



Risk assessment *Tools* for severe side *Effects* after *breasT* Radiotherapy:  
radiation safety through biological extended models and *digital twinS*

**Eva Onjukka (assoc. prof.), medical physicist, Karolinska University Hospital**

### Consortium leaders

**Tiziana Rancati (PI)**, *Fondazione IRCCS Istituto Nazionale dei Tumori*,  
Milan, Italy

**Eva Onjukka**, *Region Stockholm*, Stockholm, Sweden

**Claudio Fiorino**, *UniSR Università Vita-Salute San Raffaele*, Milan, Italy

**Sara Gutiérrez Enriquez**, *Fundació Privada Institut d'Investigació  
Oncològica de Vall d'Hebron*, Barcelona, Spain

**Ana Vega**, *Fundación Pública Galega de Medicina Xenómica*,  
Santiago de Compostela, Spain

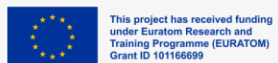
**David Gibon**, *AQUILAB by Coexya*, France

**Paolo Zunino**, *Politecnico di Milano*, Milan, Italy

**Sandrine Pereira**, *Neolys Diagnostics*, France

Cancer Core Europe's 10th Annual meeting & Karolinska CCC days

Karolinska Institutet 23-24 March 2026



EU Grant Agreement n. 101166699



**Karolinska  
Institutet**



**Karolinska Comprehensive Cancer Center**

# Participating countries and Partners

## ITALY

**Fondazione IRCCS Istituto Nazionale dei Tumori**

**Politecnico di Milano**

**UniSR Università Vita-Salute San Raffaele**

## SPAIN

**Fundació Privada Institut d'Investigació**

**Oncològica de Vall d'Hebro (VHIO)**

**Fundación Pública Galega de Medicina**

**Xenómica**

## FRANCE

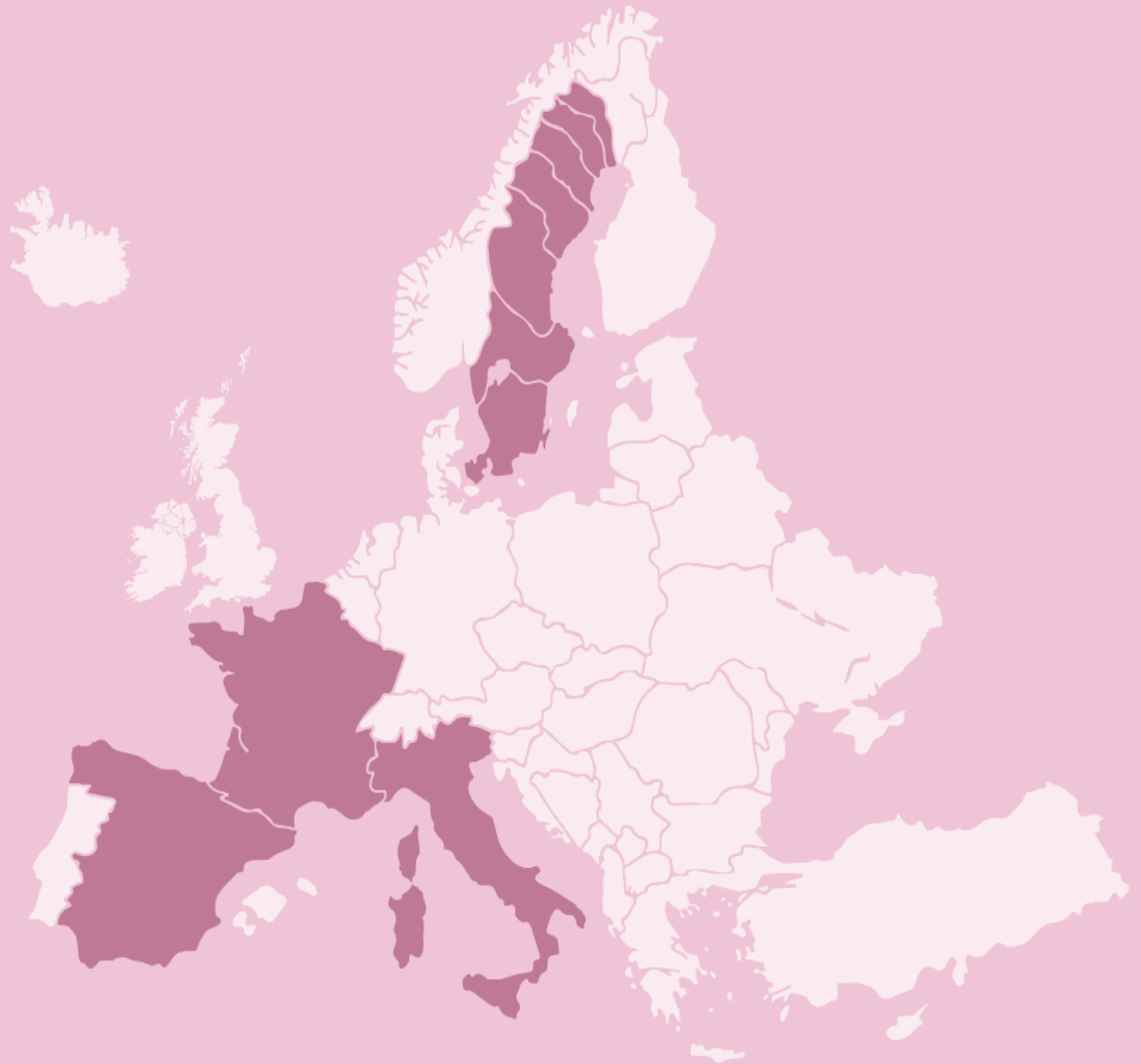
**Neolys Diagnostics**

**AQUILAB by Coexya**

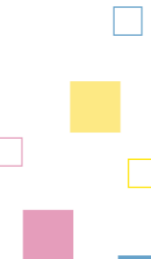
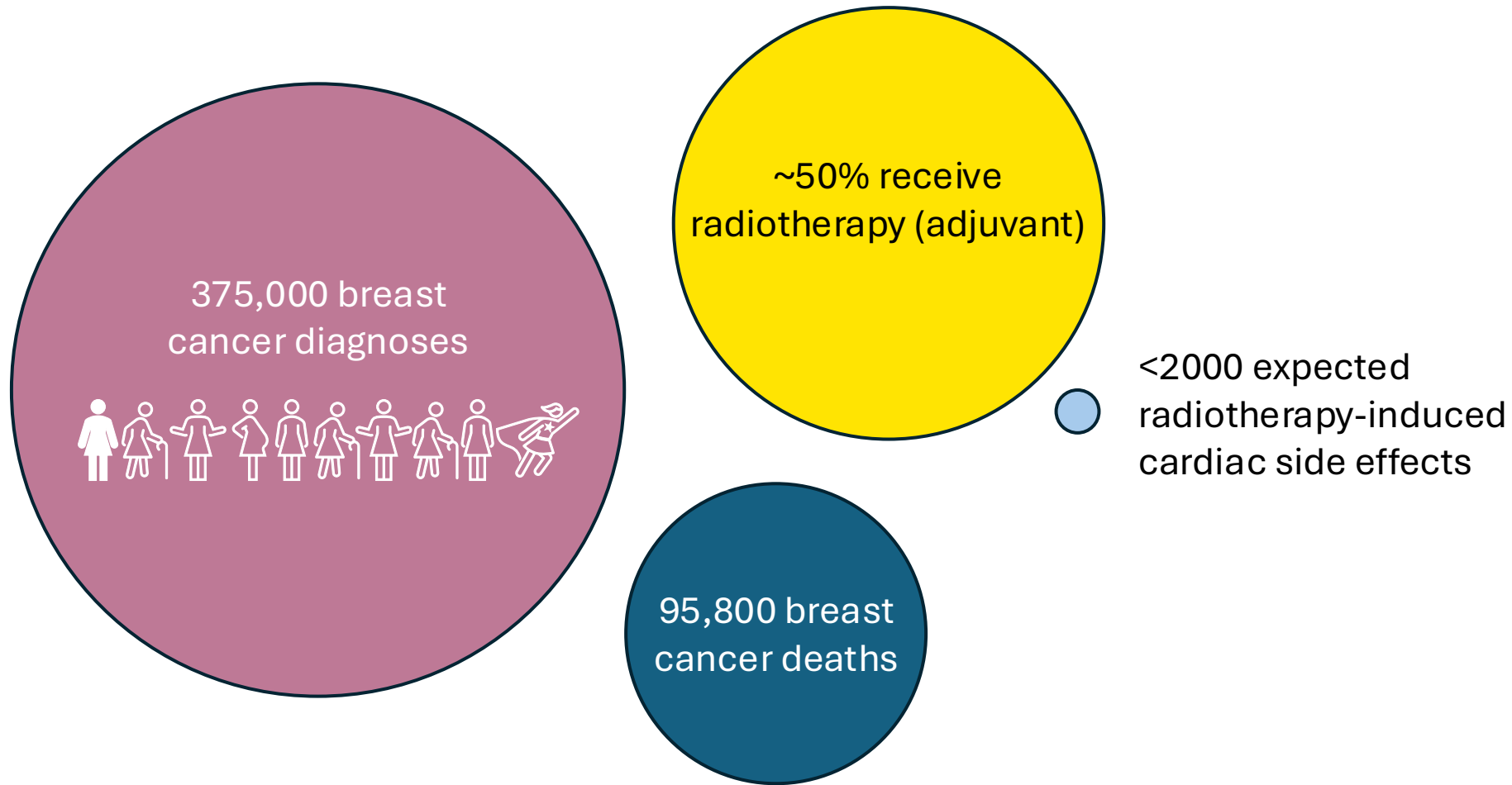
## SWEDEN

