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Mortality and Longevity Seminar: "What-if" scenarios

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Content

- Scenario types
- Vitagion types
- Parameterisation approach
- Timing and uptake
- Examples
  - 'Cure for cancer'
  - Slowing ageing

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4 scenario types

- Risk factor variations
  - e.g. reduction in smoking, increase in obesity
- Cause of death variations
  - e.g. massive reduction in cancer mortality
- Base mortality variations
  - e.g. socioeconomic differences
- Ageing reduction
  - e.g. treatments that slow the rate of ageing

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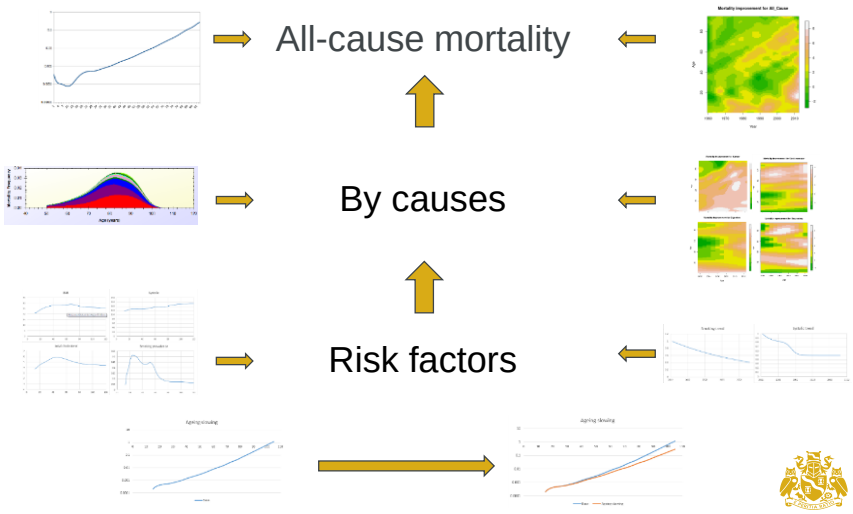
Scenario levels



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Parameterisation

- Possibility limits
- Plausibility limits
- Best estimate
- Time, duration and rate

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Vitagion types

- Healthcare – medicines, surgery, medical technology.
- Lifestyle – smoking, alcohol, drugs, risk taking behaviours…..
- Environmental – pollution, political, organisation & economic (e.g. NHS v non-universal healthcare).
- Catastrophe – pandemic, warfare, terrorism…..

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Timing

- Uptake:
  - Typically sigmoid.
  - Almost never to 100% - asymptotic. (set a % when considered complete – e.g. 95%).
- Identify rate limits – building, training, regulatory….

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Timeline

- Drug regulation. Typical timing from identification of ‘new molecule’.
- Typically 10-15 years of research
  - Phase I – Find dose in humans.
  - Phase II – Small studies to see if works.
  - Phase III – Big studies to measure effect size and determine safety.
- Minimum ~ 7 years with accelerated progress (e.g. orphan drugs).

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Uptake fraction

Almost never 100%.

- Adverse reaction.
- Allergic.
- Clinical uncertainty (justified or otherwise).
- Personal preference (aversion to Rx).
- Cultural factors.
- Disorganised lives.
- Disorganised healthcare service…

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Parameterisation examples

- e.g. impact of new angioplasty intervention in MI. (illustrative figures only)
- ~50% deaths occur before reaching hospital.
  - ... Possibility limit of 50%.
- Only 80% of subjects fit for intervention or accept it.
  - … Plausibility limit of 0.5*0.8 = 40%.
- Typical mortality reduction with intervention = 25%.
  - … Best estimate of 0.4*0.25 = 10%.
- Minimum time for planning and building facilities and training new staff (to 90% maximum capacity) ~ 5 years.

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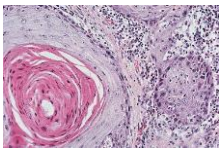
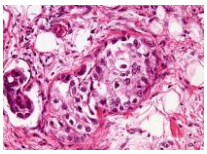
‘Cure for cancer’

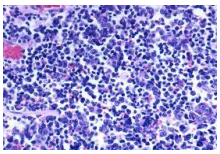
- ICD 10 – 535 separate codes for malignant neoplasms.
- E.g. Lung cancer (C34) – Three different, common categories of lung cancer. (squamous, small cell, adenocarcinoma)
- Originate in different cell types.



