Low dose exposure from pediatric CT scans and cancer risk

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Why are CTs of interest in radiation protection?

- Diagnostic radiation is an indispensable, sometimes life-saving, tool in modern medicine.
- But use of diagnostic X-rays and of high-dose techniques (CT, interventional procedures using X-rays) has grown dramatically in recent years
  - improvement of technology
  - more applications
  - markedly increased use
  - and increase in dose …

Courtesy; F. Mettler, 2008

… growing radiological protection and public health concern

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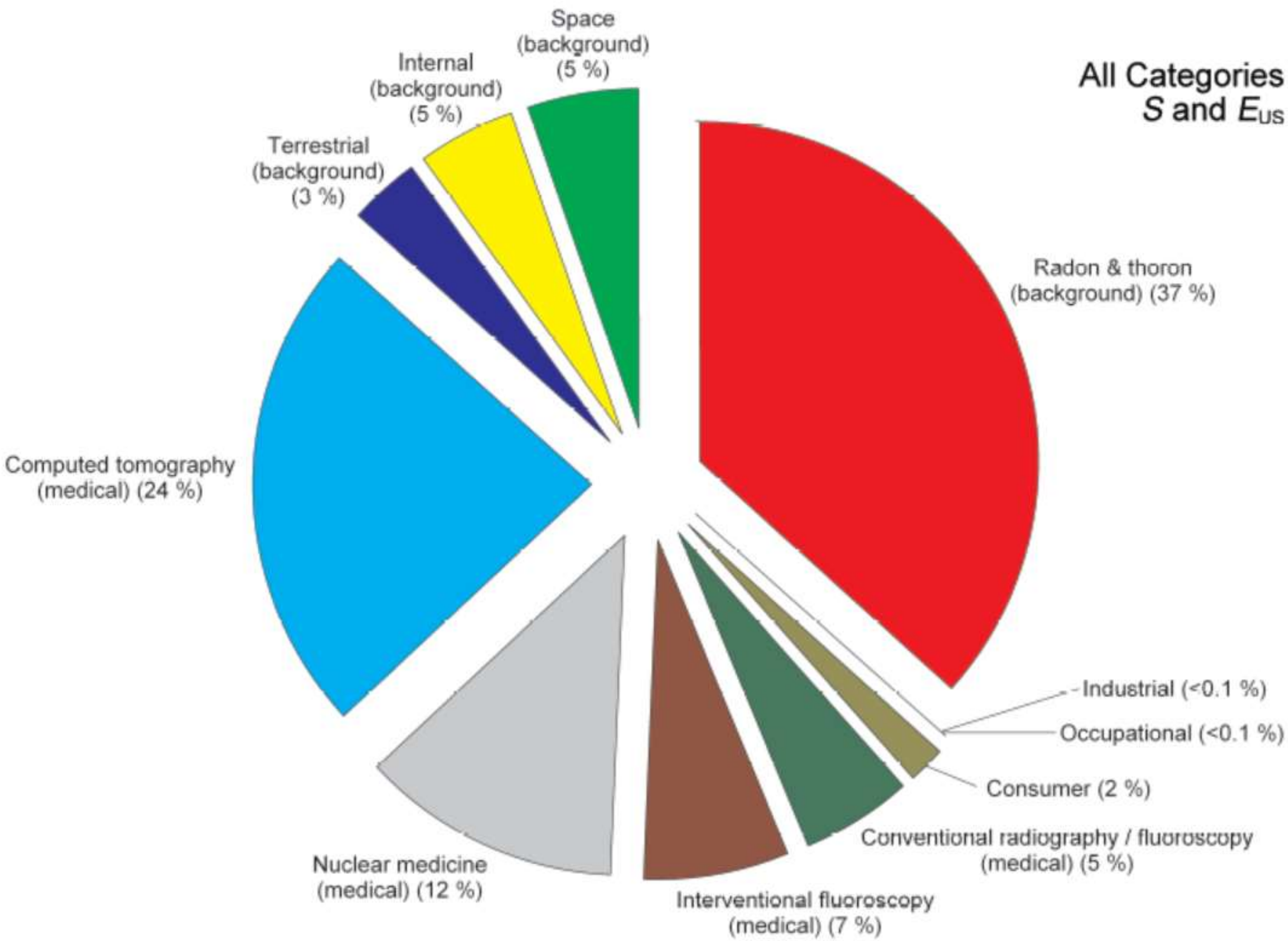
NCRP Report No. 160, *Ionizing Radiation Exposure of the Population of the United States*



Questions

- What is the public health impact of this increase ?
  - Brenner et al – predictions from A-bomb survivors
  - *But uncertainties regarding effects of low to moderate doses received in fractionated fashion*
- Are there subgroups with increased sensitivity ?
- Need to optimise imaging protocols, particularly among young people ?

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The issue of children

- 5-10% of all CTs in children
- Because of their smaller mass, children tend to receive higher doses to specific organs
  - doses to target organs can be of the order of a few tens of mGy per examination
  - cumulative doses may reach 100 – 200 mGy (or more) if procedures are repeated
  - great variability of doses and procedures not always adapted to paediatric patients
- Children have a longer life span to express any radiation-related detriment

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Studies with estimate of risk per mGy

	Population size and age range	ERR/mGy (95% CI)	
Pearce et al, 2012, Berrington et al al 2016 (UK)	178,604 CT patients 0-22 years old	**Leukaemia** (74 cases) 0.036 (0.005, 0.120) 0.033 (0.004, 0.114) 0.037 (0.005, 0.125) **Brain tumours** (135 cases) 0.023 (0.010, 0.049) 0.012 (0.004, 0.031)	**Limitations - Organ-dose** - Overall - excluding previous cancers - excluding leukaemia related cond. - Overall - excluding previous cancers, conditions
Matthews et al, 2013 (Australia)	680,211 CT patients 0-19 years old	**Leukaemia** (246 cases) 0.039 (0.014, 0.070) **Brain tumours** (283 cases) 0.021 (0.014, 0.029)	**- Exposure misclassification** **- Increase for all cancer types**
Journy et al, 2014, 2015 (France)	67,274 patients 0-10 years old	**Leukaemia** (17 cases) 0.057 (-0.079, 0.193) 0.187 (NA) **Brain/CNS tumours** (22) 0.022 (-0.016, 0.061) 0.028 (NA)	**- Short follow-up (4 years), few cases** - Overall - excluding predisposing factors - Overall - excluding predisposing factors

