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Can and should radiological protection be individualised?

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Current system of protection

- Avoid tissue injury (deterministic effects)
- Minimise risk of stochastic effects (cancer/hereditary)
    - justification, optimisation, dose limitation
    - limits derived from notional average that does not exist

…a population-based system

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The reality

- Not everyone is identical
- Sex-specific differences in risk, especially in breast (ERR incidence per Gy, 0.58 in females vs 0.35 in males)
- Age dependency of risk

Categories requiring protection

Radiosensitivity syndromes

Rare recessive disorders leading to cellular and sometimes clinical radiosensitivity, include for example:

- Ataxia telangiectasia
- Fanconi anaemia
- Nijmegen breakage syndrome
- Cornelia de Lange syndrome
- Severe combined immuno-deficiency (SCID)

Radiation sensitive paediatric sub-populations

- Retinoblastoma (Rb)
  - soft tissue sarcomas in radiation fields
- Neurofibromatosis type 1 (NF1)
  - second cancers associated with R/T of gliomas
- Li Fraumeni Syndrome (LFS)
  - high RR of 2nd and 3rd cancers related to R/T
- Nevoid basal cell carcinoma syndrome (NBCCS)
  - multiple basal cell skin cancers in radiation fields

See Kleinerman RA (2009) Paediatr. Radiol. 39 Suppl 1: S27-S31

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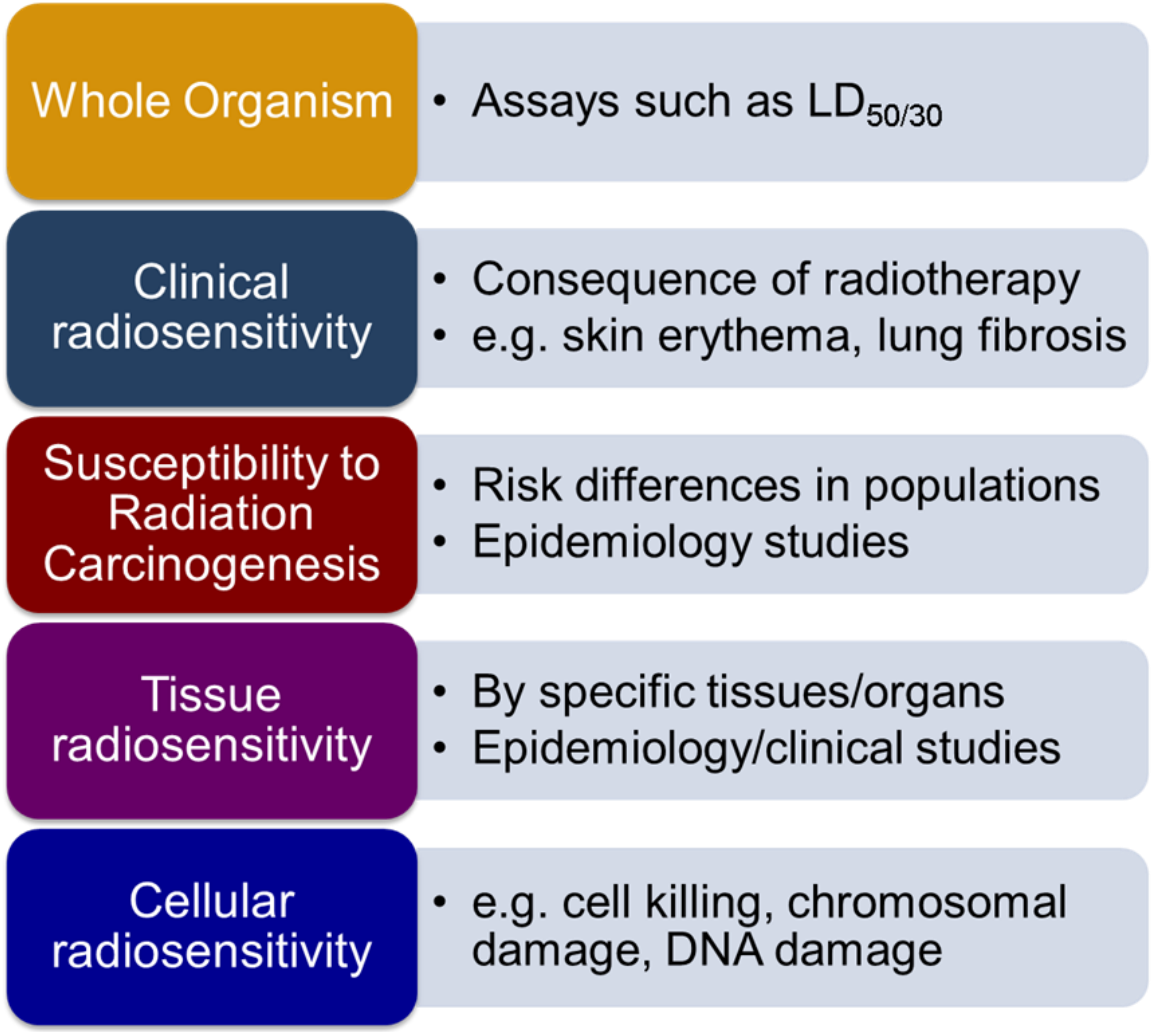
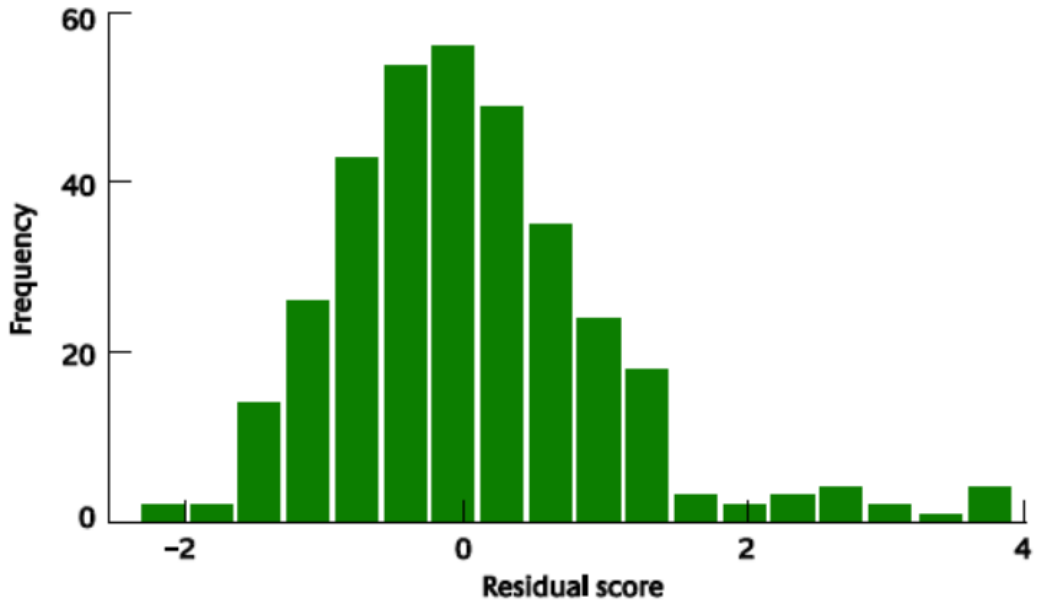
Measuring radiosensitivity



Clinical radiosensitivity –severity of normal tissue reactions



1010 breast cancer patients: residual score standardized and accounts for patient and treatment related factors

Barnett et al 2011, Int. J. Radiat. Oncol. Biol. Phys. 82: 1065-1074

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Modifiable risk factors - smoking

TABLE 2.2 Additional cumulative absolute risk of radon-induced lung cancer per 100,000 people (to age 75 years)

Long-term average radon exposure (Bq m^{-3})	Non-smokers *A*	Continuing smokers *B*	*B/A*
100	0.06	2.2	36.7
200	0.12	4.3	35.8
400	0.25	8.3	33.2
800	0.51	15.8	31.6

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Modifiable risk factors - diet

- Dietary/calorie restriction known to extend life and reduce cancer burdens
- DR/CR found to modulate cancer incidence in irradiated animals – evidence from 1940s onwards
- Assumed to be due to epigenetic modification of gene expression