**Region Stockholm Karolinska University**

**Hospital**



# Breast cancer in the EU



# Personalising follow-up needs

Severe late side effects are rare, but after the end of treatment patients often feel abandoned by the experts.

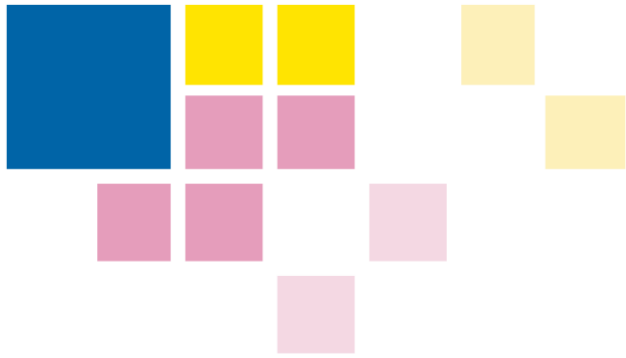
*'You end up doing it on your own, without any guidance.'*

Fairweather et al. Healthcare (Basel). 2025;13:1351

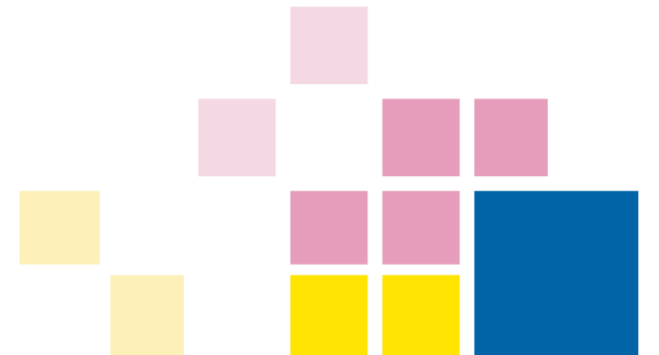
*'I experienced shortness of breath. When I asked if it could be a side effect, I received no answers.'*