Studies with no estimate of dose-related risk

	Population size and age range	Risk measures (95% CI)	
Huang et al, 2014	24,418 patients with brain CTs 0-18 years old	HR compared to population in health system **All cancers** (39) 1.29 (0.90, 1.85) **Leukaemia** (8) 1.90 (0.82–4.40) **Brain tumours** – all (19) 2.56 (1.44–4.54) ***HR increased with numbers of CTs***	- **Short follow-up** - **Small numbers of cases** - **No dose estimation**
Krille et al, 2015	80,000 patients 0-15 years old	SIR **Leukaemia** (12 cases) 1.72 (0.89–3.01) 1.79 (0.92–3.12) **CNS** (7 cases) 1.35 (0.54–2.78) 1.79 (0.92–3.12)	- **No dose used in analysis** - **Small numbers** Overall Excluding subjects at risk Overall Excluding subjects at risk

Issues in interpreting results

- Confounding by predisposing condition
  - UK, Netherlands, France … little evidence
  - Miglioretti – US …
- Assessment of doses
  - Very variable - type of scans, machine, protocol, organ, age/size variability
  - Missing doses (CTs in other hospitals, other procedures)
- Individual sensitivity ?

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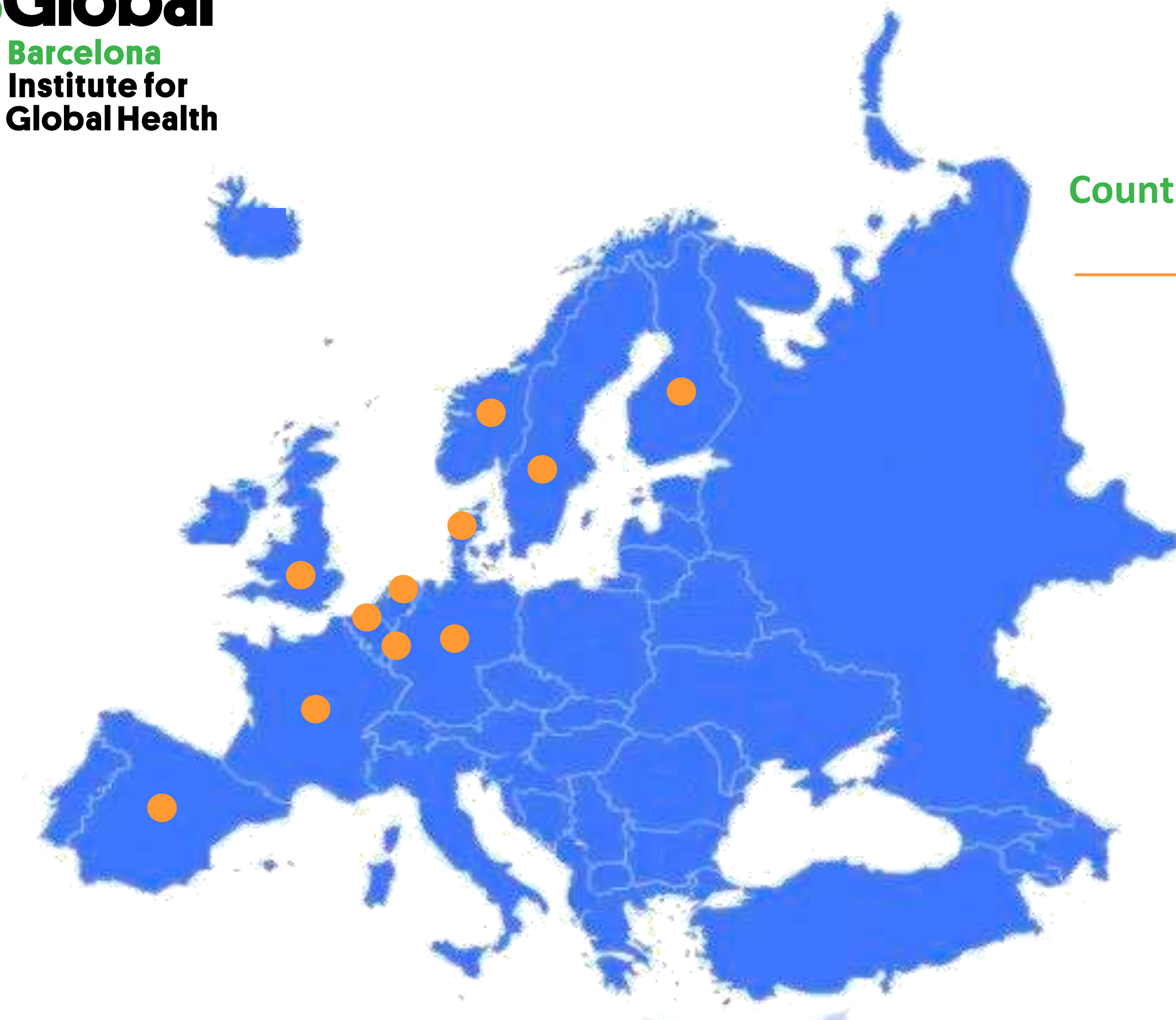
EPI-CT

Countries participating in EPI-CT



France

UK

Germany

Denmark

Belgium

Netherlands

Norway

Sweden

Spain

International Agency for Research on Cancer

World Health Organization

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Study design

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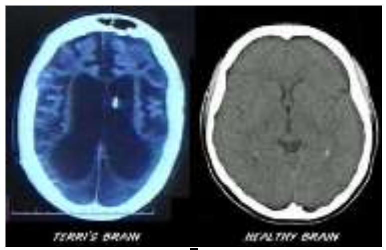
Records of radiology departments

