Overview the European MEDIRAD project

Isabelle THIERRY-CHEF

ISGlobal
Barcelona Institute for Global Health

Institució CERCA
Centres de Recerca de Catalunya

A partnership of:

"la Caixa" Foundation

CLÍNIC BARCELONA Hospital Universitari
Parc de Salut MAR
UNIVERSITAT DE BARCELONA
upf. Universitat Pompeu Fabra Barcelona
Generalitat de Catalunya
GOBIERNO DE ESPAÑA
Ajuntament de Barcelona
FUNDACIÓN RAMÓN ARECES

SPECIFICITIES OF MEDICAL EXPOSURES

Medical radiation differs from most other exposure in that :

- The radiation is purposefully administrered
- In a <u>CONTROLLED</u> fashion
- to individuals who are expected to received direct <u>BENEFIT</u>

Radiation therapy

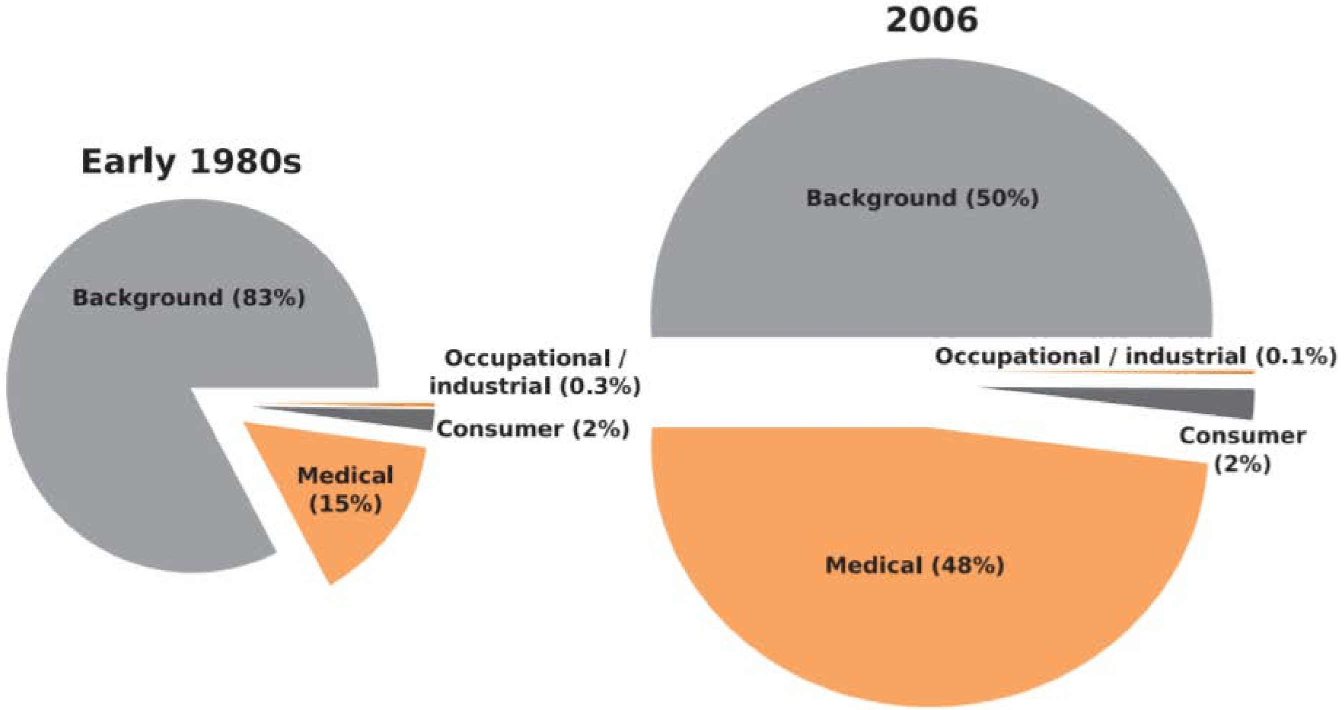
- Doses are high enough to ensure cell killing (few 10´s of Gy)
- Radiation protection : limitation of dose to neighbour organs/tissues

Radiodiagnostic

- Radiation protection : balance between image quality and doses (as low as reasonably achievable)

MEDICAL EXPOSURE OF THE POPULATION

Fig. 1.5 Comparison of distribution of collective dose values (S) or effective dose (Eus) for the categories of exposure as reported for the early 1980s and for 2006