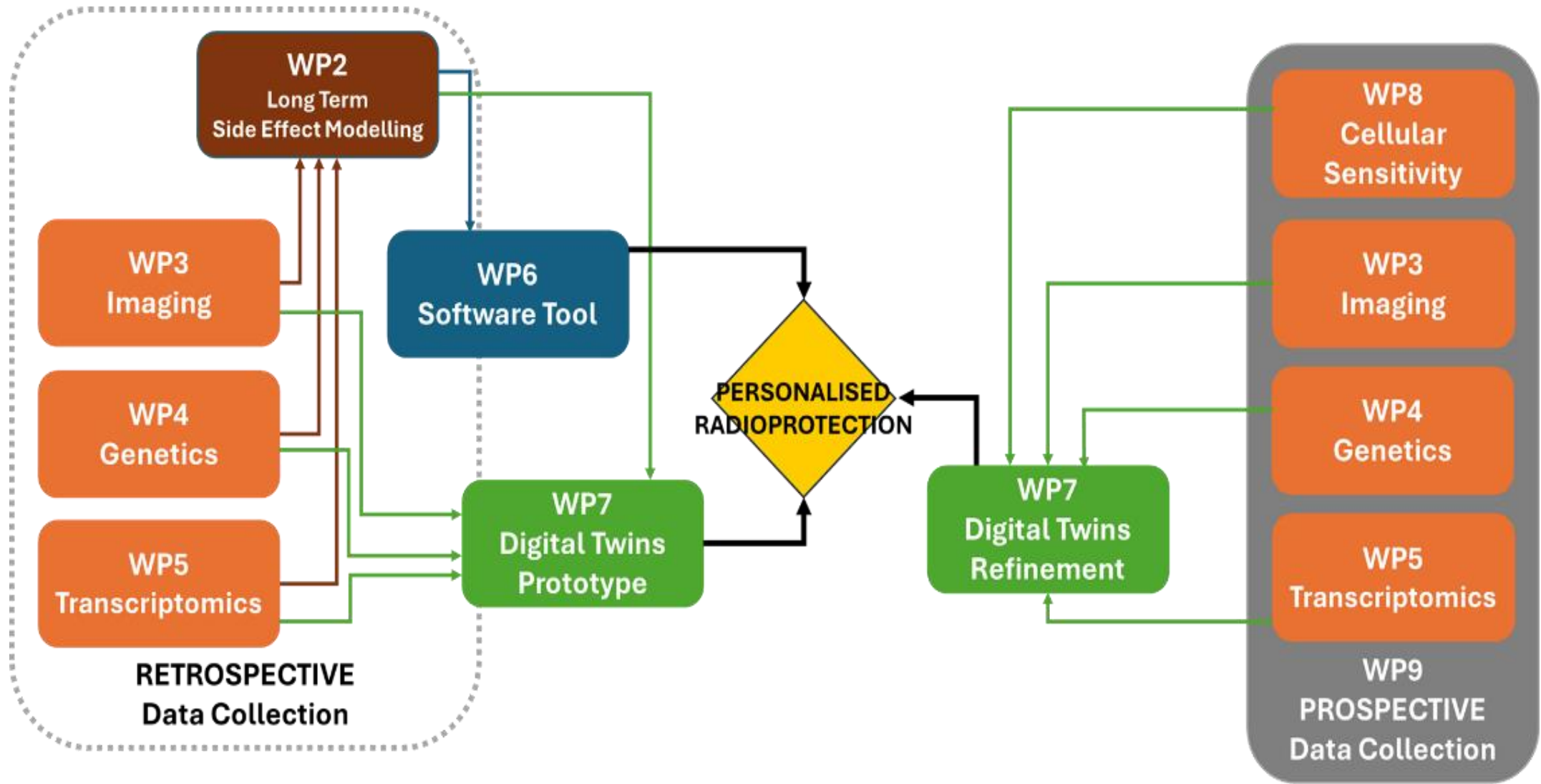
Medicinsk Vetenskap 2024:4





***TETRIS will bring innovation to communication about risk,  
meeting the needs of patients and their doctors.***





# TETRIS retrospective cohort

The **REQUITE\*/RADprecise breast cohort** (2000 patients)

