

How can biomarkers bridge the gap between exposure and final health effects in terms of individual sensitivity?

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Health effects of exposure depend upon dose and time.

High dose exposures (therapy, spaceflight, terrorism, accidental or intentional exposures)

- Acute tissue damage
- Delayed tissue damage
- Secondary cancers
- Cardiovascular effects

Low dose exposures (workplace, diagnostics, natural sources)

- Cancer
- Cardiovascular effects
- Cognitive impairment
- Cataracts
- ?

What is the potential role of biomarkers ?

Risk of high dose exposures

- Triage
- Prevent predictable adverse outcomes
- Advise on potential clinical treatment
- Follow up
- Informed consent

Risk of low dose exposures

- Prevention of damage
- Informed consent
- Selection for follow up

Prediction of risk has a significant impact on the human rights of the individual!

Role of individual susceptibility

- Is there a common dose response curve and therefore a single risk estimate that fits all individuals?
- or are differences between individuals or even between populations ?

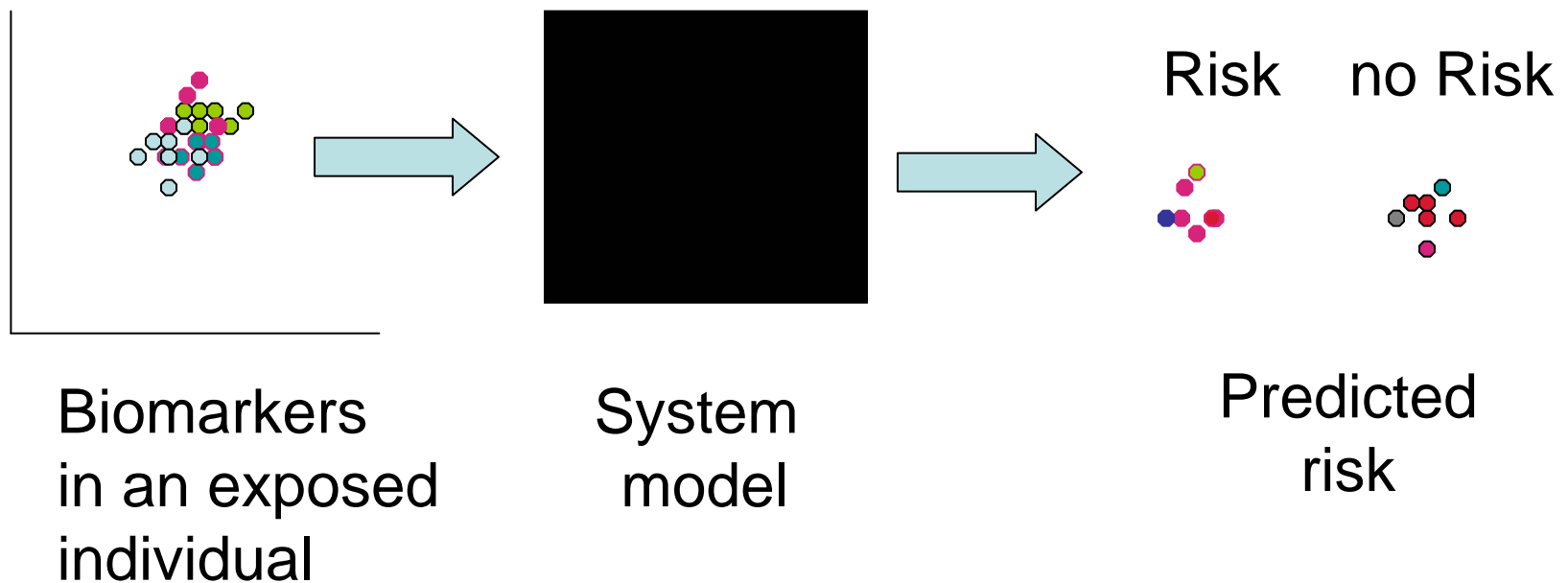
Individual differences in sensitivity to radiation occur:

- acute normal tissue response to therapy (repair defects)
- secondary cancers (Gorlin, Li-Fraumeni syndrome)

Accommodation of individual variability into biomarker-based risk projections may require a systems approach ?

How can biomarkers bridge the gap between exposure and final health effects in terms of individual sensitivity?

What systems biology can do for you (in an ideal world) ?



Did anyone notice the problems.....

- 1) Biomarkers of a cellular response may not predict anything, other than DNA damage.
- 2) Causes of radiation-induced and “sporadic” diseases are unclear, may even be different.
- 3) Extent of, and mechanism of, individual sensitivity unknown
- 4) Long term health effects may have multiple confounders that may even change during latency.
- 5) No systems model of adverse radiation response.

Biological uncertainties in the search for biomarkers

- Do DNA damage indicators predict anything?
- What is the mechanism by which radiation causes disease after a long latency ?
- What measurable changes precede development of the disease ?
- How do individual differences influence the processes ?

But the journey starts with one step....

Candidate biomarkers may include:

- DNA mutations fixed into the genome
- Ultrastructural changes (protein foci, chromosome breaks, translocations, micronucleii)
- Transcriptional and translational shifts, protein modification
- micro RNA & epigenetic changes (genome and chromatin)
- Metabolite changes (e.g. lipid peroxides, ROS/NOS)

The challenge to develop a systems approach

- Shift from descriptive to mechanistic viewpoint
- Must start quantitative radiation biology
- Partnerships of experimentalists and theoreticians
- Replace DNA “centricism” and model-based dogma
- Re-evaluate if there is a “unifying” mechanism of health effects
- Need to integrate responses at different scales
- Do we need to confuse the issue with individual differences?

Assessment of risk,.....in the dose region from fractions of mGy to a few tens of mGy, would be greatly facilitated by knowledge of the ***shapes of the dose-response relationships*** for radiation induced cancers in humans.

.....not available and not likely to be obtained by direct observations.

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But maybe a systems approach can provide this information ?

Or maybe we need to start
to understand
the proteomics ?

QuickTime™ and a
decompressor
are needed to see this picture.

3rd RadSysBio Rovaniemi: Suggested topics

- What biomarkers are used to predict individual sensitivity to radiation exposures?
- Are they all reliable enough? Do we need more of them?
- Could high throughput techniques be helpful in finding new biomarkers for individual sensitivity studies?
- Could we use experience of cancer biology biomarker studies for radiation protection?
- What is the role of systems biology in all this ?