Reviewed by Karabulutoglu et al. Int J Radiat Biol. 2019, 95(4):452-479

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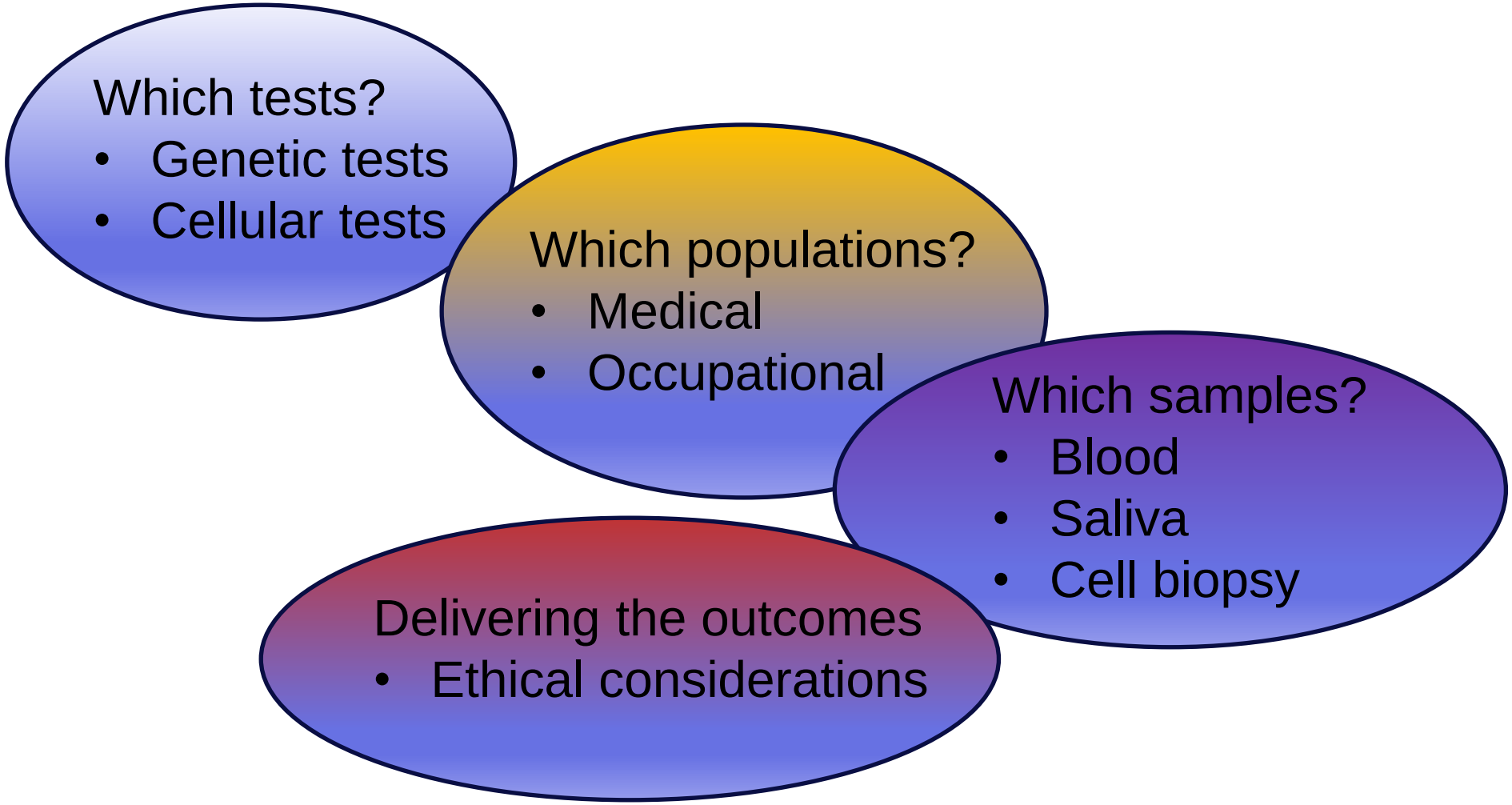
Measuring radiosensitivity



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What tests have been proposed?

