Review of biomarkers that could potentially be used for molecular epidemiological studies in radiation-exposed cohorts

MELODI Workshop 2012, Helsinki

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on behalf of the DOREMI working group on biomarkers for molecular epidemiological studies

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DoReMi
Integrating Low Dose Research

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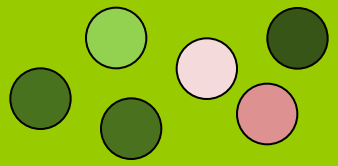
SEVENTH FRAMEWORK PROGRAMME

DOREMI working group on biomarkers

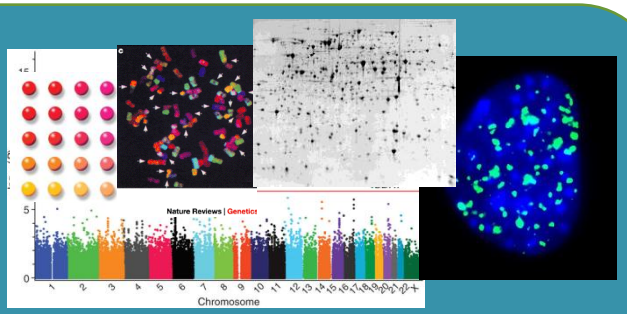
Information needed to conduct a molecular epidemiological study ?

WP6 meeting in CREAL (E.Cardis), Barcelona 2010

Do we have enough information on received doses?



Is the size of the cohort suitable to attain enough statistical power?



Which biomarkers will be measured in the biological samples?

Are biological samples available/collectible?

What are the requirements for the study to be approved by relevant ethical committees ?