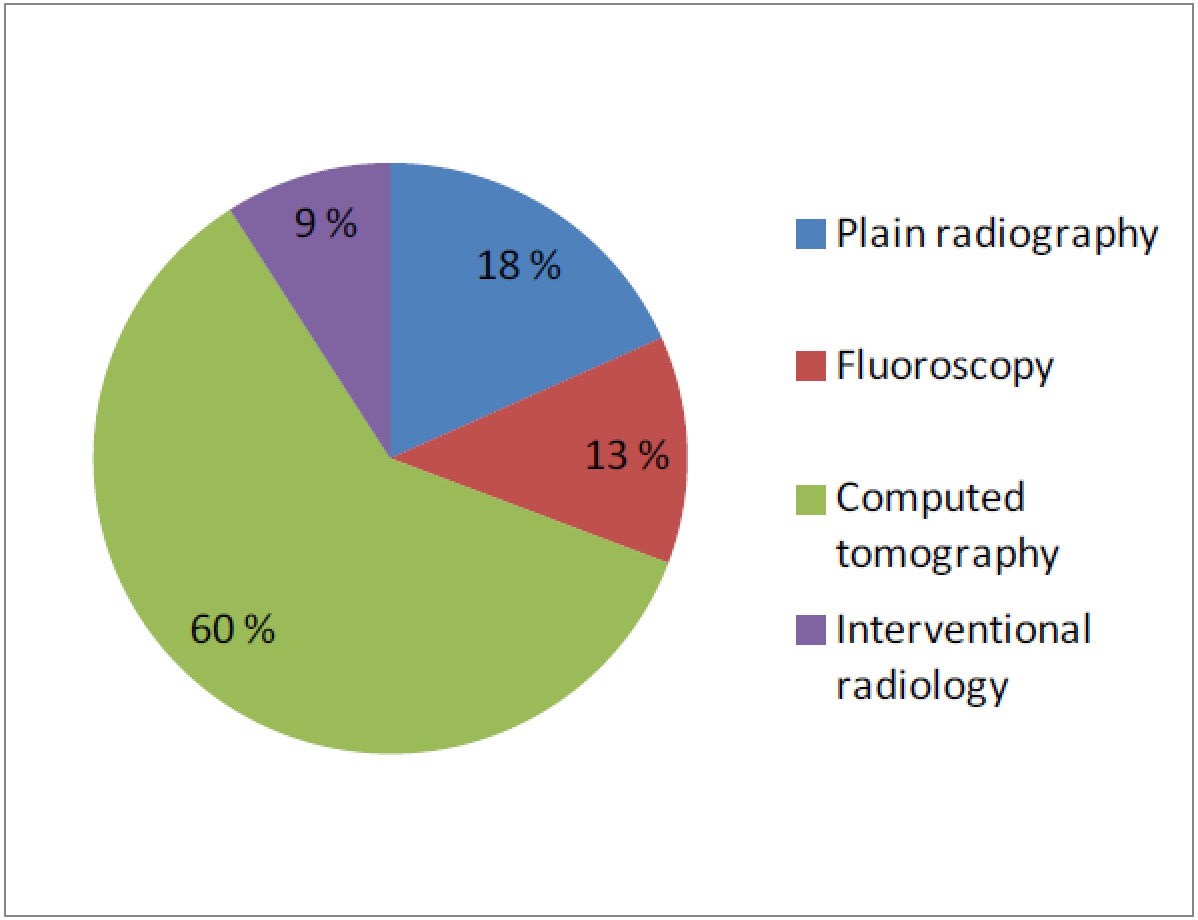


	Early 1980s	2006
S: Collective effective dose (person-Sv)	835,000	1,870,000
E_{us} : Effective dose per individual in the US population (mSv)	3.6	6.2

Adapted from NCRP (1987, 2009)

ISGlobal

Relative contribution of main examination types to collective effective dose in EU members states (+ Switzerland, Iceland & Norway)



From EU radiation protection report 180: Medical Radiation Exposure of the European Population (2014)

ISGlobal

ISGlobal

MEDIRAD

Implications of Medical Low Dose Radiation Exposure

A European, multi-disciplinary project to enhance the scientific bases and practice of radiation protection in the medical field

This project has received funding from the Euratom research and training programme 2014-2018 under grant agreement No 755523.

ISGlobal

www.medirad-project.eu

SCIENTIFIC COORDINATOR
Prof. Elisabeth Cardis
Barcelona Institute for Global Health (ISGlobal), ES

CLINICAL COORDINATOR
Prof. Guy Frija
Paris Descartes University, FR

PROJECT COORDINATOR
Monika Hierath

PROJECT MANAGER
Ulrike Mayerhofer-Sebera
European Institute for Biomedical Imaging Research (EIBIR), AT
umayerhofer-sebera@eibir.org

STRUCTURE

Pillar 1	Pillar 2	Pillar 3
Development of innovative tools to increase the efficiency of future radiation protection research activities and support good clinical practice	Improvement of the understanding of low-dose ionising radiation risks associated with major medical radiation procedures	Development of recommendations based on research results and establishment of information exchange infrastructures to facilitate consensus

A **multi-disciplinary consortium** involving research groups focusing on radiology, nuclear medicine, radiotherapy, dosimetry, epidemiology, radiation protection and public health;

A **Scientific Advisory Board** with world-renowned experts in the fields of imaging, radiobiology, dosimetry, medical physics, radiation protection, epidemiology and ethics;

A **Stakeholder Board** with representatives from the medical associations **EANM**, **EFOMP**, **EFRS**, **ESR** and **ESTRO**, as well as the **MELODI**, **EURADOS** and **EURAMED** platforms on radiation protection research, the **WHO** and the **EPF**;

A wider **Stakeholder Forum**, including health professionals, patients, nuclear scientists, policy-makers, competent authorities and representatives from international organisations;

MAIN OBJECTIVES

Improve organ dose estimation and registration to:

- Inform clinical practice
- Optimise doses
- Provide adequate dosimetry for clinical-epidemiological studies on the effects of medical radiation

Evaluate and understand the effects of medical exposure focusing on

- cardiovascular effects of low to moderate doses of radiation from RT in breast cancer treatment
- Doses to healthy organs in I^{131} radioiodine ablation of thyroid
- long-term effects on cancer risk of low doses from CT in children

Develop science-based consensus policy recommendations for the effective protection of patients, workers and the general public