Pediatric patients CT scans



Pediatric patients CT scans

Estimate individual radiation dose

Quantification of health risks from CT doses

Linkage with registries

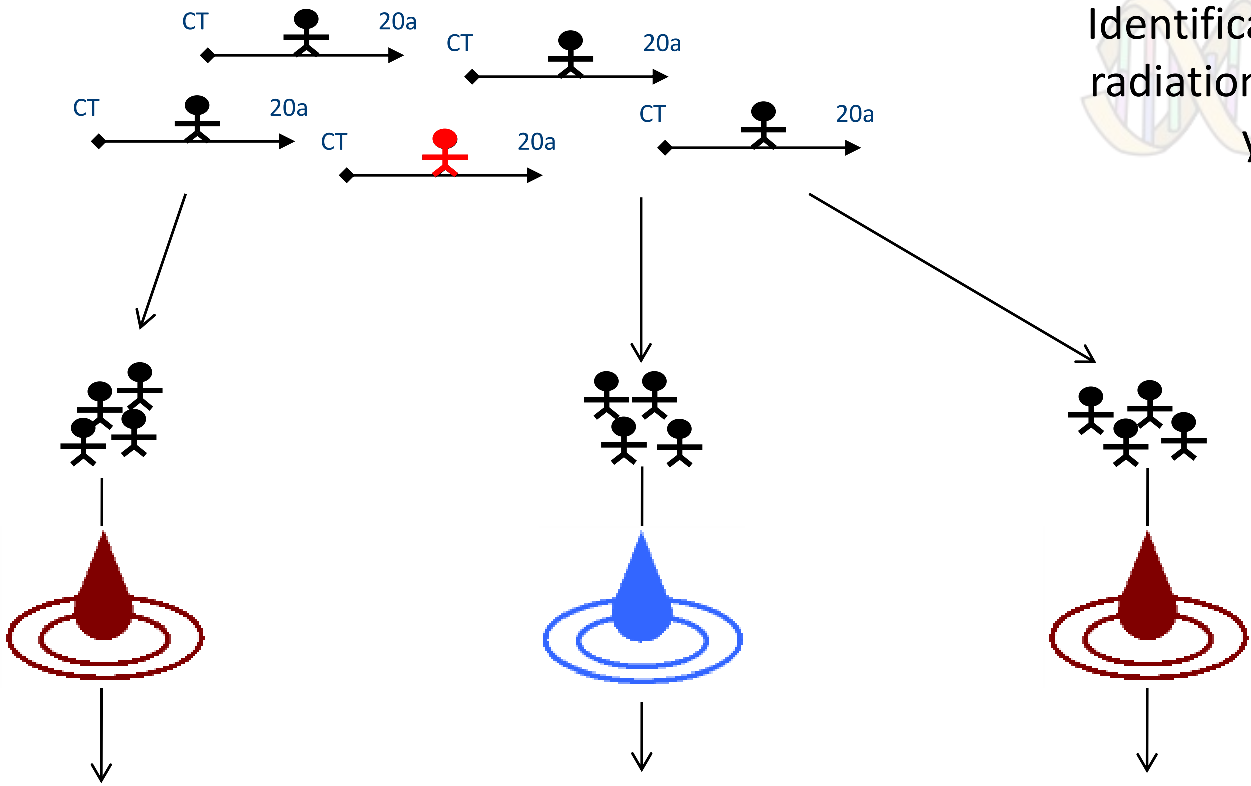
Country	Recruitment period	Age at 1st CT	Number of patients
Belgium	2002 - 2012	0-18	14,002
Denmark	2002 - 2012	0-18	21,649
France	2000 - 2011	0-9	121,101
Germany	1983 - 2013	0-14	63,998
Netherlands	1970 - 2014	0-17	158,130
Norway	1980 - 2013	0-20	80,225
Spain	1987 - 2013	0-20	171,336
Sweden	1984 - 2013	0-17	128,699
UK	1985 - 2013	0-21	411,046
Total			**1,170,186**

Particular attention was paid to

- *Identification and assessment of sources of bias and uncertainty:*
  - SES
  - missing CTs
  - missed doses from other procedures
  - confounding by indication
  - confounding by cancer susceptibility syndromes
  - incomplete follow-up (mortality, emigration, ...)
  - others (epidemiological surveillance ....)
- *Individual dose (and uncertainty) reconstruction*
- *Feasibility of identifying biomarkers*

Biological pilot study

Identification of markers of radiation sensitivity in very young ages



In vitro chromosomal and comparative study of gamma-H2AX biomarker in blood

Radiation-induced stress response in saliva

Gene expression patterns before and after CT exposure

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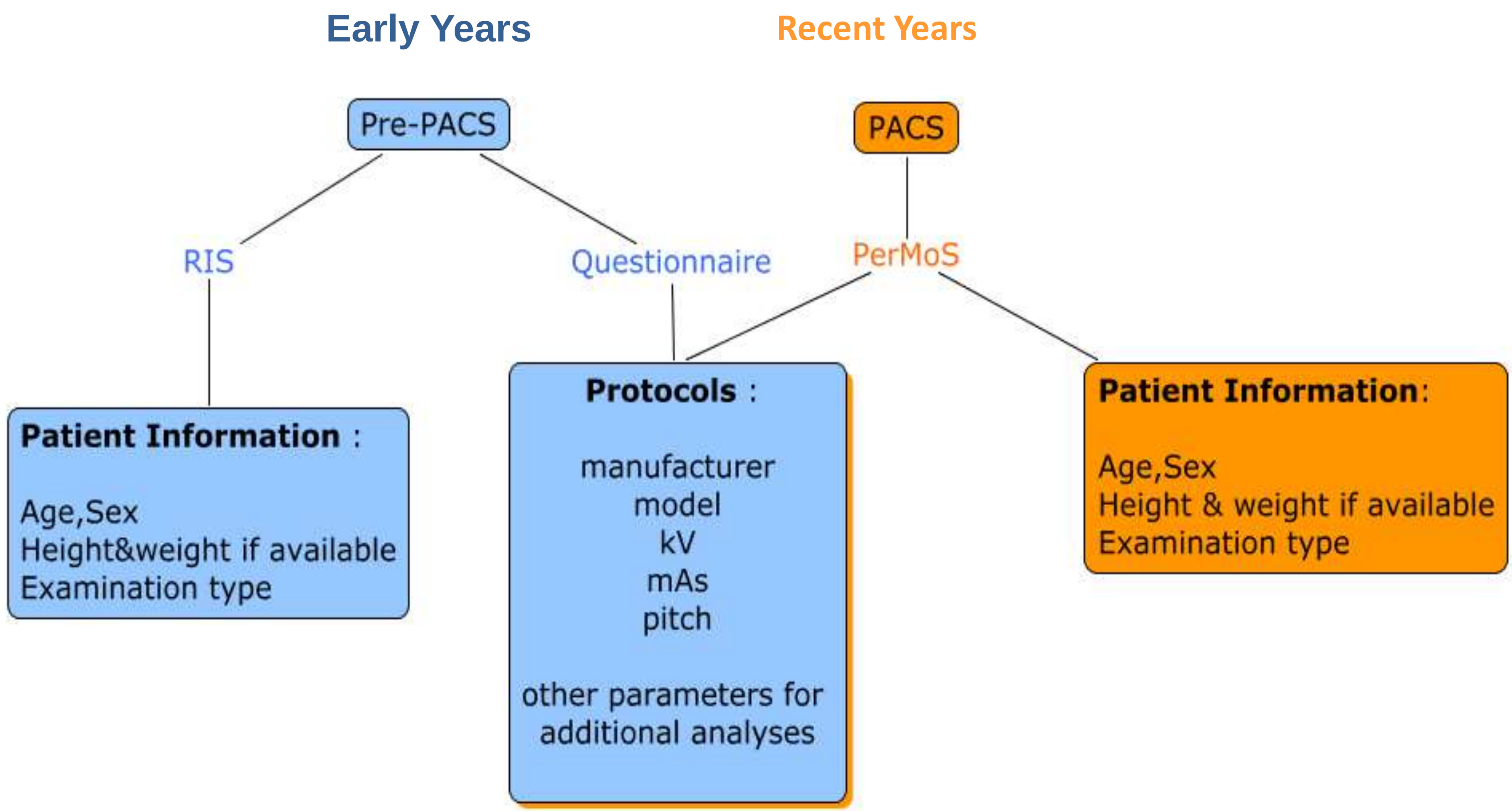
Biological pilot study: some results