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ELSEVIER

Review

Ionizing radiation biomarkers for potential use in epidemiological studies

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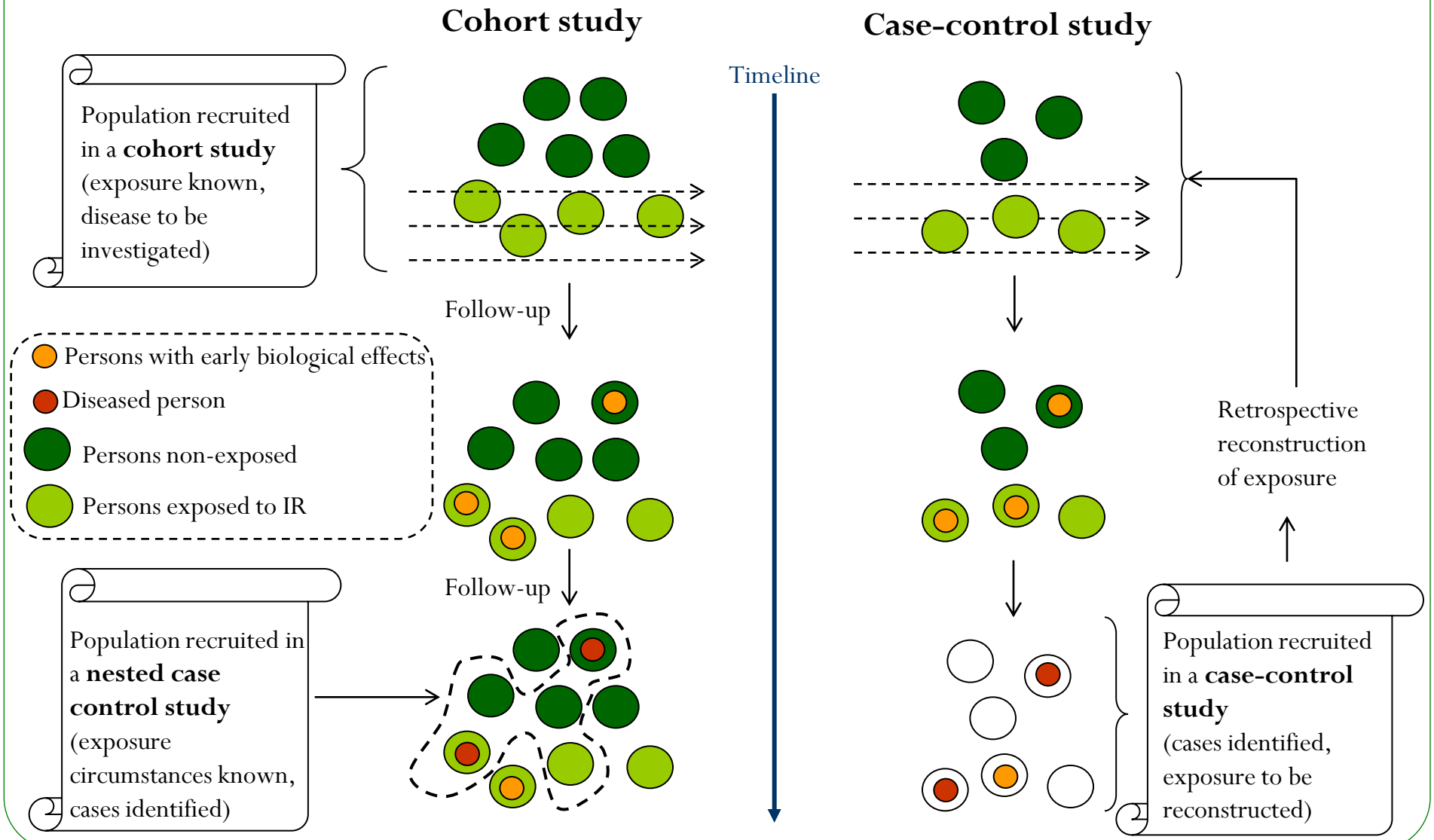
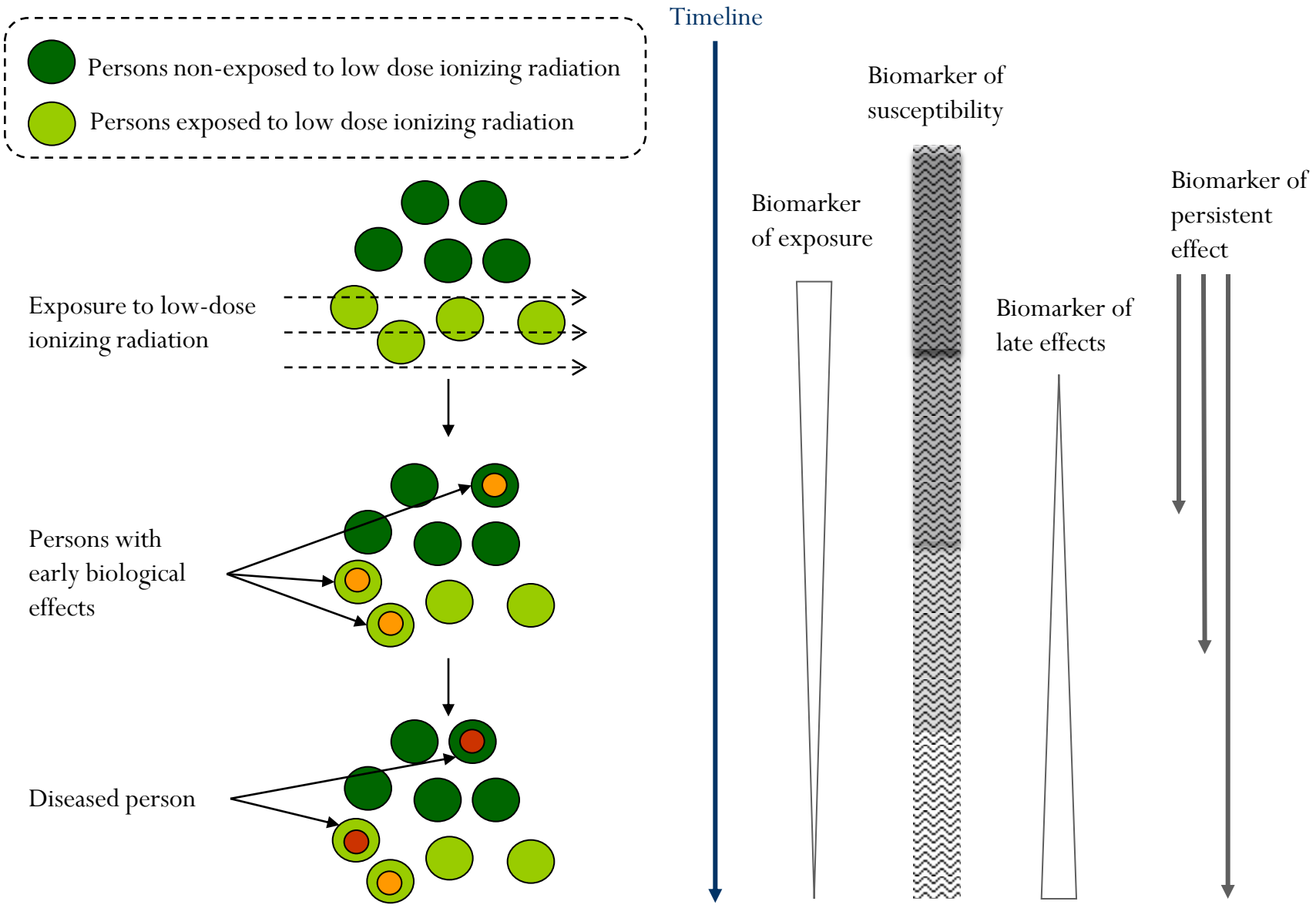
Epidemiological study designs