MEDIRAD

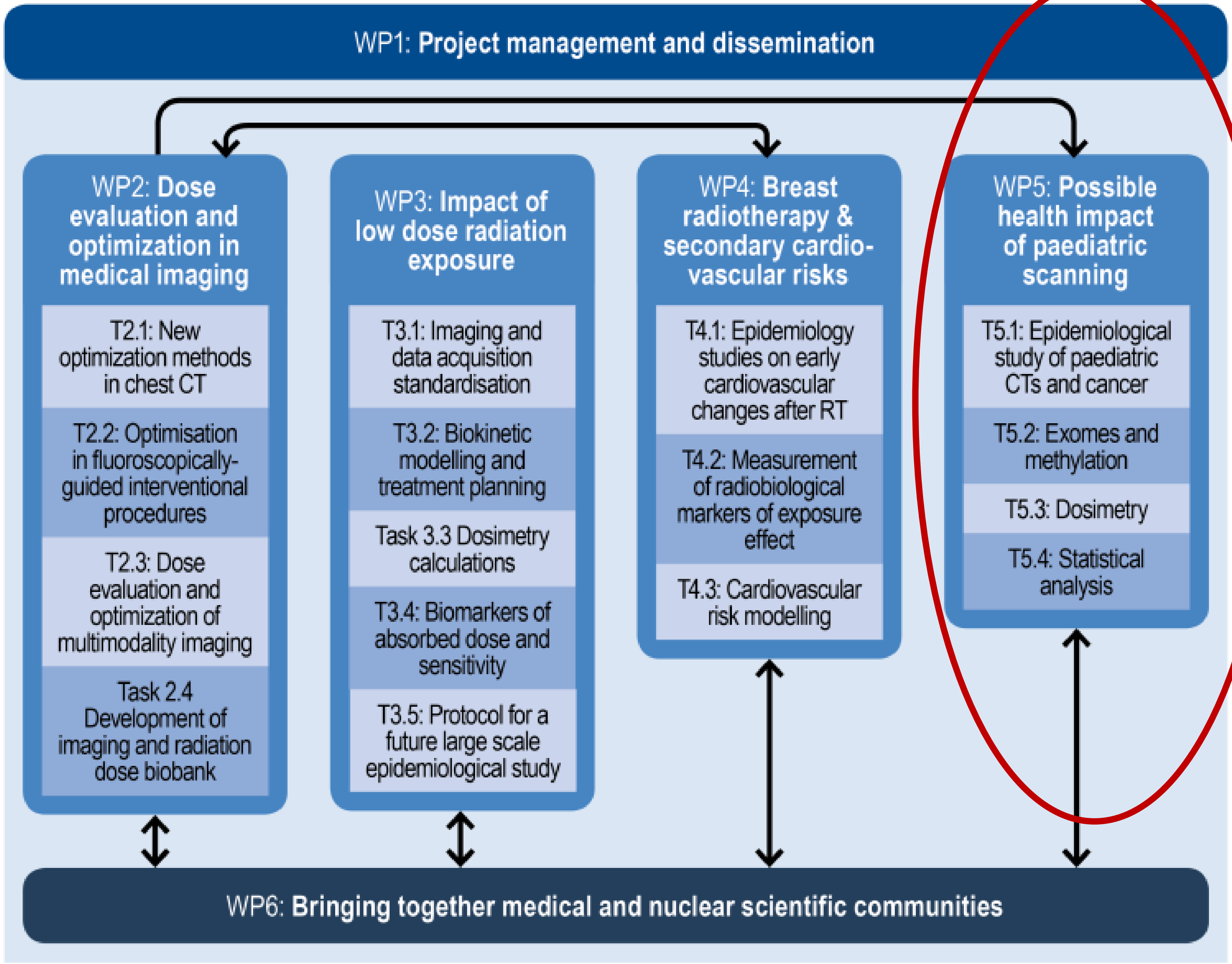
ACTIVITIES

The multi-disciplinary consortium will, in close interaction with European medical associations MELODI and EURADOS:

- develop a tool to determine image quality and maximise optimisation
- improve and develop new individual organ/anatomical structure dosimetry from chest CT, I131 administration, fluoroscopy-guided procedures, hybrid imaging, and RT for breast cancer
- conduct epidemiological studies of consequences of RT and CT,
- identify potential novel imaging and circulating biomarkers and mechanisms of radiation effects,
- develop innovative risk models,
- develop and implement a European repository of patient dose and imaging data,
- develop science-based recommendations, and
- introduce novel approaches to bring together the nuclear and medical sectors.

MEDIRAD

WORK PLAN


WP1: Project management and dissemination
WP2: Dose evaluation and optimization in medical imaging
T2.1: New optimization methods in chest CT
T2.2: Optimisation in fluoroscopically-guided interventional procedures
T2.3: Dose evaluation and optimization of multimodality imaging
Task 2.4 Development of imaging and radiation dose biobank
WP3: Impact of low dose radiation exposure
T3.1: Imaging and data acquisition standardisation
T3.2: Biokinetic modelling and treatment planning
Task 3.3 Dosimetry calculations
T3.4: Biomarkers of absorbed dose and sensitivity
T3.5: Protocol for a future large scale epidemiological study
WP4: Breast radiotherapy & secondary cardio-vascular risks
T4.1: Epidemiology studies on early cardiovascular changes after RT
T4.2: Measurement of radiobiological markers of exposure effect
T4.3: Cardiovascular risk modelling
WP5: Possible health impact of paediatric scanning
T5.1: Epidemiological study of paediatric CTs and cancer
T5.2: Exomes and methylation
T5.3: Dosimetry
T5.4: Statistical analysis
WP6: Bringing together medical and nuclear scientific communities

WP 2 Dose evaluation and optimisation in medical imaging (UoC)

As Low As Reaonably Achievable:

- Justification – Is the exam necesary & are there other options (MRI...)
- Optimization – Achieve the lowest dose for the quality required

