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Individual radiosensitivity and possibilities for prediction

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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

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But….

- We are all different!
- Gender specific differences in risk, especially in breast (ERR incidence per Gy, 0.58 in females vs 0.35 in males)
- Age dependency of risk

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Ways to assess radiosensitivity

Whole Organism	• Assays such as $LD_{50/30}$
Clinical radiosensitivity	• Consequence of radiotherapy • e.g. skin erythema, lung fibrosis
Susceptibility to Radiation Carcinogenesis	• Risk differences in populations • Epidemiology studies
Tissue radiosensitivity	• By specific tissues/organs • Epidemiology/clinical studies
Cellular radiosensitivity	• e.g. cell killing, chromosomal damage, DNA damage

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Definitions

Britel et al 2018 Int J Radiat Biol. 2018 94:503-512 The use of the term 'radiosensitivity' through history of radiation: from clarity to confusion.

Proposal:

- To restrict use of ‘radiosensitivity’ to *‘…any clinical and cellular consequences of radiation attributable to cell death.’*
- To use ‘radiosusceptibility’ to *‘…describe the radiation-induced cancers or any feature that is attributable to cell transformation.’*

Difficulties (Wojcik et al 2018 J Radiol Prot. 2018 38:N25-N29):

- ‘susceptibility’ and ‘sensitivity’ considered synonymous in most Thersauruses
- ‘resistance’/’resistant’ commonly used as antonym for both
- Suggests a different mechanistic basis for each phenomenon

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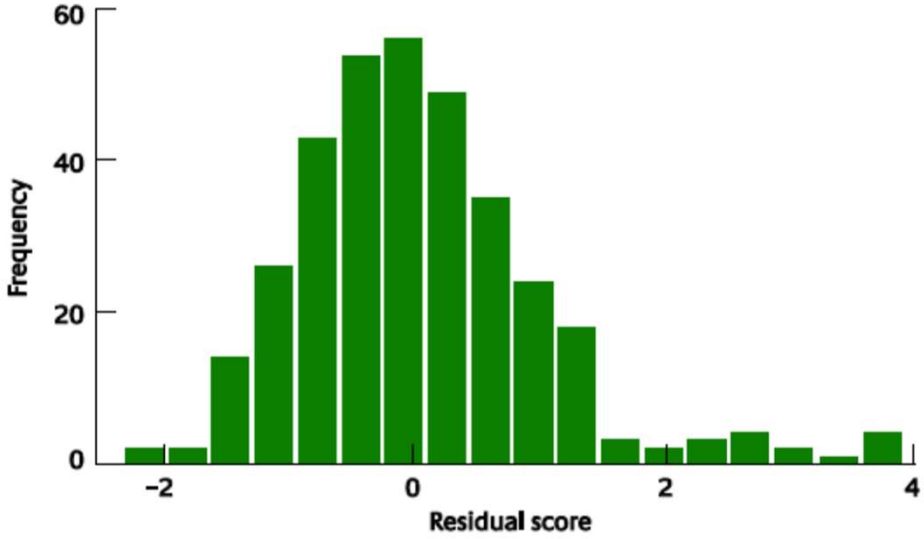
Clinical radiosensivity



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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Clinical radiosensitivity factors

- Increasing age in adults
- Smoking
- Diabetes and collagen vascular diseases
- Genetics
- Mixed evidence for sex, ethnicity, BMI, diet, alcohol

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Radiosensitivity syndromes

Rare recessive disorders leading to cellular and sometimes clinical radiosensitivity

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

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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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Breast cancer mutation carrier and radiotherapy

- ATM heterozygotes – approx 2 fold elevated BC risk

  (Goldgar et al 2011, Breast Cancer Res 13: R73)

- ATM and radiotherapy – somewhat greater risk of contralateral second breast cancer

  (Bernstein et al 2010, JNCI 102: 475-483)

- Case-only studies indicates BRCA1, BRCA2, CHEK2 and ATM increase risk of secondary breast cancer (RR=2.18)

  (Broeks et al 2007, Breast Cancer Res J: R26)

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How difficult can it be?

WECARE study - ~52500 women with Breast cancer
Nested association studies with ~708 CBC cases and ~1397 UBC controls
http://skiweb.mskcc.org/WeCare/front.html

• CHEK2 variant	↑RR with IR but NS
• ATM, full scan	1 rare variant ↑RR 2.8 with IR
• 152 SNPs in 6 ATM targets	no associations
• BRCA1/2 variants	no associations
• 21 SNPs in BC loci	no associations
• Pregnancy factors	one strong association ↑RR 6

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Diagnostic exposure

- BRCA1/2 carriers at increased risk of breast cancer following multiple chest x-rays (Andrieu et al 2006, J. Clin. Oncol. 24: 3361-3366)

- BRCA1/2 and mammography

  Mixed evidence

  Screening from 35 years beneficial

  (Berrington de Gonzalez 2009, JNCI 101: 205-209)

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Interactions may be important

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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Effects of 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. 2018 Sep 24:1-27.

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Integrating genetics and epigenetics?

Epigenetic DNA methylation based ‘clocks’

- methylation status of a sub-set of sites alters predictably with age
- Clocks can be slowed by adopting a healthy lifestyle
- Clocks can predict time to death
- Clocks run fast in progerias
- Clocks run fast in those with non-communicable diseases
- Environmental agents, eg high levels of air pollution can speed up clocks

What will radiation do?