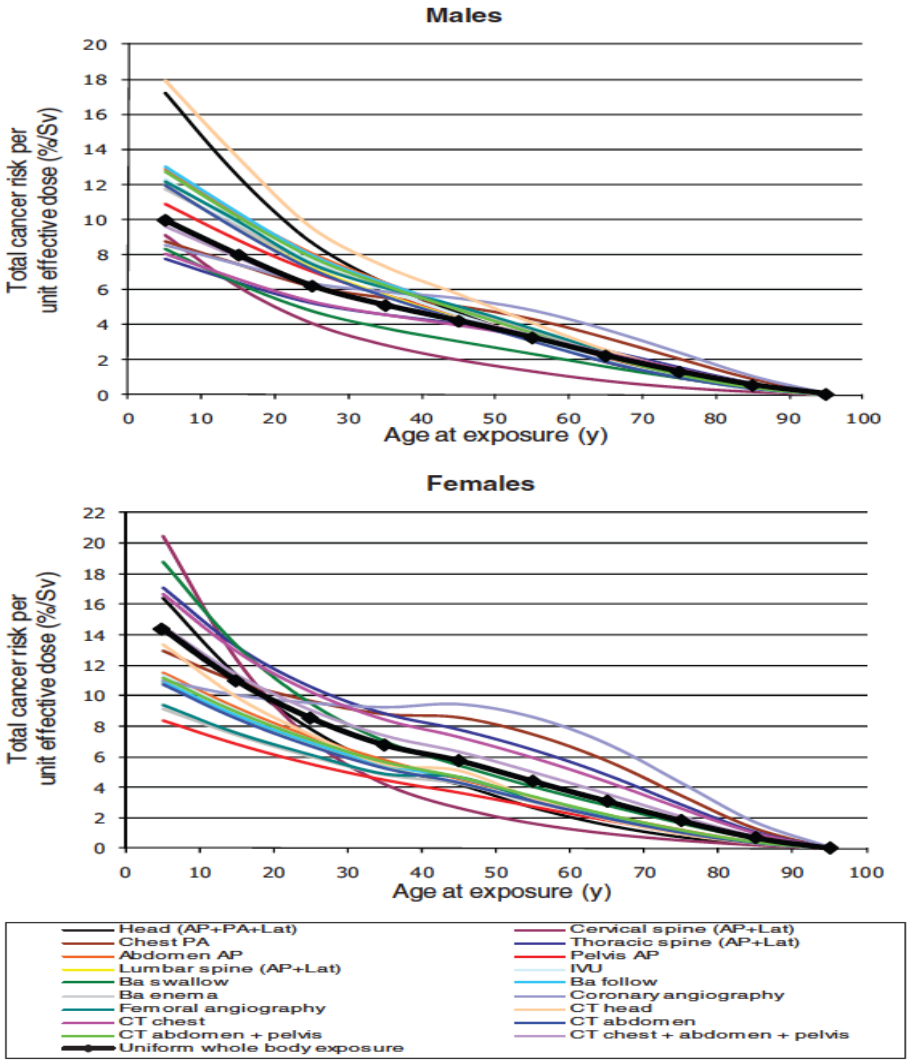
- Apoptosis in CD4/CD8 T-lymphocytes exposed to 8Gy found predictive of late normal tissue reactions in 399 patients (31% grade 2 toxicity, 7% grade 3). *Ozsahin et al 2005 Clin. Cancer Res. 11:7426-33.*

- ATM foci numbers in cultured skin biopsy fibroblasts at short times after exposure. *Vogin et al. Int J Radiat Oncol Biol Phys. 2018 101:690-693*. Also see http://www.neolysdiagnostics.com/en/

- Gene expression tests, eg using CDKN1 post-radiation upregulation. *Badie et al 2008 Br J Cancer. 98(11):1845-51*

Cancer risk variation by age at exposure – medical diagnostic exposures

The variation of lifetime Risk of Exposure-Induced Cancer incidence per unit effective dose (expressed as %/Sv) by sex and age-at-exposure for the ICRP Euro-American composite population, for 18 types of medical diagnostic X-ray examinations and a uniform whole-body dose of 10 mGy of reference low-LET radiation. Cancer incidence excludes non-melanoma skin and bone cancers, and no weighting by health detriment is included (Wall et al. 2011; Harrison et al. 2016).



Refined risk estimates for informed decision making?