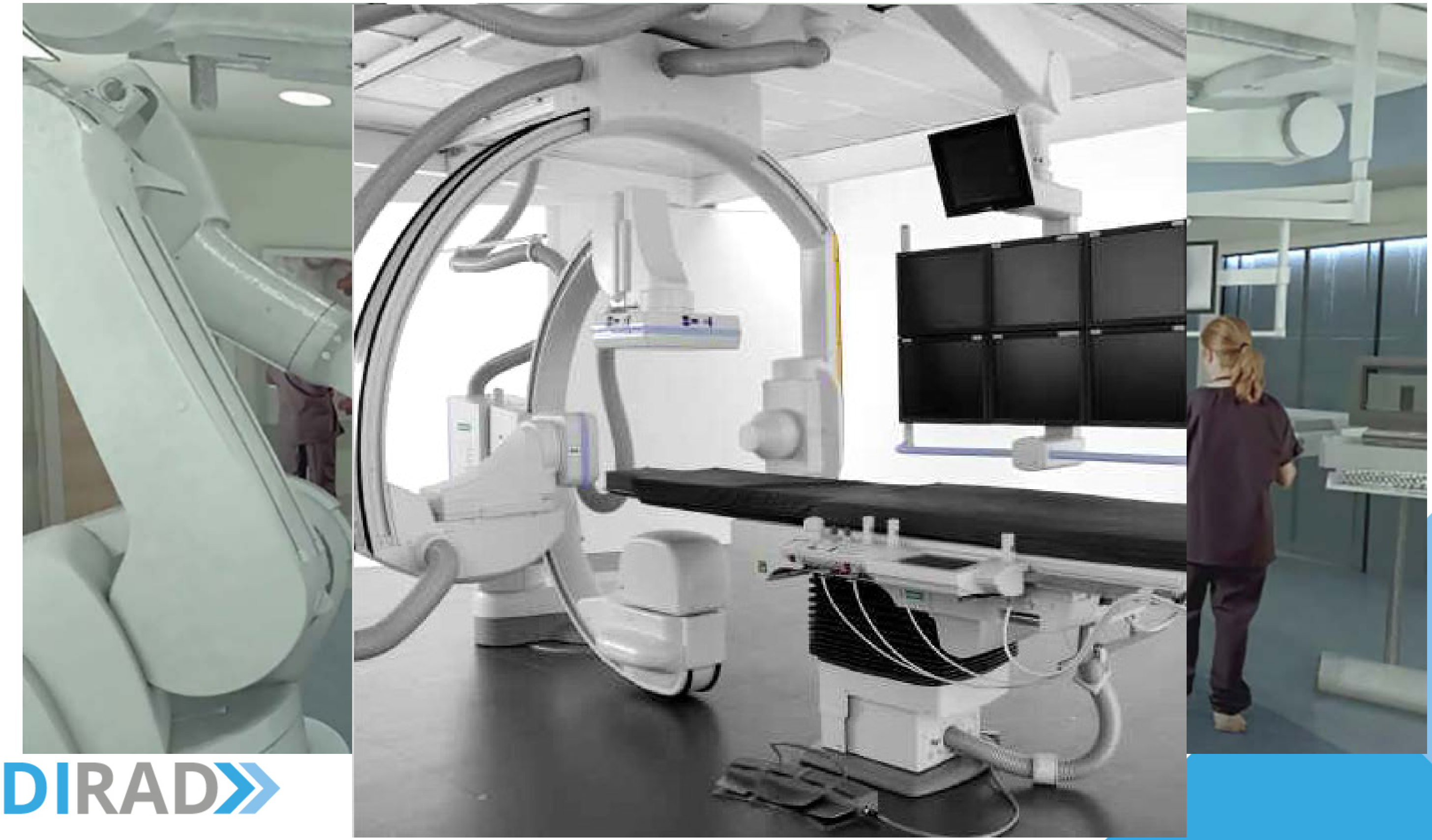
Optimization in chest CT scanning

- Development of a software tool on image quality and radiation doses

WP 2 Dose evaluation and optimisation in medical imaging

Optimization in Interventional Radiology

- Estimation of doses to patients (real time evaluation doses)
- Evaluation of efficiency and effectiveness of staff radiation protection tool

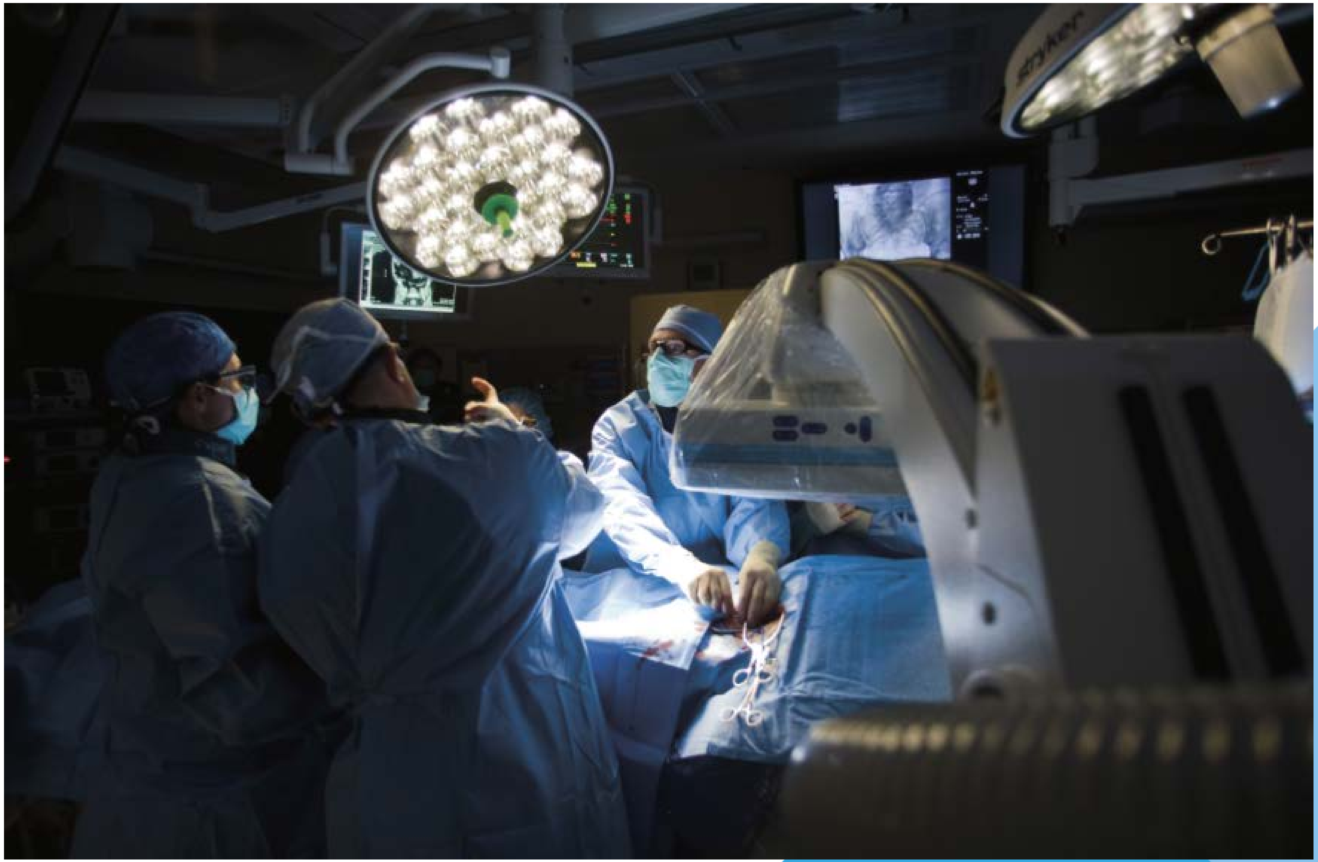


MEDIRAD

WP 2 Dose evaluation and optimisation in medical imaging

Optimization in Interventional Radiology

- Estimation of doses to patients (real time evaluation doses)
- Evaluation of efficiency and effectiveness of staff radiation protection tool