- Chromosomal aberrations and induction of DNA double strand breaks following CT scanning - increased in blood samples from newborns and young children when compared to adults
- Differences also visible in the *γ*-H_2AX-foci assay

➢ Currently no biomarkers that can be obtained in non-invasive way - *this makes difficult integration of molecular biology component in a large scale paediatric CT study*

DOSE RECONSTRUCTION – AVAILABLE DATA



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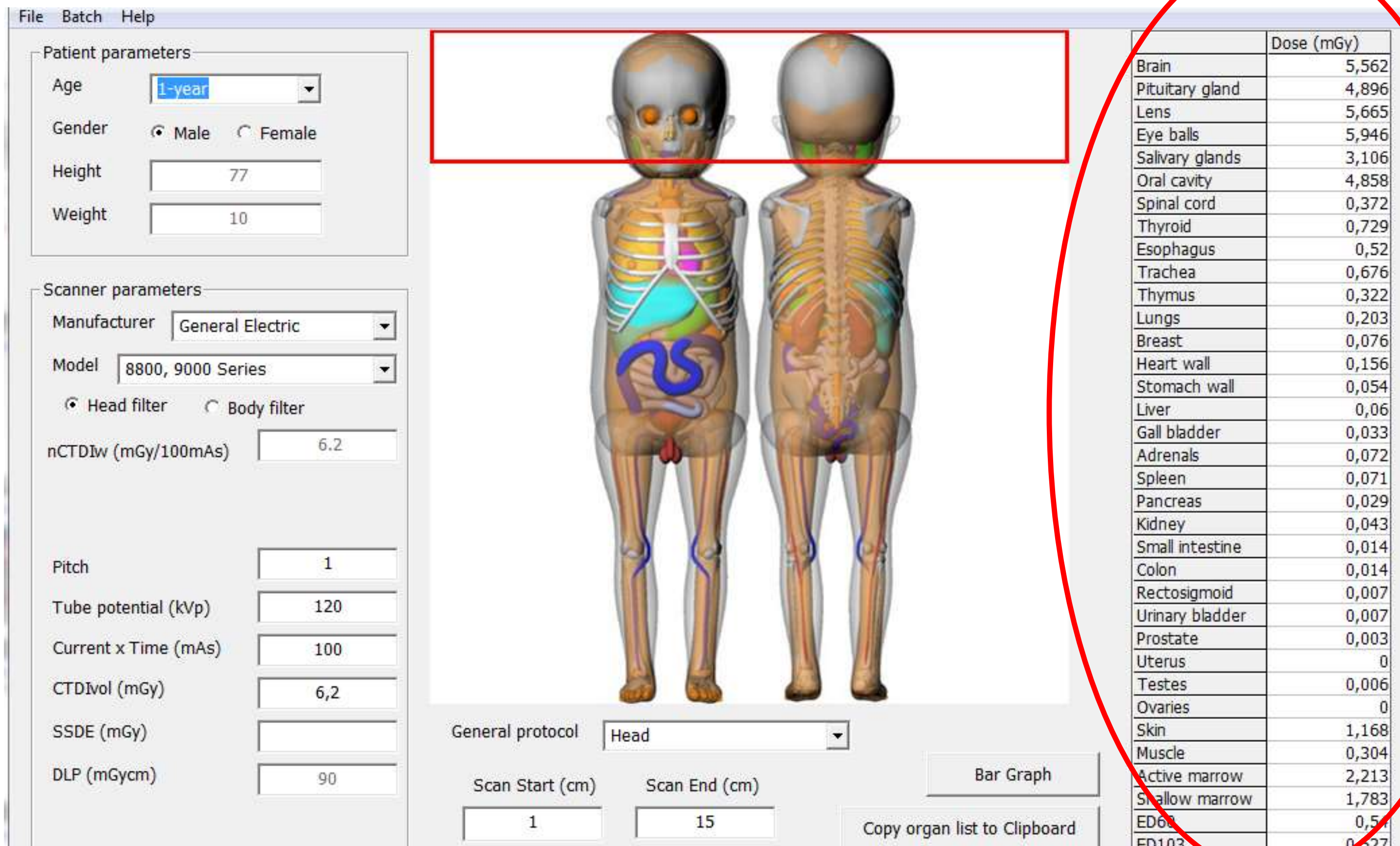
DICOM header

OVERALL STRATEGY FOR DOSE RECONSTRUCTION

- Analysis based on NCICT
  - To obtain an **ESTIMATION** of dose to the organs of the patients