- ICRP publication 147 suggests that in diagnostic medical settings, Effective doses could be adjusted for age and sex to provide a more accurate estimate of risk to individuals to inform decision making/consent for procedures
- Developments in medical dosimetry, notably due to the availability of a much larger and more representative range of phantoms for dose calculation have the potential to allow for a more refined estimate of dose to the body for individual medical diagnostic examinations
- While individualised dosimetry appears realistic, and computationally feasible, the uncertainties in risk remain considerable, most importantly at low doses in the range used in medical imaging

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ICRP activities

Task Group 111 - Factors Governing the Individual Response of Humans to Ionising Radiation

- Established 2018
- A joint TG of Committee 1 (Radiation Effects) and Committee 3 (Medical Aspects of Protection)

- Preceded by: joint C1/C3 meetings at Abu Dhabi Symposium, 2013 and Seoul Symposium, 2015; formation of a C1 working party on 'Individual Radiosensitivity' during C1 meeting in Chennai, 2016; presentations on the topic during Paris Symposium, 2017

TG111 ToR

The TG will review the currently available information on individual radiation responses with special focus on the following questions and issues:

- What is the impact of age, sex and other determinants on normal ti… and incidence of cancers and other diseases following radiation exposure?
- What is the contribution of genetics to individual… esponses with respect to adverse reactions to varying doses such as given d… apy? Would predictive tests contribute to a better radiation protection of radi… nts without compromising cancer cure rates?
- What is the contributio… d epigenetic factors to tissue radiation response with respect to cancer inductio… oses and dose rates?
- What i… that modifiable factors can affect individual risk of radiation-induced cancer, …ons and other non-cancer diseases?
- …hat are the ways to quantify the potential impact of individual response to radiation on the incidence of cancers, non-cancer diseases and normal tissue reactions?

Literature review – no consideration of the implications for RP

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Scope

Health effects under consideration:

- Normal tissue reactions after radiotherapy
- Cancers
- Circulatory diseases
- Cognitive impairment
- Cataract

Types of evidence/study under consideration:

- Clinical studies
- Epidemiological studies
- Experimental animal studies
- Cellular assays

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Publications

- **Applegate et al (2020) Individual response of humans to ionising radiation: governing factors and importance for radiological protection. Radiat Environ Biophys. 2020 May;59(2):185-209.**

- **Abdelkarem et al (2022)– Effect of Race and Ethnicity on Risk of Radiotherapy Toxicity and Implications for Radiogenomics. Clin Oncol, online ahead of print - doi: 10.1016/j.clon.2022.03.013**

- **Barnard & Hamada (2022) Individual response of the ocular lens to ionizing radiation. Int J Radiat Biol, online ahead of print - doi: 10.1080/09553002.2022.2074166**

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Returning to ‘Can’ and ‘Should’

- The answers are inter-dependent and different for different categories of exposure

A. Medicine – radiotherapy

- There are indications that some assays can be predictive of normal tissue reactions, these are limited in use to just a few centres; there is no universally adopted assay.
- So, *can* protection against normal tissue injury in radiotherapy be indiviulaised?
- I think it *could* but we are not there yet
- Therefore, *should* individual protection be adopted
- I think yes, as and when rapid, robust, reliable and transferable assays are available
- Currently, patients can be provided with information on the ‘lifestyle’/modifyable factors that affect the severity of normal tissue reactions

‘Can’and ‘Should’ II

B. Medicine – diagnostic exposures

- Age, sex and body form can provide improved dose information
- There is a reasonable understanding of how cancer risk varies with age and sex, but the uncertainties are considerable, particularly at the lowest diagnostic doses, and at younger ages
- So to a limited extent and with considerable uncertainty, a more individual approach *could* be adopted
- This latter point makes me somewhat uneasy in suggesting to patients that an individual risk estimate can be provided to them, at best they are age- and sex-adjusted
- Professionals might be concerned that patients could consider legal action if they did in fact develop a cancer after a procedure or set of procedures

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‘Can’ and ‘Should’ III

C. Occupational exposure

- The ILO are clearly against the use of genetic testing in the workplace
- The age- and sex- dependence of cancer risk is of course present and could in principle be used to assign lower risk groups to higher risk tasks
- How would this fit with legislation regarding age- and sex- discrimination, and how would trades union groups view this?
- NB that in the special case of space flight crew, NASA adopted different dose limits for males and females – ICRP is developing a report in protection in space
- A case *could* be made for some sort of stratification, but I think it would be a very sensitive issue and unlikely to be adopted
- *Should* we individualise? Perhaps a case can be made in the case of high risk work in emergency recovery, but more generally, no

‘Can’ and ‘Should’ IV

D. Public protection

- The public dose limit is currently 1 mSv/y, ad so is already in the range where uncertainties are very high
- There is substantial variation in natural background radiation exposures around the world
- To me, these two factors alone make it clear that protection neither *can* nor *should* be individualised

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Thanks for your attention

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www.icrp.org