MEDIRAD

WP 2 Dose evaluation and optimisation in medical imaging

Optimization in chest multimodality imaging

- Establishment of **DRL values**
- Optimization of patient organ doses

Development of imaging and radiation dose biobank

- Collection, storage and retrieval of de-identified image data and dose data for future use in research

WP 3 Impact of low dose radiation exposure from I-131 Radioiodine (NaI) ablation of thyroid cancer (RMH/ICR)

Assess absorbed doses delivered to healthy organs and to thyroid remnants in thyroid ablation

- Develop and implement tools to establish the range of doses
- 100 patients from 4 centres

Risk/benefit individualised treatment planning for these procedures

- Analysing patient-specific biokinetics
- Recommendations and protocols

Biomarker studies to assess individualized radiosensitivities

Plan a large scale study that will evaluate long term risk

MEDIRAD

WP 4 Breast Radiotherapy and Secondary Cardiovascular Risks: Establishing Risk Models for Clinical Support (UMCG)

Gain insight into the mechanisms of radiation-induced cardiotoxicity in breast cancer patients

- integrate clinical epidemiology, radiobiology, and modelling approaches

Two clinical studies :

- EARLY HEARTH: to identify and validate most important cardiac imaging biomarkers and circulating biomarkers of radiation-induced cardiovascular changes arising in the first 2 years after breast RT

- BRACE: to determine the relationship between 3D dose distributions in cardiac substructures and the risk of acute coronary events (ACE) and other cardiac complications in BC patients

MEDIRAD

WP5 - Possible health impact of paediatric scanning – a molecular epidemiology study (ISGLOBAL)

Why studying paediatric population involved in CTs?

Benefits of CT (computed tomography)

- Improved diagnostic
- Great image quality for organs in motion i.e. heart, lungs
- Short exam time
- No sedation of children

Potential risks?

- Increase in CT examinations, particularly among paediatric populations
- CT exposure has the most contributions to the annual collective dose from medical radiation exposure.

MEDIRAD

ISGlobal

First results from national studies

First results show:

- The first study in the UK reported increased **risk of leukemia and brain tumors** (Pearce)
- Results were similar in studies in Germany (Krille & Pokora), France (Journy, Bernier), Taiwan (Huang) , Australia (Mathew)

Critics:

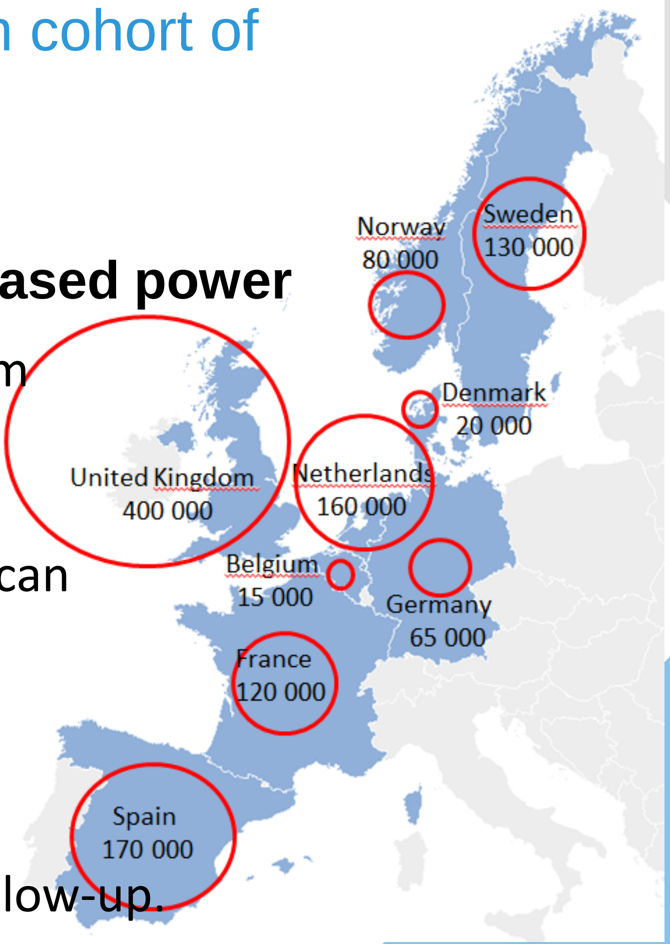
- Underlying conditions/cancer predisposing conditions: predisposing syndromes, acquired immune deficiencies which may influence the development of cancer.
- Reverse causation : participant showing symptoms of the undetected cancer which then is the reason for them to obtain a CT scan.
- Uncertainties on doses and lack of individual data for dose reconstruction

MEDIRAD ISGlobal

The EPI-CT study (2011-2017): A European cohort of paediatric patients involved in CT scanning

Total of more than 1,000,000 patients – increased power

- National cohorts are defined retrospectively from records of participating radiology departments
- Eligible subjects have at least one recorded CT-scan before age 21 and are cancer-free at the time of the first CT.
- Only residents of participating countries are included to ensure feasibility of follow-up.