See review, Horvath & Raj Nat Rev Genet. 2018 19:371-384

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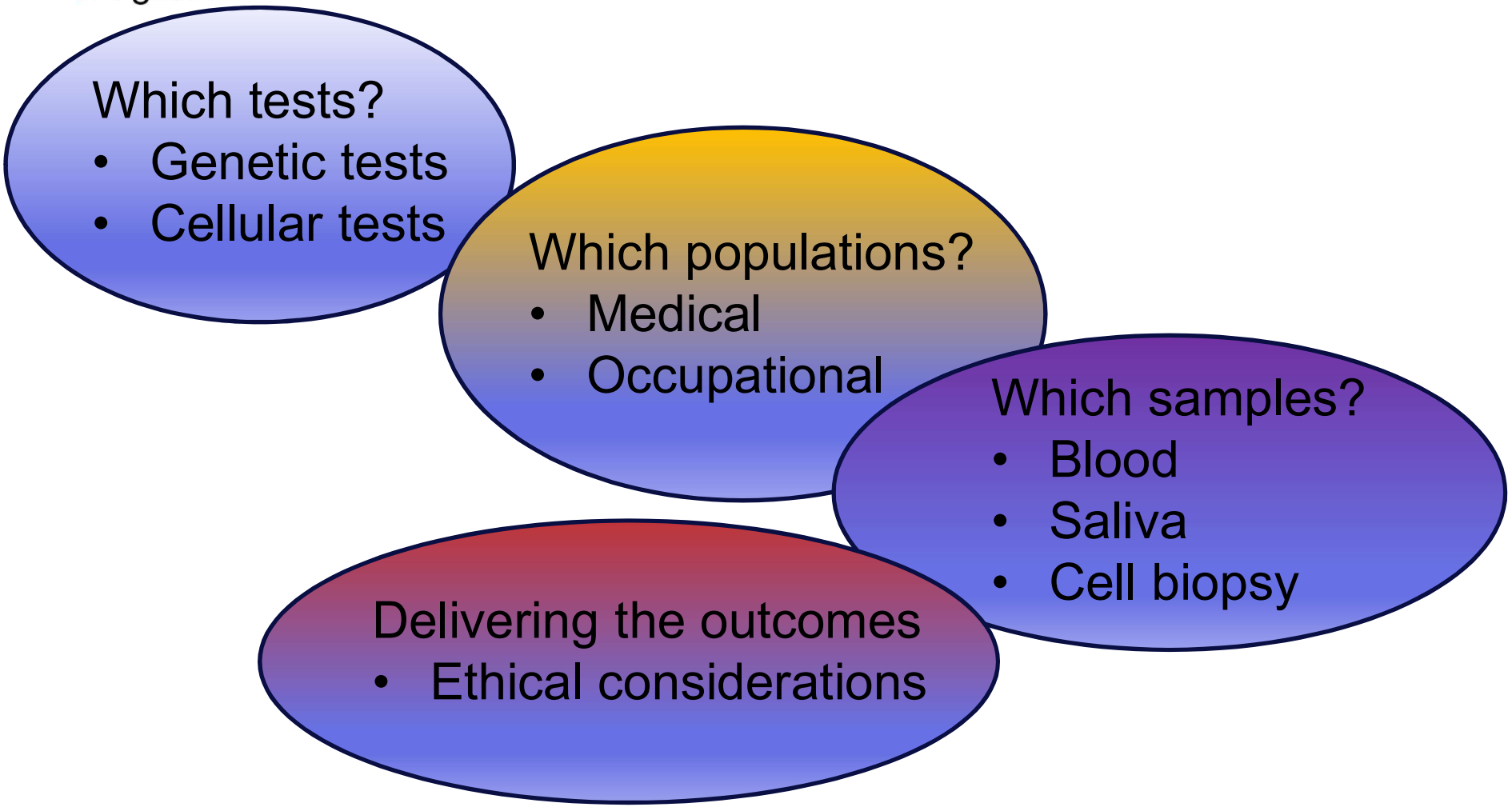
So, what about prediction?



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The hunt for genetic predictors of R/T reaction

REQUITE

Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-Effects and Improve Quality of Life in Cancer Survivors

Collecting blood from 5300 cancer patients undergoing R/T, Oct 2013 – Sept 2018. Around 4430 recruited so far…

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Prediction of radio-sensitivity

Radiotherapy reactions – no tests in widespread clinical use internationally, a long held aspiration:

- 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/

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At diagnostic levels?

- gH2AX foci in 2-4mGy exposed mammary epithelial cells, more foci in cells from patients with high breast cancer risk (at least 20% on basis of family history or known mutation carrier). *Colin et al 2011 Int. J. Radiat. Biol. 87:1103-1112.*

- Undoubtedly will be more challenging

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How to utilise the knowledge?

Reliable prediction will be key:

- Genetic testing
- Cellular / molecular endpoints
- Epigenetic clocks

Requires:

Accuracy, speed, reproducibility/transferability, acceptance

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Implications for RP - ethics

- The ability to identify sensitive groups or individuals will need careful consideration, especially for occupational exposure.
- Possible need to consider the justice in protecting small numbers of very high risk individuals
- In the absence of routine tests, provision of information on risk modifiers and reduction/avoidance should be the main focus.
- *…and what might the legal implications be?*

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Requirements

- Knowledge of the range of radiosensitivity
- Reliable methods to predict
- Agreement that there may be benefits
- Robust framework in which to operate
- Acceptance

ICRP TG on individual response to radiation – just approved

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https://www.gov.uk/government/publications/human-radiosensitivity