Getting to Grips with Biological Age

Tom Kirkwood

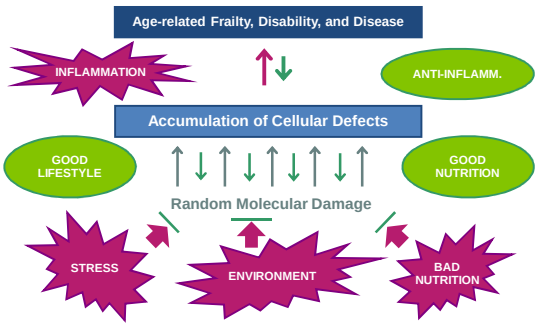
Newcastle University Institute for Ageing
and University of Copenhagen
Center for Healthy Ageing

Newcastle University

UNIVERSITY OF COPENHAGEN

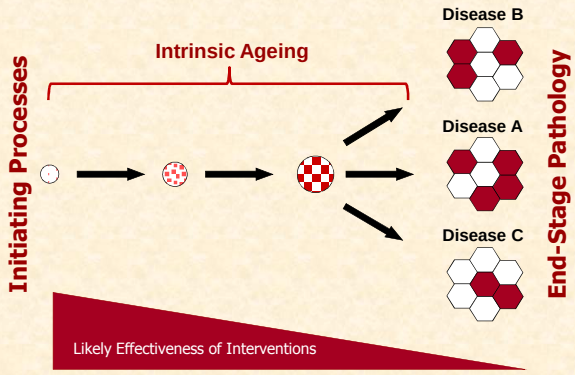
AGEING PROCESS AND ITS MALLEABILITY

Kirkwood *Cell* 2005



Intrinsic Ageing and Age-Related Disease

Accumulation of Molecular and Cellular Damage



A "Holy Grail" of Ageing Science

Can we relate health status to intrinsic markers of biological age?

Success would enable:

- Early evaluation of interventions to improve healthy life expectancy.
- Personalised monitoring of age-related health trajectories.

Test-battery to measure ageing-rate in man

Comfort A. *The Lancet* 1969;27:1411-1415

"A technique for the short-term measurement of the rate of human aging is now both necessary and possible."

It would "provide important experience with, and knowledge of, aging variables other than mortality, … [and] offer a method of attacking the real possibility that drugs and environmental agents already current may affect that rate".

Comfort's proposed battery included 45 tests to be performed on living subjects.

Criteria for Satisfactory Aging Biomarkers

Adapted from Baker & Sprott 1988

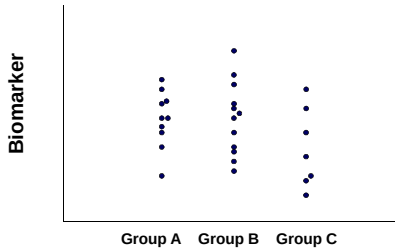
1. The rate of change of a biomarker must, at least in mathematical terms, reflect some measurable parameter which can be predicted at a later chronological age;
2. The biomarker should reflect some basic biological process of aging rather than predisposition toward a disease state;
3. Biomarkers should change independently with the passage of time and reflect physiological (functional) age;
4. Assessment of biomarkers should be minimally invasive;
5. The biomarker should be reproducible and measurable during a relatively short time interval compared to the life span.

The Different Roles for Biological Markers of Aging

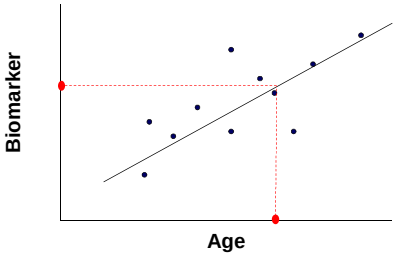
- Investigation
  - Probing the mechanistic complexity of the aging process.
- Comparison
  - Comparing rates of aging in different species or populations.
- Prediction
  - Making inferences, based on measurements in individuals, of future events.

Kirkwood TBL *Experimental Gerontology* 1998; 33:135-140.

Comparative Use of Biomarkers



Predictive Use of Biomarkers



1. Determine relationship between age and biomarker.
2. Measure biomarker for individual.
3. Calculate corresponding age from above.
4. Compare calculated age (biological age) with chronological age.
5. Use biological age to predict outcomes.

Factors Influencing Health Trajectories in Old Age

- Genes
- Nutrition
- Lifestyle
- Environment
- Socioeconomic status
- Attitude

These factors and their interactions have been studied in the **Newcastle 85+ Study**; a prospective study in more than 1000 individuals born in 1921 of the biological, clinical and psychosocial factors associated with healthy ageing.