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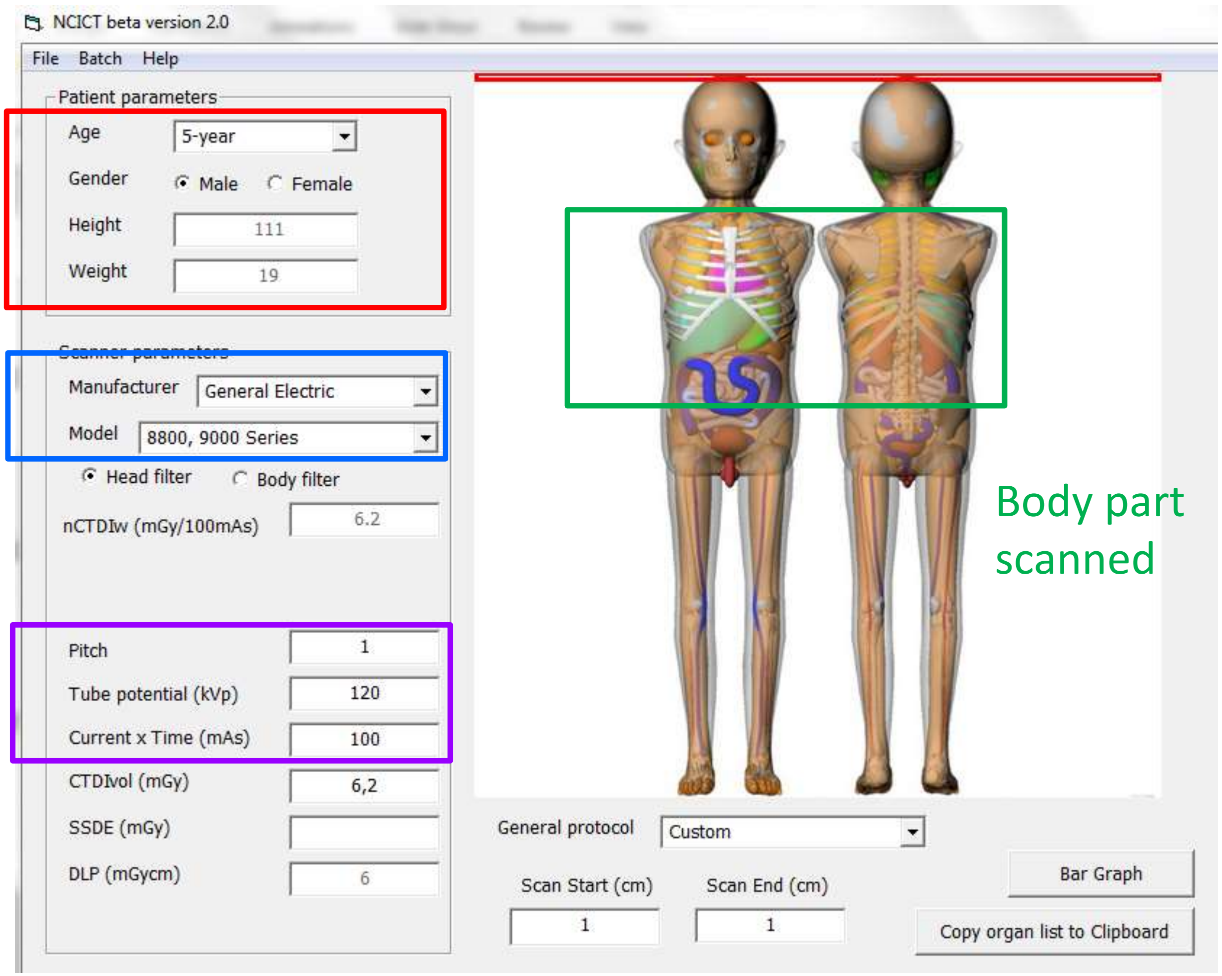
THE problem ... missing data



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2D Monte Carlo simulation

- Provides alternative realizations of possibly true sets of doses
  - The variability of dose for subjects with similar attributes is represented within each realization of the cohort;
  - The uncertainty of dose-related model parameters is represented across all the realizations of the cohort.

Subject ID	Realization 1	Realization 2	Realization 3	…	…	…	Realization 1000
1	$D_{1,1}$	$D_{1,2}$	$D_{1,3}$				$D_{1,1000}$
2	$D_{2,1}$	$D_{2,2}$	$D_{2,3}$				$D_{2,1000}$
3	$D_{3,1}$	$D_{3,2}$	$D_{3,3}$				$D_{3,1000}$
….							
N	$D_{N,1}$	$D_{N,2}$	$D_{N,3}$				$D_{N,1000}$

- 2DMC is meant to separate uncertainties which are shared among individuals from those that are individual-specific

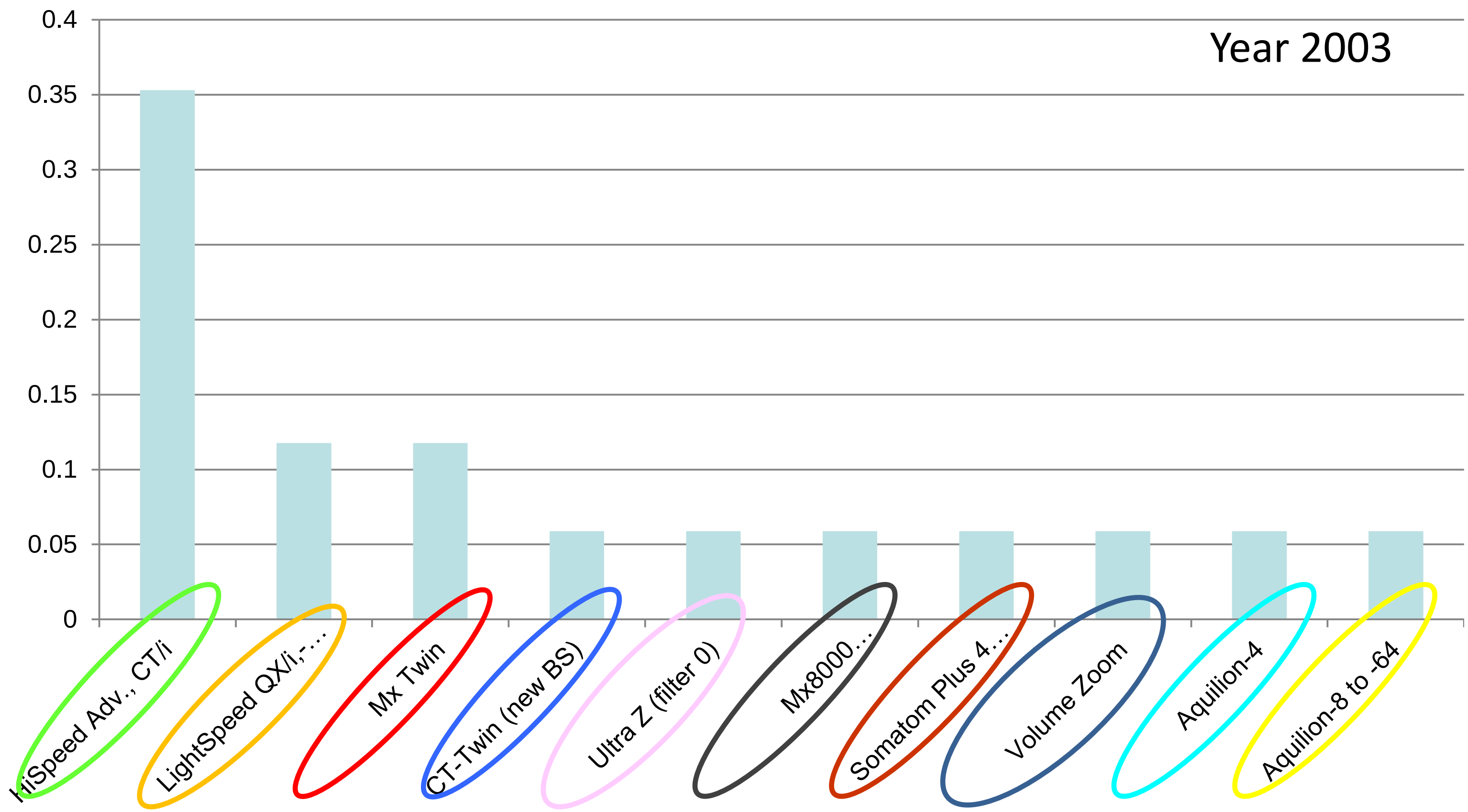
Example 1 – Missing questionnaires about scanner type and protocols

