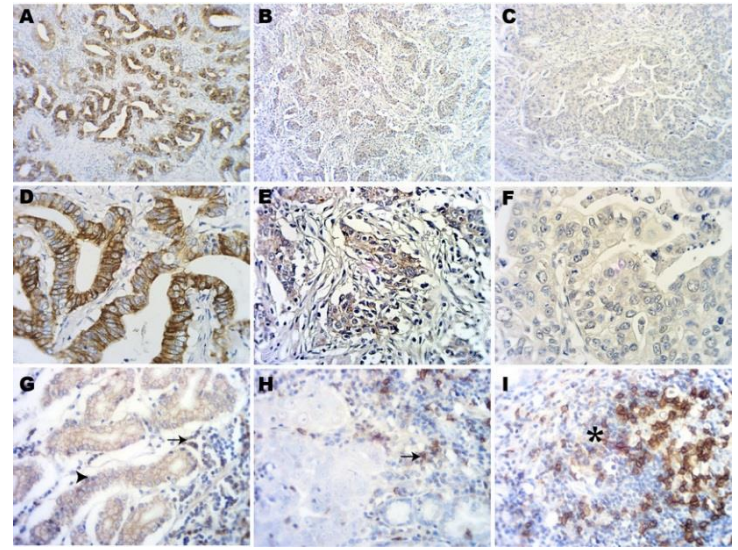
# Does it matter?

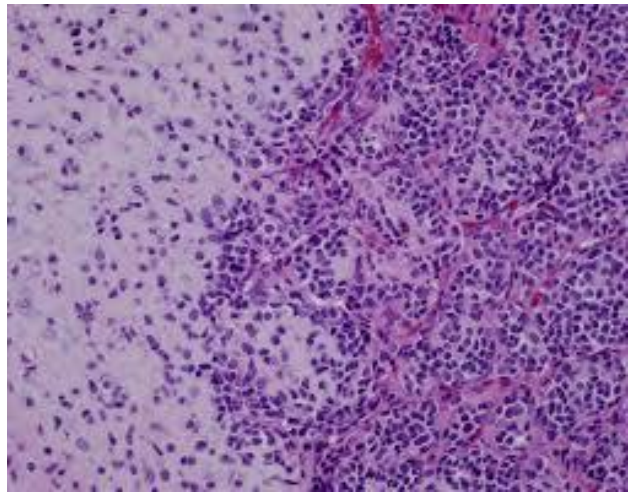
- Yes and No
- New test and very specific scoring criteria have been offered.
- For stomach – combined positivity score
- Lung – total positivity score

- Studies suggest that differences between 22C3 and 28.8 aren’t hugely significant.
- Lots of contradictory studies and seems to be genuine variation amongst other antibodies

# Practical thoughts

- Human interpretation – large interobserver variability
- Sampling – designed for biopsies. As we have discussed, tumours have 1000s of mutations and no two areas of a tumour may be indentical
- So two biopsies from the same tumour in the same patients two weeks apart will have a different PD-L1 score



# Practical thoughts

- Levels??
- The CPS will change on levels as different cells appear and disappear.
- Having a specific cut off of 5 or 10 seems strange. What if it scores 4 or 9?????
- Pragmatic oncologists – often a desperate “Hail Mary”

# Future thoughts

- Likely to be used in combination with other “precision medicines”
- Ideally we will look at a range of things – guide which tablets to take

- I suspect – no PD-L1 testing at all in most cases
- In a few cases – PD-L1 test or alternative
- Microsatellite instability – surrogate
- AI – 100,000 genes. Which drug?

# The philosopher

- New advances and research are great
- Dostarlimab – wow!
- Not without cost
- Merk – 22 billion a year from Pembro (Keytruda)
- NHS Scotland – 14 billion to run it for a year

Hospitals told to shed staff as NHS funding crisis deepens

Nurses most at risk despite ruling that increased staffing is vital for better care

Denis Campbell
Health policy editor

Hospitals are being told to shed staff to rescue the NHS from an acute funding crisis, leaving nurses and other frontline medical workers at risk of losing their jobs.

NHS regulators have taken the controversial decision despite intense concern among hospital bosses and health unions Mid Staffordshire care scandal in 2013 by saying staffing levels must be increased to improve the standard of care.