Squamous cell



Adenocarcinoma



Small cell

- Cancer is not one disease but many.
- Different causes, different mechanisms, different treatments.

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Characteristics of cancers

- Uncontrolled cell replication.
  - Keep dividing (no Hayflick limit).
  - Loss of regulatory controls (switches).
- Self-destruct mechanisms fail.
- Loss of invasion control. (No ‘personal space’).
- Recruitment of ancillary support – stimulation of extra blood supply etc.

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No single cure for all cancers.

- Will require a range of interventions covering a range of mechanisms.

However:

- Some exposures increase risk of a range of cancers. (e.g. smoking).
- Some interventions reduce risk of a range of cancers with shared characteristics (e.g. aspirin).

- Not a single scenario – but multiple scenarios.

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The 'unknown unknowns' Example: ageing reduction

- Parameterisation
- Model structure
- Representation of results
- Interpretation of results

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Ageing reduction parameterisation

Illustrative only…..

- Possibility limit…
  - Maximum ageing reduction achieved in mammals ~60%. (LSP Biology of Ageing Report)
- Plausibility limit….
  - Projection of maximum reduction by size of mammal ~ 25%.
- Best estimate…
  - Potential of existing interventions (exercise, diet etc.) ~25%. Potential uptake ~ 20% -> 5%.
- Timescale...
  - Large scale building of sports facilities, training of staff, public information programmes….. ~ 15 years.

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Model structure

Think …. 'dog-years'

- Fit spline to mortality rate to give continuous prediction (e.g. 57.6 years)
- Calculate biological age - function for yearly increment…
- $a(n) = r * f(n)$
- $b(n) = c(0) + (1-a(1)) + (1-a(2)) + \ldots (1-a(n))$
- Look up mortality for slowed chronological age using the calculated 'biological age'.

•n = years passed f(n) = function for uptake of mortality factor r = reduction factor

•b(n)= biological age at n years c(n) = chronological age at n years.

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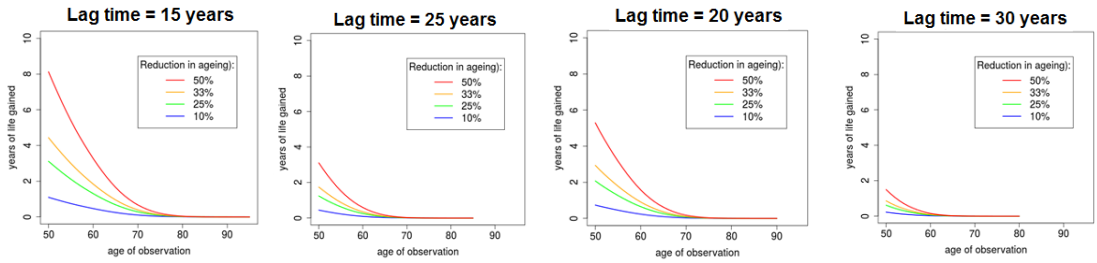
Representation of results



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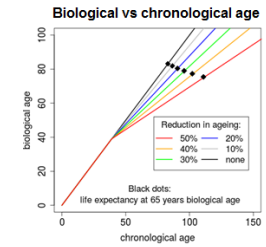
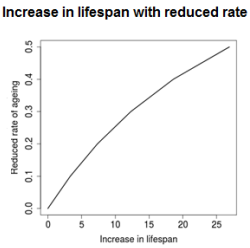
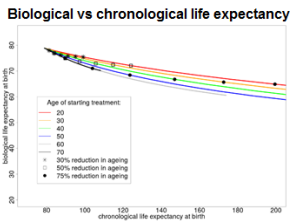
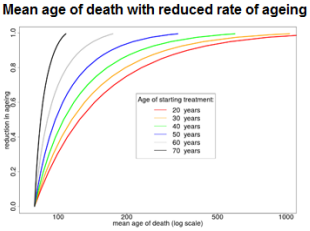
Interpretation of results









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From The Longevity Science Panel report: "What is ageing? Can we delay it?" http://www.longevitypanel.co.uk/viewpoint/what-is-ageing-can-we-delay-it/