Biomarker Domains in Newcastle 85+ Study

Anthropometry, blood pressure and physical function

- Weight, body fat percentage, body fat mass, fat free mass and total body water
- Diastolic and systolic blood pressures
- Right and left hand-grip strength
- Timed Up-and-Go (TUG) test; 7-day continuous activity monitoring
- Respiratory function

Blood-based biomarkers

- Haematology and biochemistry:
- Nutritional markers
- Inflammatory response
- Lymphocyte subpopulations
- Telomere length
- DNA Damage and Repair
- Plasma isoprostanes

Martin-Ruiz et al *Mech Ageing Dev* 2011

Biomarker as Risk Factors

(multimorbidity, disability, cognitive impairment, mortality)

- Low BMI (or fat) is protective for multimorbidity and disability, but a risk factor for mortality.
- High blood pressure is a risk factor in younger populations, but in 85+ low blood pressure is a risk factor for cognitive impairment and disability.
- Anemia is a risk factor for multimorbidity and disability.
- High B-natriuretic peptide (BNP) is confirmed as a risk factor for heart disease in 85+ and is also a predictor of mortality and cognitive impairment in those without heart disease.
- Low Apolipoprotein B (ApoB) levels is associated with disability and mortality. High HDL is protective against disability, and low total cholesterol is a risk factor for multimorbidity and mortality.
- Surprisingly, no strong associations with inflammation (high-sensitivity C-reactive protein; hsCRP), telomere length or immune risk profile.

Martin-Ruiz et al *Mech Ageing Dev* 2011

Unexpected negative biomarker findings

- Inflammation - high levels of high-sensitivity C-reactive protein (hsCRP) and serum interleukins have been associated with various age-related outcomes. High levels of hsCRP were associated with multi-morbidity, disability and mortality risk, however, only the association with disability remained in a multivariate approach.
- Short telomeres have been repeatedly shown to be associated with cognitive dysfunction, various age-associated diseases and mortality. However, we and others previously observed no association between telomere length and morbidity/mortality in another group of the oldest-old.
- A low CD4/CD8 T-lymphocyte ratio is a central feature of an 'immune risk profile', associated with low survival in Swedish longitudinal studies of 80- and 90-year olds. We did not find any significant association of the extreme percentiles of the CD4/CD8 ratios with any of the outcome measures tested.

Martin-Ruiz et al *Mech Ageing Dev* 2011

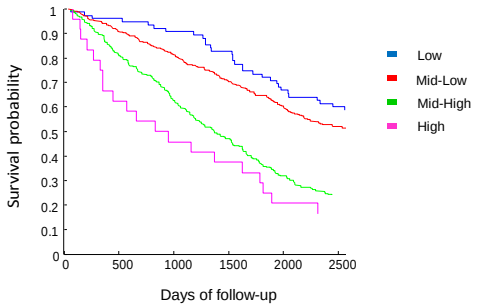
Frailty Index

(Searle et al *BMC Geriatrics* 2008, Clegg et al *Lancet* 2013)

Each biomarker was dichotomized into 'deficit' vs. 'no deficit' using empirically determined cut-points.

Frailty Index = Total number of deficits/Number of biomarkers evaluated.

Biomarker-based Frailty Index Predicts 7-year Mortality



Mitnitski et al *BMC Medicine* 2015

Other Relevant Studies

Gunn et al. *J Gerontol Med Sci* 2015
187 Danish twin pairs aged 70+. Perceived age (based on photographs) associated with survival over 7+ years.

Mariani et al. *Genome Biology* 2015
DNA methylation levels change with age but it is not yet known whether this captures aspects of biological age. In four longitudinal ageing studies, DNA methylation-derived measures predicted mortality independently of health status, lifestyle factors, and known genetic factors.

Sood et al. *Genome Biology* 2015
Samples from multiple cohorts used to create "healthy ageing RNA classifier" associated with cognitive health status.

Sayer & Kirkwood *Lancet* 2015
Overview on role of grip strength as biomarker of ageing.

Waaijer et al. *Exp Gerontol* 2016
178 participants in Leiden Longevity Study (age range 42-82). Molecular measures more weakly associated with age than functional measures.

So although we cannot measure biological age precisely, we can see that there are many biological factors that relate to increasing frailty and mortality.

How can we relate this to the evident malleability of the ageing process?

As life expectancy increases:
- do biomarkers show changes later?
- do diseases develop later?
- do we see compression of morbidity?

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