Critics warn that, as some NHS trusts sink as much as £60m into the red, the move could lead to hospitals being forced to shed hundreds of staff, with nurses and managers the most vulnerable to being axed. Nurses make up around 40% of the NHS workforce.

Addenbrooke's hospital in Cambridge, for example, has been losing £1.2m a week during 2015-16 and could end the year as much as £60m in the red. St George's in south London is expected to record a deficit of about £46.2m. To save £1m, a trust would have to lose 25 nurses, according to the King's Fund thinktank.

The decision to jettison the three-year-long approach to prioritising staffing levels over balancing the books has been prompted by the NHS's increasingly frantic efforts to tackle the deficit which

told trusts to dramatically reduce their "financial distress" if they want to receive money from a £1.8bn bailout available in April, aimed at finally stabilising NHS finances. The letter states: "We will be meeting a number of challenged providers this month to agree a set of actions, including headcount reduction."

The move prompted immediate warnings that patients would suffer. "If trusts do begin to reduce headcount the impact on patients would be swift, through either

£60m

The annual deficit Addenbrooke's hospital in Cambridge is heading for, while St George's, south London, is expected to be £46m in the red

rising waiting times or reduced quality of care or both," said Richard Murray, the

promised to ensure hospitals had e staff to meet patient demand. Less year later they're asking hospitals t up plans to reduce staff numbers."

Howard Catton, the Royal C of Nursing's director of policy, "Patients will suffer without the number of skilled and experienced line staff in place."

Almost all the foundation trust tals regulated by Monitor are deer be "financially challenged" and 2 overspent by so much that they are ing government bailouts to help pa bills. The cost of expensive agency set to be £4bn this year, is the sing gest reason for the £2.22bn overspe

The chief executive of one of Eng biggest trusts said the drive to r staff numbers was reckless and co productive. "What they don't se appreciate is that it's hands-on bu and you need the hands on. If we

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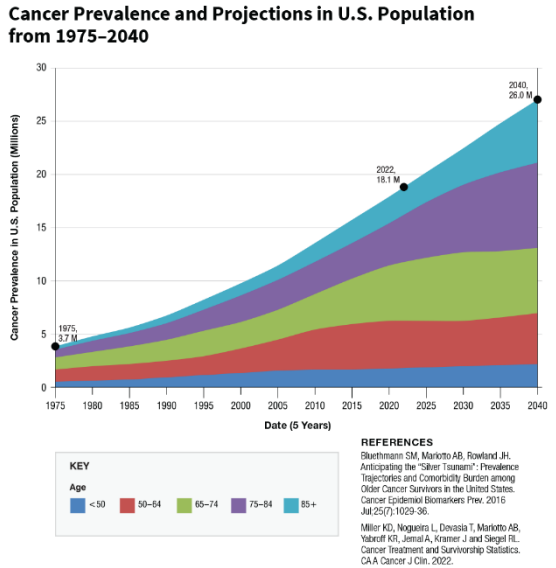
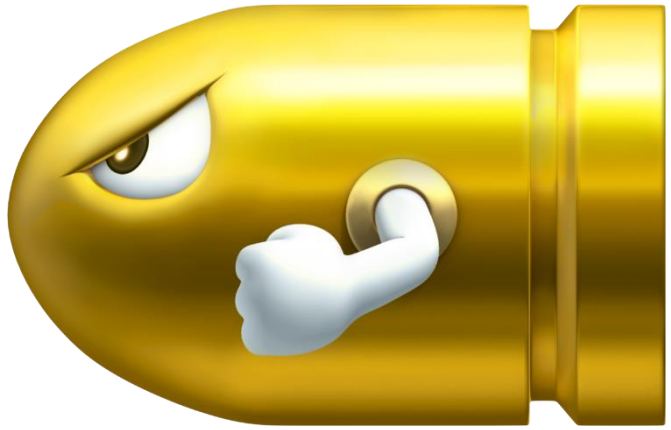


# Might be worth the investment

- KEYNOTE859 – combination of trastuzamab (Herceptin) and pembrolizumab licensed up front without PD-L1 testing

- So – it is possible that with a broad “profile” of ICC and molecular genetics we can select a cocktail of drugs to cure people

- We have to start somewhere. At the moment it is very costly for marginal benefit. Eventually, combination of markers may reveal successful drug combinations



# Thanks!

Any thoughts or questions welcome