- Questionnaires to assess characteristics of typical protocols used over time sent to each participating hospital (by machine type, examination type and age group).

- No answer to our questionnaire for some hospitals
  - ➢ Unknown machine type (manufacturer and model)
  - ➢ Unknown protocols (kV, mAs and pitch)

Manufacturer and models

- **Subjective probability density function**
  - we believe it represents the relative likelihood of the use of CT machines in the country



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Selection of machine

Hospital 1

Child 1: 2y/ Thorax

Child 2: 5y/ Thorax

Child 3: newborn/ head

………

Hospital 2

Child 1: 2y/ Thorax

Child 2: newborn/head

Child 3: 5y/ head

………

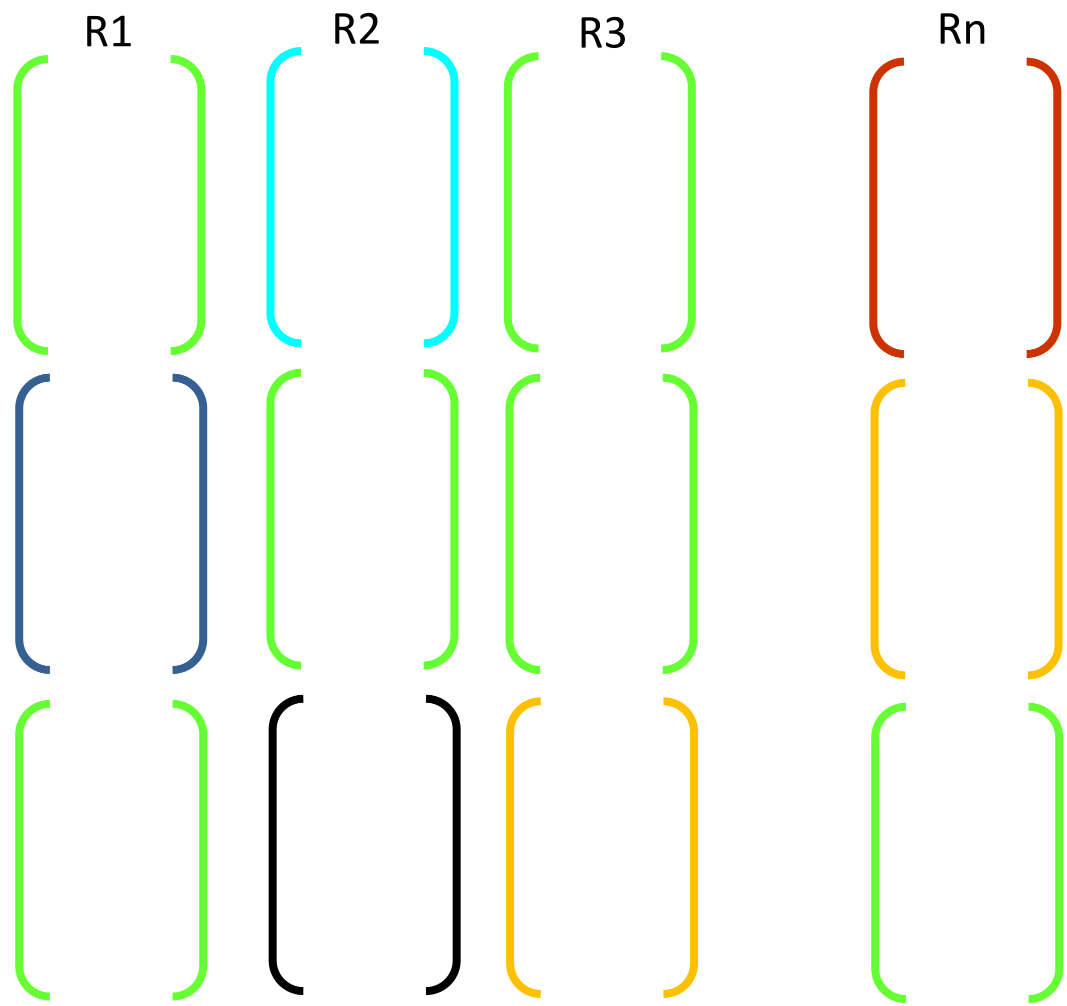
Hospital 3

Child 1: newborn/head

Child 2: newborn/thorax

Child 3: 5y/ head

………

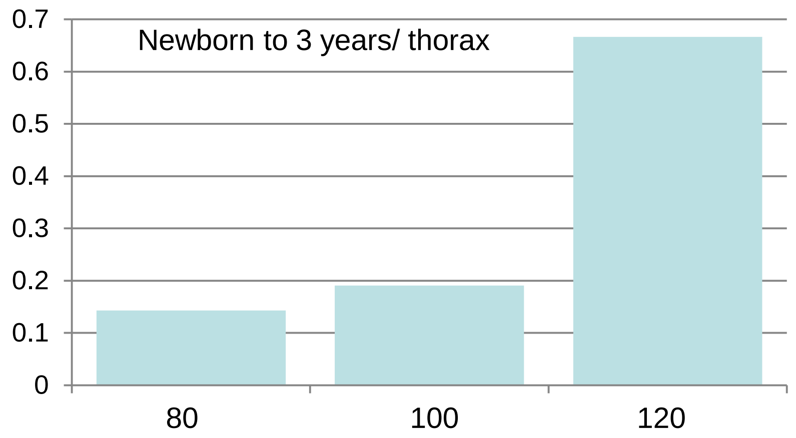


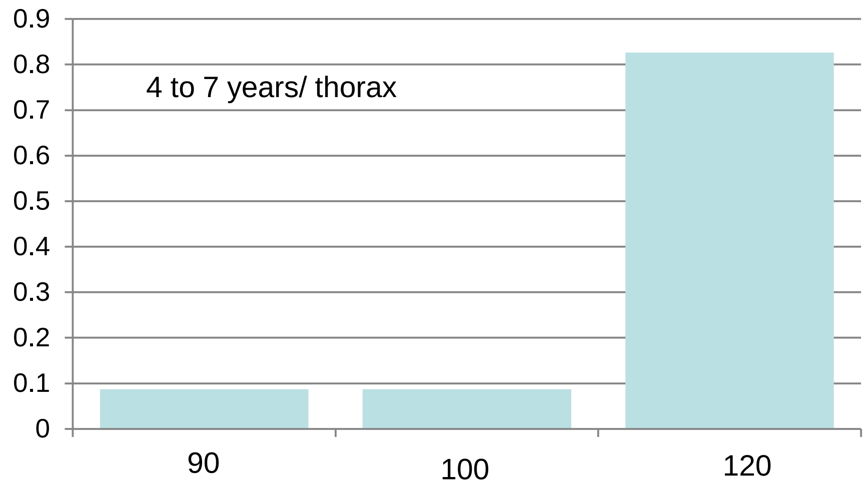
Next steps

- Scanner model is determined for each realization
- All other parameters have to be considered
  - kVp, mAs, pitch

Example: tube potential kV

- Probability density functions for GE Hispeed CT/i





- Similarly for all CT machines and examination types

KVP

		R1	R2	R3	Rn
Hospital 1	Child 1: 2y/ Thorax	120	80	100	100
	Child 2: 5y/ Thorax	100	100	120	100
	Child 3: newborn/ head	150	150	100	120
	………				
Hospital 2	Child 1: 2y/ Thorax	120	80	120	120
	Child 2: newborn/head	100	120	120	100
	Child 3: 5y/ head	150	120	100	100