Individual doses for more than 1,500,000 CT examinations

MEDIRAD EPI-CT

EPI-CT : Number of examinations in EPI-CT

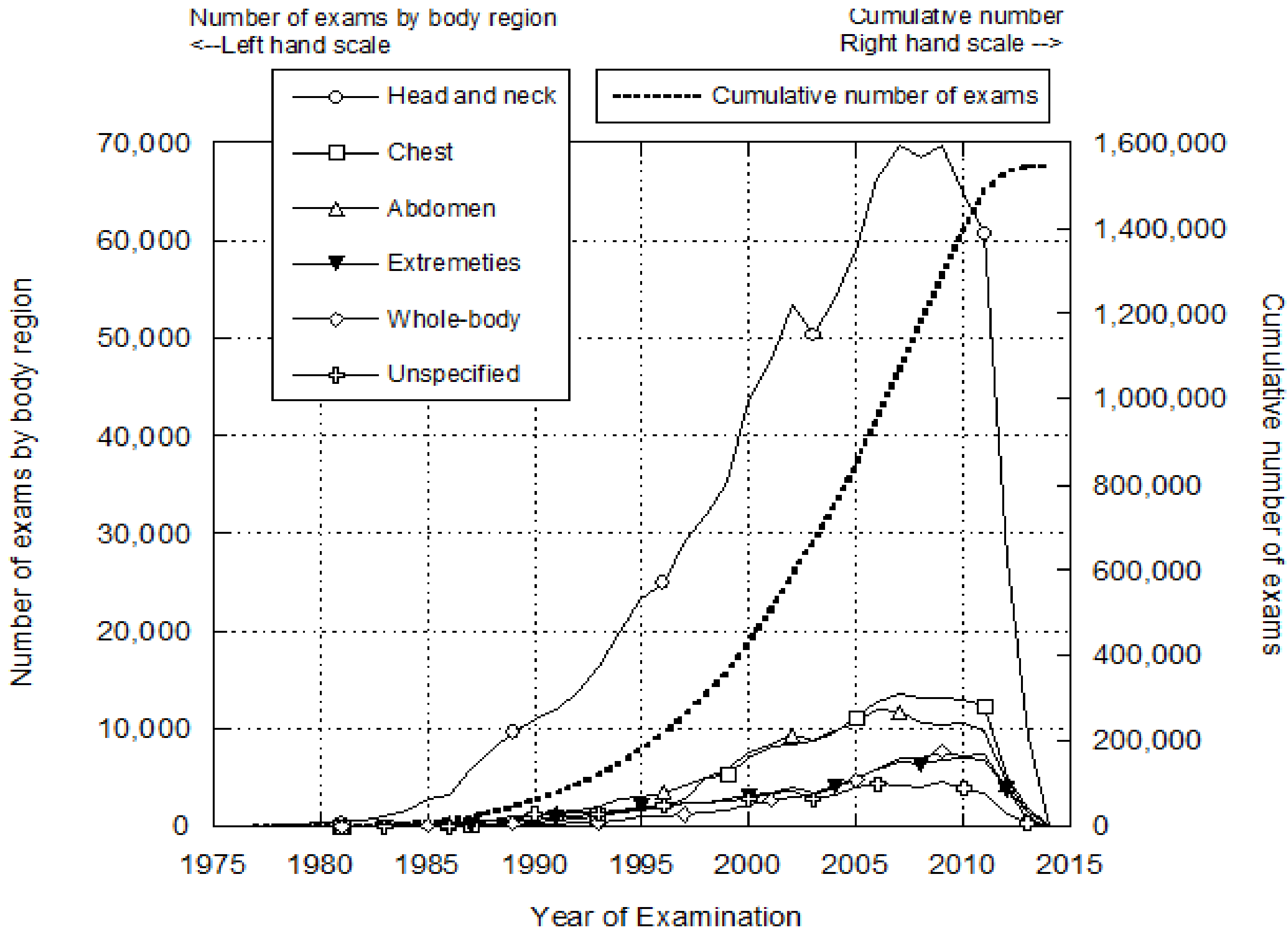


Figure 3 Number of CT examinations by body region as a function of examination year.

MEDIRAD

EPI-CT

WP5 - Possible health impact of paediatric scanning – a molecular epidemiology study (ISGLOBAL)

Task 5.1 : Epidemiological study of paediatric CTs and cancer

- 5.1.1 Update of the follow-up of the cohorts
- 5.1.2 Conduct of a case-control study of brain and haematological malignancies nested within the EPI-CT cohort

Task 5.2 : Exomes and methylation

Task 5.3 : Dosimetry

Task 5.4 : Analyses

ISGlobal

MEDIRAD

WORKPACKAGE 5

FOLLOW-UP OF EXISTING PAEDIATRIC CT COHORTS

MEDIRAD

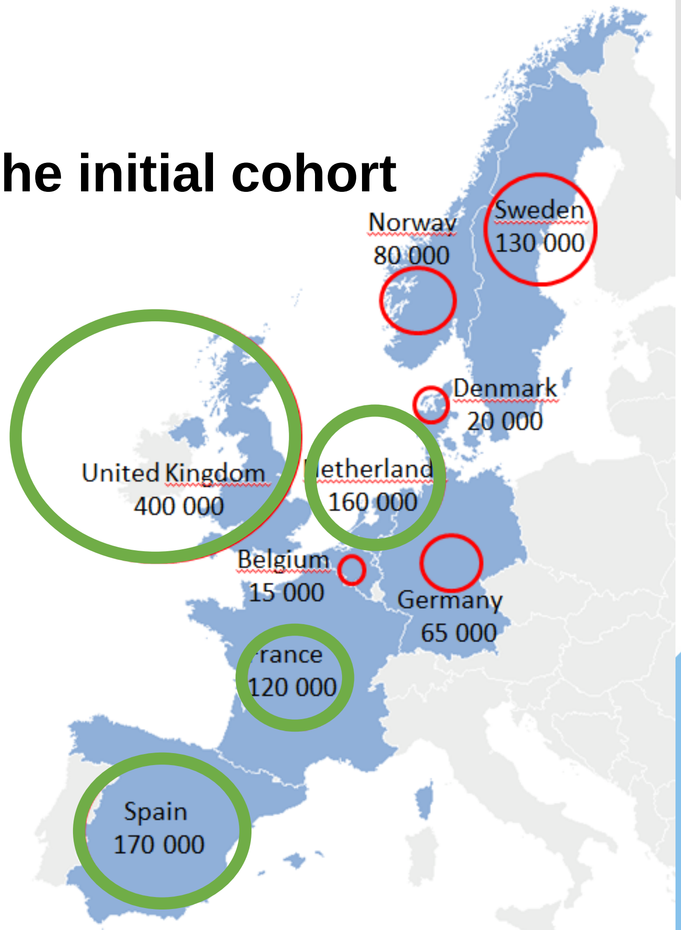
ISGlobal

The EPI-CT Follow-up

In 4 countries representing the majority of the initial cohort

- ❑ France, Netherlands, Spain and the UK
- ❑ About 730,000 patients
- ❑ 5 additional years of follow-up (up to 2017)

- ❑ Activities:
  - ✓ Ethics in year 2,
  - ✓ Data collect in year 3,
  - ✓ Analyses in year 4