Temporal classification of biomarkers

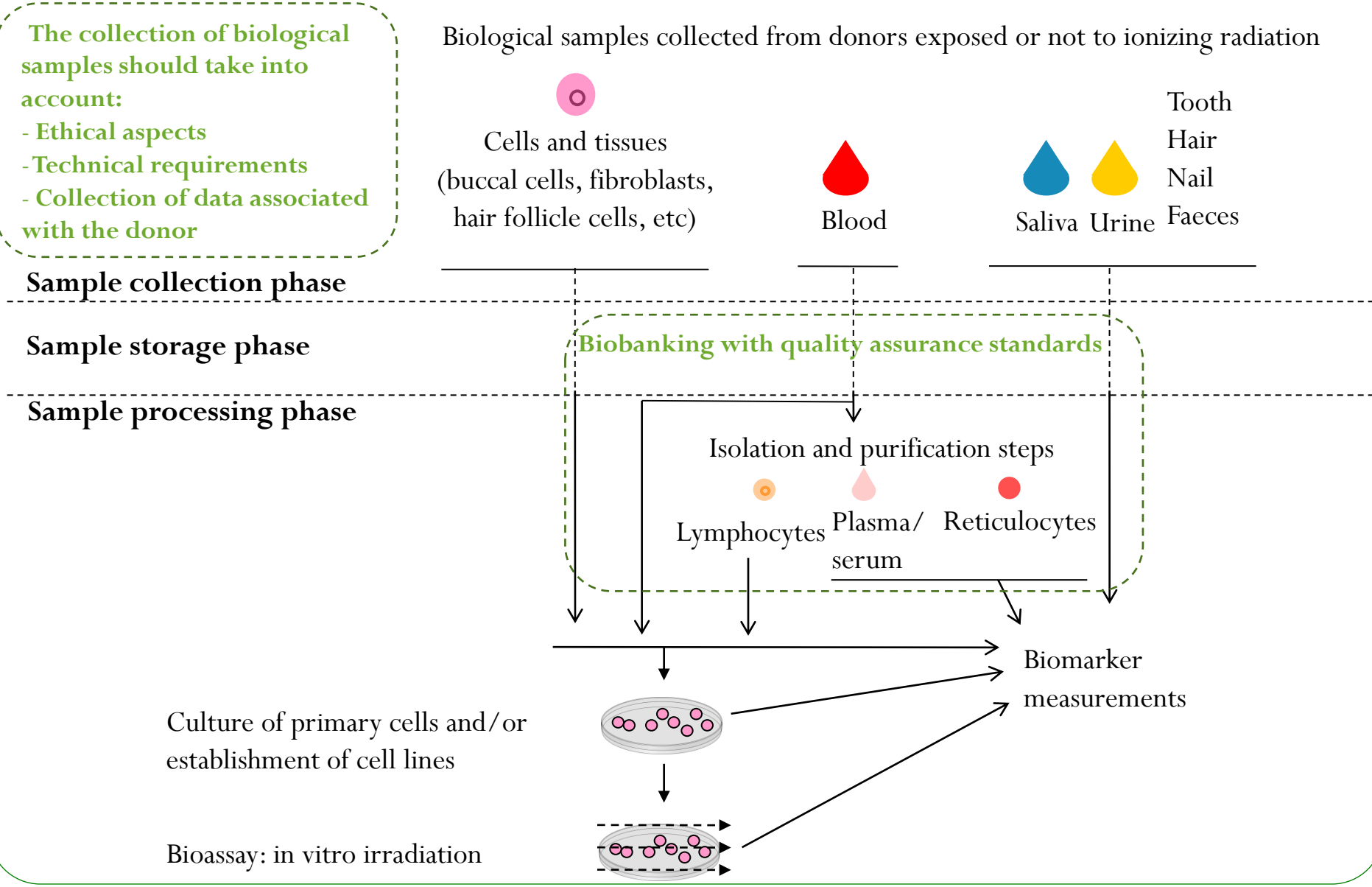


Aspects to be considered to select a biomarker for molecular epidemiological studies in low dose radiation-exposed cohorts

- Validity of the assay measuring the biomarker
- Sensitivity, specificity, reproducibility, and biological plausibility.
- Suitability of the biomarker and assay for use in an epidemiological study:
  - study design
  - timing of sample collection
  - Logistics and cost
- Invasiveness and acceptability of the sample collection.

Collection of biological samples

The collection of biological samples should take into account:
- Ethical aspects
- Technical requirements
- Collection of data associated with the donor



Cytogenetic biomarkers (I)

- Upon exposure, the persistence of most cytogenetic biomarkers is impaired by the renewal of peripheral blood lymphocytes (6 months to 3.5 years).
- Whole blood and peripheral blood mononuclear cells (PBMC) are frequently used.

Biomarkers	Sensitivity	Specificity to IR and confounders
Dicentrics	0.1-5Gy	Almost exclusively indu ced by IR, possible confounding factor: smoking
Translocations	0.25-4Gy	Confounding factors: smoking; strong age effect
Complex Chromosomal Rearrangement (CCR)	Unknown	High LET and heavy ion exposure
Premature Chromosome Condensation (PCC)	PCC fragments: 0.2-20Gy PCC rings: 1-20Gy	IR specific to a large extent
Telomere length	Not yet established	Not specific: modulated by viral infection; Potential confounders: age, oxidative stress
Micronuclei	0.2-4Gy but limited sensitivity at doses <1Gy. Selective scoring after centromere FISH : ~100 mGy	Not specific: modulated by genotoxins Confounding factors: age, gender

Cytogenetic biomarkers (II)

	Temporal classification of IR biomarkers			
	Exposure	Susceptibility	Late effects	Persistent effects
Dicentrics	√	P	P	P
Translocations	√	P	P	√
CCR	√ (high LET IR)	P	P	P
PCC rings and fragments	√			
Telomere length	P	P	P	P
Micronuclei	√	P	P	

√: direct evidence that this biomarker could be used as such

P: potential or theoretical use

Biomarkers of DNA damage and nucleotide pool damage (I)

- Biomarkers should be measured minutes to days post-irradiation.
- Wide variety of biological samples can be used (whole blood, PBMC, fibroblasts, buccal cells, saliva, hair bulb, …).