	………				
Hospital 3	Child 1: newborn/head	100	80	120	120
	Child 2: newborn/thorax	100	100	80	80
	Child 3: 5y/ head	100	140	100	100
	………				

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First case – Thorax boy 2 years old

- For each realization, we have selected **kVp**, **mAs and pitch** from the appropriate probability density functions

	R1	R2	R3
CT machine	GE-HiSpeed Adv., CT/i	Toshiba-Aquilion-4	GE-HiSpeed Adv., CT/i
kVp	120	80	100
mAs	160	80	200
pitch	1	1	1

- **Resulting organ doses (mGy)**

Thyroid	20	7	25
Breast	17	6	20
Heart wall	21	7	26
RBM	8	2	8,5

Uncertainty on scanned area not taken into account

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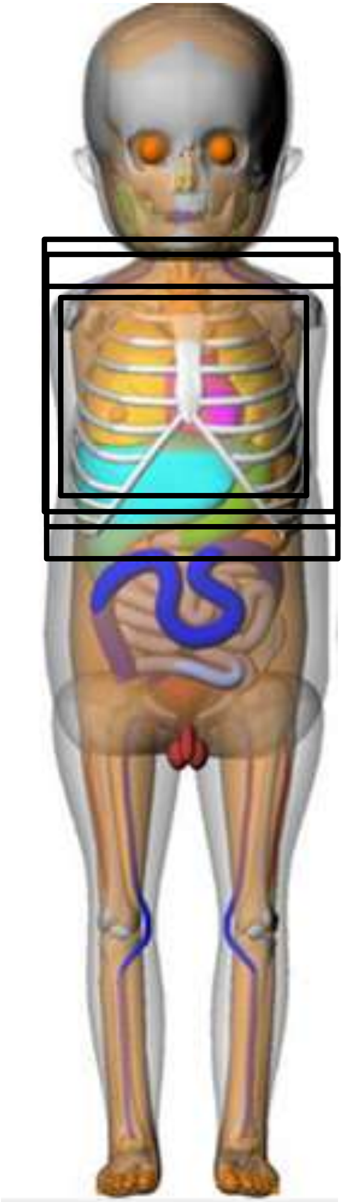
EXAMPLE 2– SCANNED AREA UNCERTAIN



- **The exposed part of the body assessed based on**
  - Type of examination
    - EU classification using 7 body regions divided into body part and specific organs
    - Expert judgment on scan position (uncertainty assessed)
  - Analysis of mathematical descriptions of contours of the organs (for recent years)
    - Segmentation of the image for the HU (Hounsfield Unit) of bone, soft tissue and air, separately during data collection
    - Only segmented outlines are transferred to the database without collection of images

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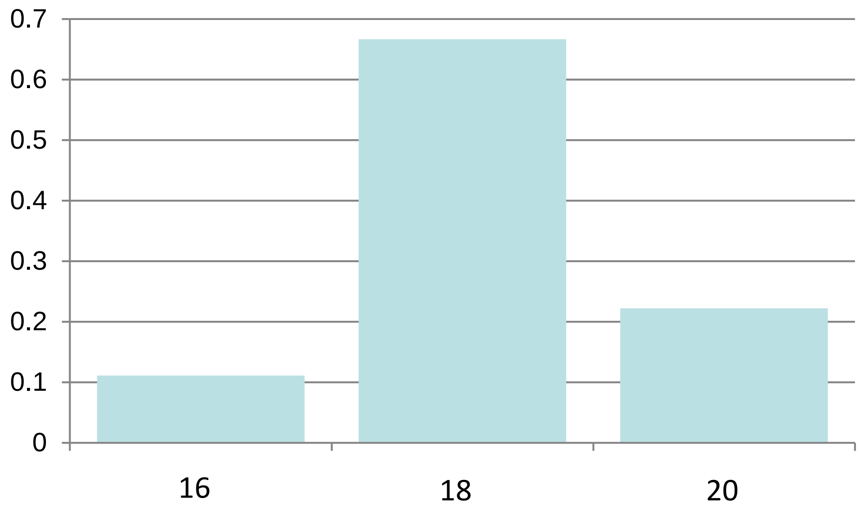
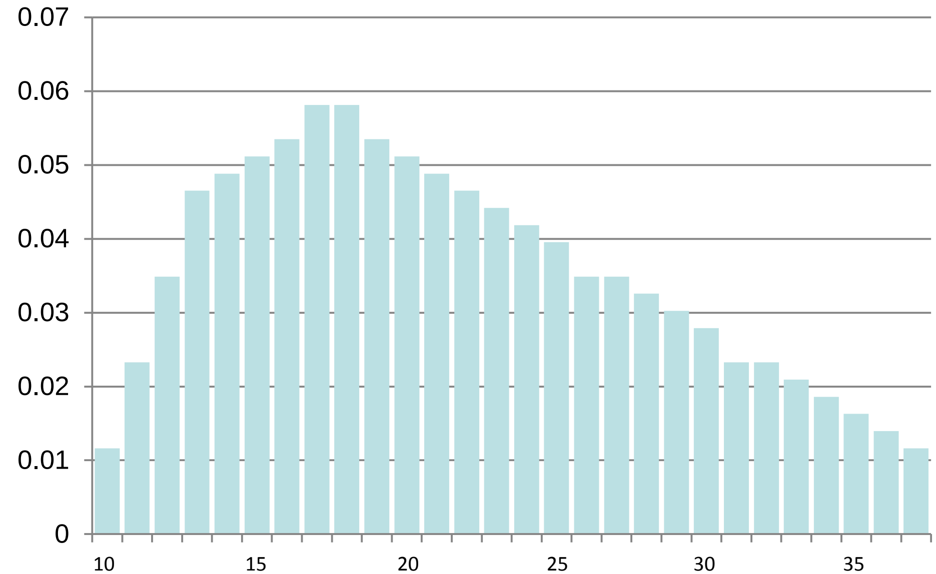
Probability density functions