MEDIRAD

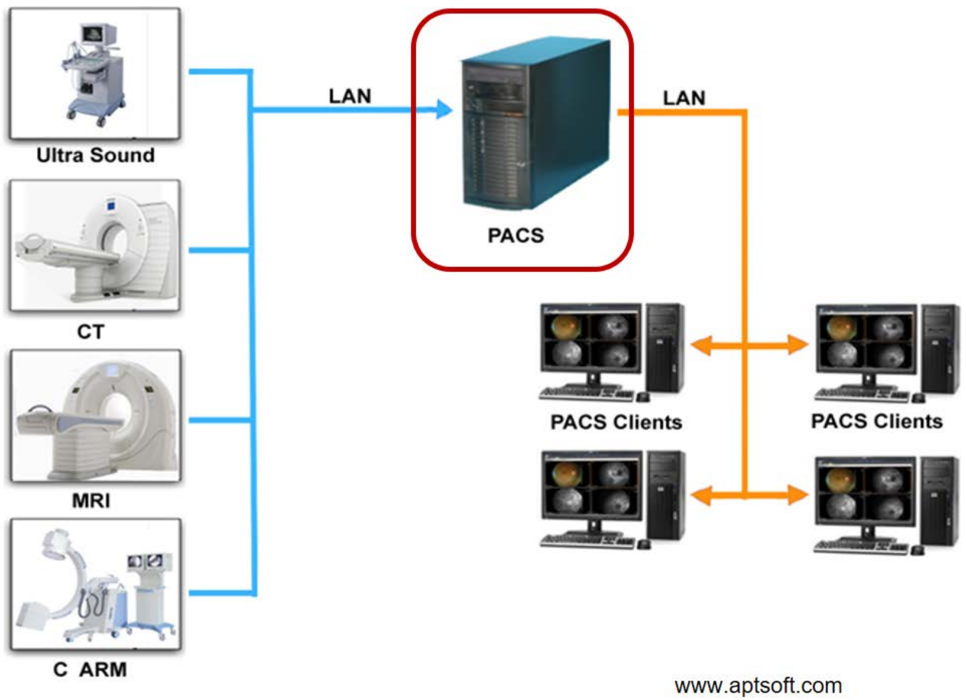
ISGlobal

The EPI-CT Follow-up – Challenges in data collection

In EPI-CT, anonymised data collected at the hospital (RIS & PACS)

RIS

PACS



MEDIRAD

ISGlobal

The EPI-CT Follow-up - Challenges

Need to collect data on additional scans performed in the last 5 years

- About 57 000 additional scans
- 1 year for data collection - we can´t go back to all hospitals

Possible ways under evaluation to collect data

- Collect data through social security (in France) … need a lot of data treatment & no information on doses
- Collect dosimetric data in only a few hospitals per country to assess evolutions in doses in recent years.
- Use of the “dose management system” instead of PerMoS

MEDIRAD

Nested Case Control

EPI-CT

WORKPACKAGE 5

NESTED CASE-CONTROL STUDY

MEDIRAD

ISGlobal

Nested Case Control

EPI-CT

Objectives

Further study haematological malignancies and central nervous system tumours via

- A case-control study nested within the EPI-CT cohorts (France, Spain, possibly Sweden)

To better estimate cancer risk following low doses of IR from CTs

- Taking into account potential bias factors
- And the role of factors modifying the risk

MEDIRAD

Nested Case Control

EPI-CT

Study population

Cases from the EPI-CT cohorts

- Who have undergone at least 1 CT before the age of 21

Controls matched on

- 2 controls: Age, sex and residence
- 1 control: Age, sex, residence and dose for genetic and epigenetic analyses
- Controls should be free of cancer at the time cases are diagnosed

Outcome of interest

- Brain tumours, leukemia, lymphoma

Ethics approval obtained in Cataloña and submitted in France

MEDIRAD

Main source of information

Online questionnaire (or paper if requested) to collect information on

- Socioeconomic status, present and past residences
- Individual and familial medical history, including cancer and cancer predisposing conditions
- Ionizing radiation exposure: including medical exposures (CTs, other diagnostic procedures) and, where applicable, occupational exposure.
- Other potential environmental exposure, residential and school address history (possibly)
- Lifestyle factors: such as smoking and alcohol drinking habits.

Informed consent signed

Main source of information

Questionnaire to the parents

- General questions about pregnancy
- specific exposure during pregancy (medicine, medical radiation)
- Lifestyle during pregancy: such as smoking and alcohol drinking habits
- General questions on birth and first days of life of the child:
  - ✓ Weight at birth
  - ✓ Premature birth, Intensive care unit , Oxygen ?

- Occupational history of mother and father

Informed consent signed

Main source of information

Access medical records

- Radiology departments
- Collection of images (for dose reconstruction purposes)

Analyses in saliva samples to identify markers of radiosensitivity

- Non invasive
- DNA analyses
- RNA analyses

Informed consent signed

Nested Case Control

EPI-CT

Genetic and Epigenetic factors

Some individuals have variance in DNA repair and apoptosis genes which has been associated with increased radiosensitivity.

+

Specific epigenetic changes can also result in enhanced radiation sensitivity.

There is a need to identify genetic and/or epigenetic variants which may increase the **risk of radiation induced cancers** in patients.

More research is needed to identify radiosensitive patients and ensure alternative imaging techniques are used.

DNA : Exome sequencing focusing on genes that are believed to be related to radiosensitivity

Hypermethylation analyses on both DNA and RNA

MEDIRAD

La Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQUAS) promueve el estudio EPI-CT NCC, que investiga el efecto que las enfermedades previas, las exposiciones ambientales y en el ámbito médico, y los factores genéticos y epigenéticos, tienen o pueden tener sobre el riesgo de cáncer. Se llevará a cabo en España, Francia y Suecia.

Este estudio se está llevando a cabo en colaboración con el Instituto de Salud Global de Barcelona - ISGlobal. En Catalunya el estudio está promovido por el Departament de Salut de la Generalitat de Catalunya.

Financiado por:

Instituto de Salud Carlos III

Generalitat de Catalunya
gencat.cat

¿Alguna pregunta en relación al estudio en Catalunya?