Biomarkers	Sensitivity	Specificity to IR and confounders
SSB/DSB	0.1- 8Gy	Not specific: modulated by several mutagens and oxidative stress Confounding factors: age, smoking, diet
γ-H2AX	0.01-8Gy	Not specific: also formed in response to UV and other genotoxins
Extracellular 8-oxo-dG	1-100mGy Saturation for doses between 0.1-1 Gy	Not specific: also formed by endogenous oxidative stress Confounding factors: unknown

Biomarkers of DNA damage and nucleotide pool damage (II)

	Temporal classification of IR biomarkers			
	Exposure	Susceptibility	Late effects	Persistent effects
SSB/DSB	√	P		
γ-H2AX	√	P	P	P
Extracellular 8-oxo-dG	(oxidative stress)	P		

√: direct evidence that this biomarker could be used as such

P: potential or theoretical use

Induced mutations or germline inherited mutations or variants (I)

- SNP and copy number variants (CNV): not time dependent
- Whole blood and derivatives can be used (+ fibroblasts and tissues for SNP and CNV / copy number alteration (CNA))

Biomarkers	Sensitivity	Specificity to IR and confounders
SNP, CNV and inherited gene mutations	Unknown	Not specific Confounders unknown
CNA	Unknown	Not specific Confounders: unknown
Glycophorin A **(in heterozygous MN blood group only)**	>1Gy	Not specific: formed after exposure to other genotoxins
HPRT	>90mGy	Not specific: formed after exposure to other genotoxins

Induced mutations or germline inherited mutations or variants (II)

	Temporal classification of IR biomarkers			
	Exposure	Susceptibility	Late effects	Persistent effects
SNP, CNV and inherited gene mutations		√	P (minisatellites in offspring)	P
CNA	P		√	P
Glycophorin A	√			√
HPRT	√			√

√: direct evidence that this biomarker could be used as such

P: potential or theoretical use

Biomarkers related to transcriptional and translational changes (I)

- Most biomarkers should be measured within hours to days after exposure.

Biomarkers	Sensitivity	Specificity to IR and confounders
ATM/CH/p53 pathway	Unknown	Not specific
Changes in RNA levels identified by transcriptomics	Unknown	Unknown at present time
Serum amylase	>1Gy	Not specific
C-reactive protein	>1Gy	Not specific: modulated by levels of inflammation
Cytokines	>1.2mGy	Not specific
Proteins identified by proteomics	Moderate to very good	Unknown at present time/remains to be fully established

Biomarkers related to transcriptional and translational changes (II)

	Temporal classification of IR biomarkers			
	Exposure	Susceptibility	Late effects	Persistent effects
Changes in the mRNA levels of the ATM/CH/p53 pathway	√	P		
Changes in RNAs identified by transcriptomics	√	P	P	P
Serum amylase	√			
CRP	√			√
Proteins identified by proteomics	P	P	P	P
Cytokines	P	P	P	P

√: direct evidence that this biomarker could be used as such

P: potential or theoretical use

Epigenomic modifications

- Sensitivity, specificity, validity, etc need to be further defined.

	Temporal classification of IR biomarkers			
	Exposure	Susceptibility	Late effects	Persistent effects
Histone modifications	P	P	P	P
DNA methylation	P	P	P	P
miRNA profiling	√	P	P	P
Phosphoproteomics	P	P		

√: direct evidence that this biomarker could be used as such

P: potential or theoretical use

Other biomarkers

	Temporal classification of IR biomarkers			
	Exposure	Susceptibility	Late effects	Persistent effects
Reactive Oxygen Species	P	P	P	P
Metabolites and metabolomic	√	P	P	P
Cell cycle delay, apoptosis and survival	P	P		
EPR/ESR	√			√
Internal emitters	√			

√: direct evidence that this biomarker could be used as such

P: potential or theoretical use

Conclusions

- Constraints: sensitivity and specificity to IR, persistence, availability and quality of biosamples, ethics, logistic and costs.
- Currently, no ideal biomarkers for assessing exposure, effect or susceptibility of low dose radiation exposure but good candidates.
- Validation work is needed for many potential biomarkers of low dose IR.
- Careful planning of molecular epidemiological studies involving enhanced interaction between the epidemiology, biology and dosimetry communities is essential.

Thank you for your attention!

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