Landmark (phantom slice number) – Start

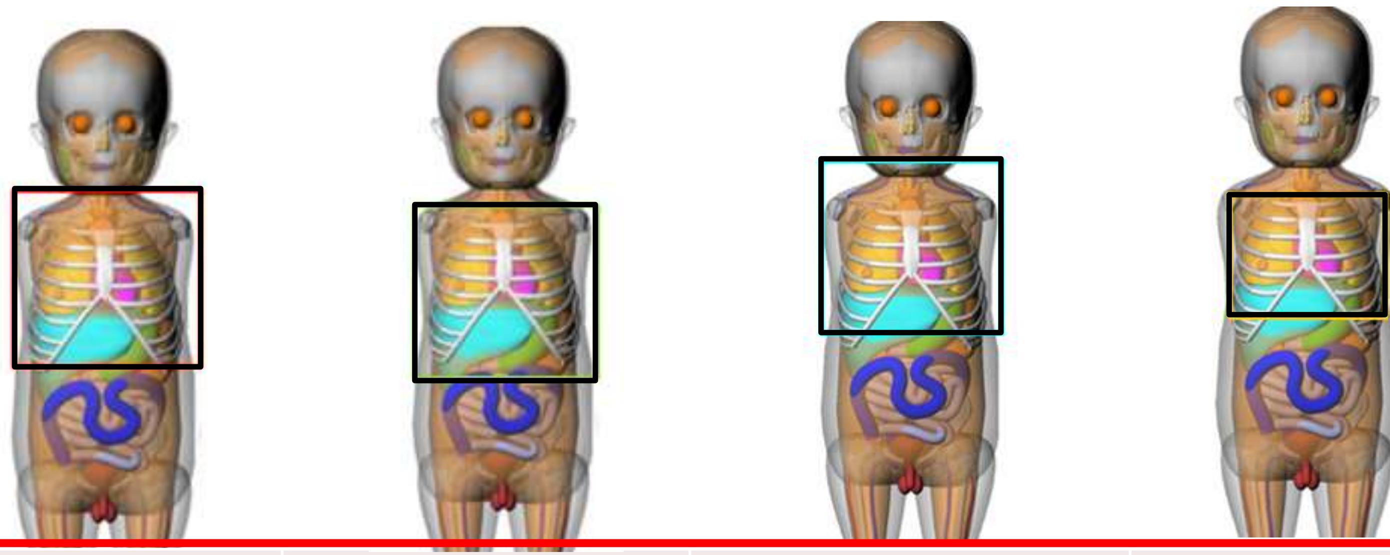


Scan length (number of slices)



	R1
CT machine	GE-HiSpeed Adv., CT/i
kVp	120
mAs	160
pitch	1

ORGAN DOSES (MGY)



Thyroid	20	9	23	5
Breast	17	17	17	16.5
Heart wall	21	21	22	20
RBM	8	7.5	8	6

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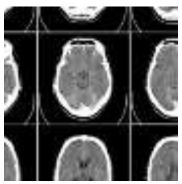
Where are we ? EPI-CT

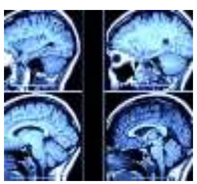
Data collection:

- Cohort accruement **finished** – EXPOSURE data
- Cancer and mortality data (**finished**) – OUTCOME data
- SES data, rare disease appraisal **finished** – CONFOUNDING data



Dose reconstruction:

- Dose reconstruction – with uncertainty – completed
- **Last validations underway**
- Final product: 500 realisations of doses



Analyses completed:

- Risk projection of radiation-related cancer for several sites (Germany, Spain, UK)
- Relation between CT scanning and SES (Netherlands, Spain, UK, Germany)
- Possible effect of cancer predisposing syndromes (France, Netherlands)
- Confounding by indication

Descriptive results

PRELIMINARY !

• Total size of cohort	~1 003 700	*(>1 year of follow-up)*
• Person years of follow-up	~ 9 500 000	
• Median duration of follow-up	~9.5 years	
• Number of deaths	~12 000	
• Age at first CT:	0-21	*(depends on country)*
• Mean age at first CT	10.8	
• Average number of CT per subject	1.5	
• % of patients with >= 5 CTs	5%	

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Analyses underway

- Estimates of leukemia and brain tumour risk and CT scan in Europe
- Simulations of impact of sources of bias on study results
- Modelling of impact of dosimetric uncertainty
- Timing – first draft result paper January 2018

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Next step

- Nested case-control study – leukaemia, brain tumours (WP5)*
  - Questionnaire and medical records
    - Information about other CTs
    - Information about other procedures
    - Medical history – previous cancers, predisposing factors
    - Improve dosimetry (antropomorphic parameters, technical parameters)
  - Biological samples (saliva)
    - Genetic and epigenetic factors which may modify individual susceptibility

**involves contact with study subjects – subject to ethics approval and informed consent*

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