Joan Albert d'Escofet (jaescofet@itteria.cat)
coordinador AQUAS

Lourdes Arjona (lourdes.arjona@isglobal.org)
coordinadora del trabajo de campo

Maëlle Canet (maelle.canet@isglobal.org)
coordinadora Nacional

Investigadoras principales:

- Dra. Thierry-Chef
(isabelle.thierrychef@isglobal.org)

- Prof. Elisabeth Cardis
(elisabeth.cardis@isglobal.org)

Centro coordinador:

Agència de Qualitat
i Avaluació Sanitàries de Catalunya

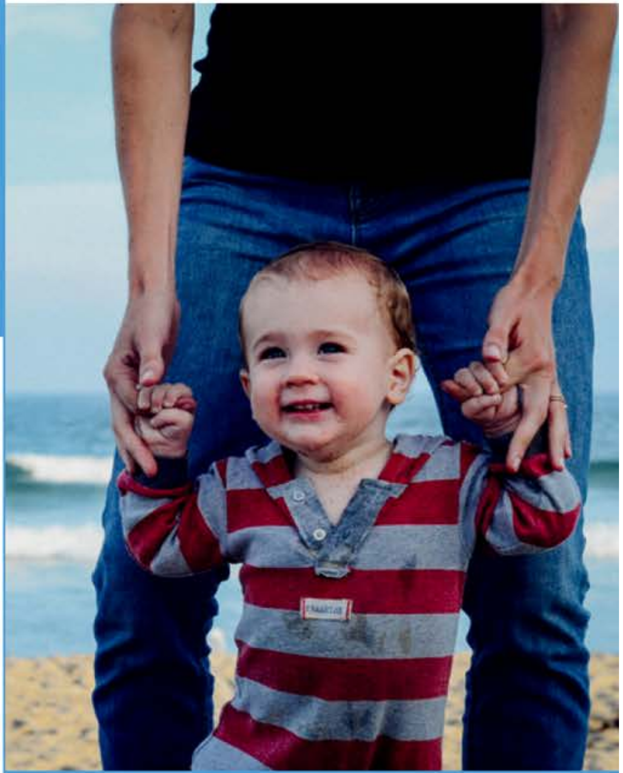
ISGlobal Institut de Salut Global Barcelona

Obra Social "la Caixa"

CLÍNIC Barcelona · Universitat de Barcelona · Generalitat de Catalunya · Gobierno de España · MAR · upf. Universitat Pompeu Fabra Barcelona · Ajuntament de Barcelona · Fundación Ramón Areces

Nested Case Control

EPI-CT



Si quiero participar en el proyecto, ¿Qué es lo que tengo que hacer?

Los conocimientos obtenidos gracias a los estudios llevados a cabo a partir de las muestras y de los cuestionarios, pueden ayudar al avance médico, contribuir al conocimiento sobre las enfermedades y, por ello, a otras personas en el futuro.

Primero de todo, tienes que darnos tu aprobación a través del "consentimiento informado". Con este consentimiento nos permitirás acceder a tus informes clínicos y contactar con tus médicos.

Seguidamente, deberás rellenar un cuestionario on-line, para conocer tu historial médico personal, hábitos de vida y exposiciones ambientales.

También, un cuestionario dirigido a tus padres de unos 20 minutos para saber más sobre tus primeros años de vida.

Y por último, si la situación lo permite, recogerte una muestra de saliva para análisis genéticos y epigenéticos.

¿POR QUÉ ES IMPORTANTE?

Para poder mejorar la salud de toda la población necesitamos comprender por qué algunas personas enferman y otras no, y por ello es fundamental obtener información detallada sobre las características y las exposiciones que han recibido tanto los que hayan tenido la enfermedad como los que no.

¡Muchas gracias por su participación! ☺

La Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQUAS) promueve el estudio EPI-CT NCC, que investiga el efecto que las enfermedades previas, las exposiciones ambientales y en el ámbito médico, y los factores genéticos y epigenéticos, tienen o pueden tener sobre el riesgo de cáncer. Se llevará a cabo en España, Francia y Suecia.

Este estudio se está llevando a cabo en colaboración con el Instituto de Salud Global de Barcelona - ISGlobal. En Catalunya el estudio está promovido por el Departament de Salut de la Generalitat de Catalunya.

Financiado por:

Instituto de Salud Carlos III

Generalitat de Catalunya
gencat.cat

¿Alguna pregunta en relación al estudio en Catalunya?

Joan Albert d'Escofet (jaescofet@itteria.cat)
coordinador AQUAS

Lourdes Arjona (lourdes.arjona@isglobal.org)
coordinadora del trabajo de campo

Maëlle Canet (maelle.canet@isglobal.org)
coordinadora Nacional

Investigadoras principales:

- Dra. Thierry-Chef (isabelle.thierrychef@isglobal.org)
- Prof. Elisabeth Cardis (elisabeth.cardis@isglobal.org)

Centro coordinador:

Agència de Qualitat i Avaluació Sanitàries de Catalunya

ISGlobal Institut de Salut Global Barcelona

Obra Social "la Caixa"

Nested Case Control

EPI-CT

Si quiere participar, en nombre de su hijo/a, en el proyecto, ¿Qué es lo que tiene que hacer?

Los conocimientos obtenidos gracias a los estudios llevados a cabo a partir de los cuestionarios, pueden ayudar al avance médico, contribuir al conocimiento sobre las enfermedades y, por ello, a otras personas en el futuro.

Primero de todo, tendría que darnos su aprobación a través del "consentimiento informado", Con este consentimiento nos permitiría acceder a los informes clínicos y contactar con los médicos que atendieron a su hijo/a.

Seguidamente, deberá rellenar un cuestionario on-line, para conocer el historial médico de su hijo/a, hábitos de vida y exposiciones ambientales a las que estuvo expuesto.

También, un cuestionario dirigido a los padres, de unos 20 minutos, para saber más sobre los primeros años de vida de su hijo/a.

¿POR QUÉ ES IMPORTANTE?

Para poder mejorar la salud de toda la población necesitamos comprender por qué algunas personas enferman y fallecen y otras no, y por ello es fundamental obtener información detallada sobre las características y las exposiciones que han recibido tanto los que hayan tenido la enfermedad como los que no.

¡Muchas gracias por su participación! ☺