- **44** severe cardiac events registered
- **16** severe chronic pulmonary events
- **25** second cancers in the irradiated area (8 breast, 4 lung, 4 lymphomas, 7 skin and 2 thyroid)

**Universita Vita-Salute San Raffaele cohort** (1000 patients)

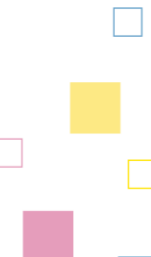
- **29** severe cardiac events registered

Fondazione IRCCS **Istituto Nazionale dei Tumori** cohort (1000 patients), retrieval of data in progress

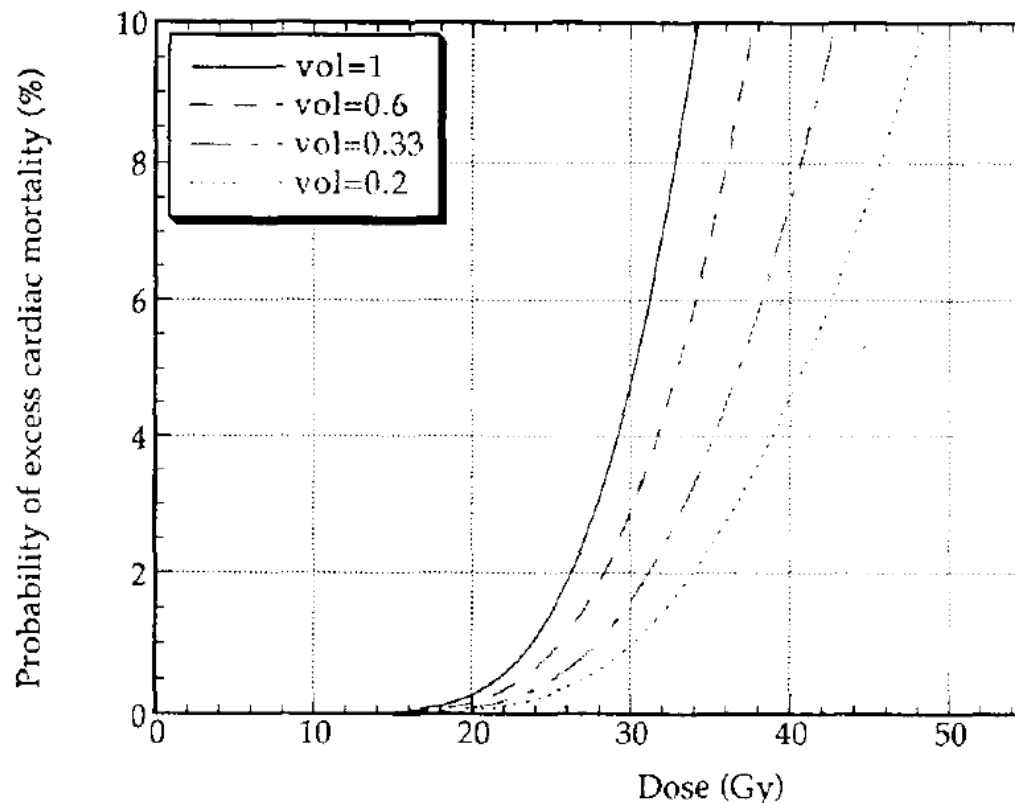
**Region Stockholm cohort** (2400 patients, high-risk selection), quality registry data

**Spanish cohort, from Val d'Hebron Institute of Oncology and Fundacion Publica Galega de Medicina Xenomica** (500 patients), retrieval of data in progress

\*Seibold et al. Radiother Oncol. 2019;138:59-67



# Severe late side effects



Gagliardi et al. Br J Radiol. 1996;69:839-46

Severe effects are rare but can appear **many years** after therapy:

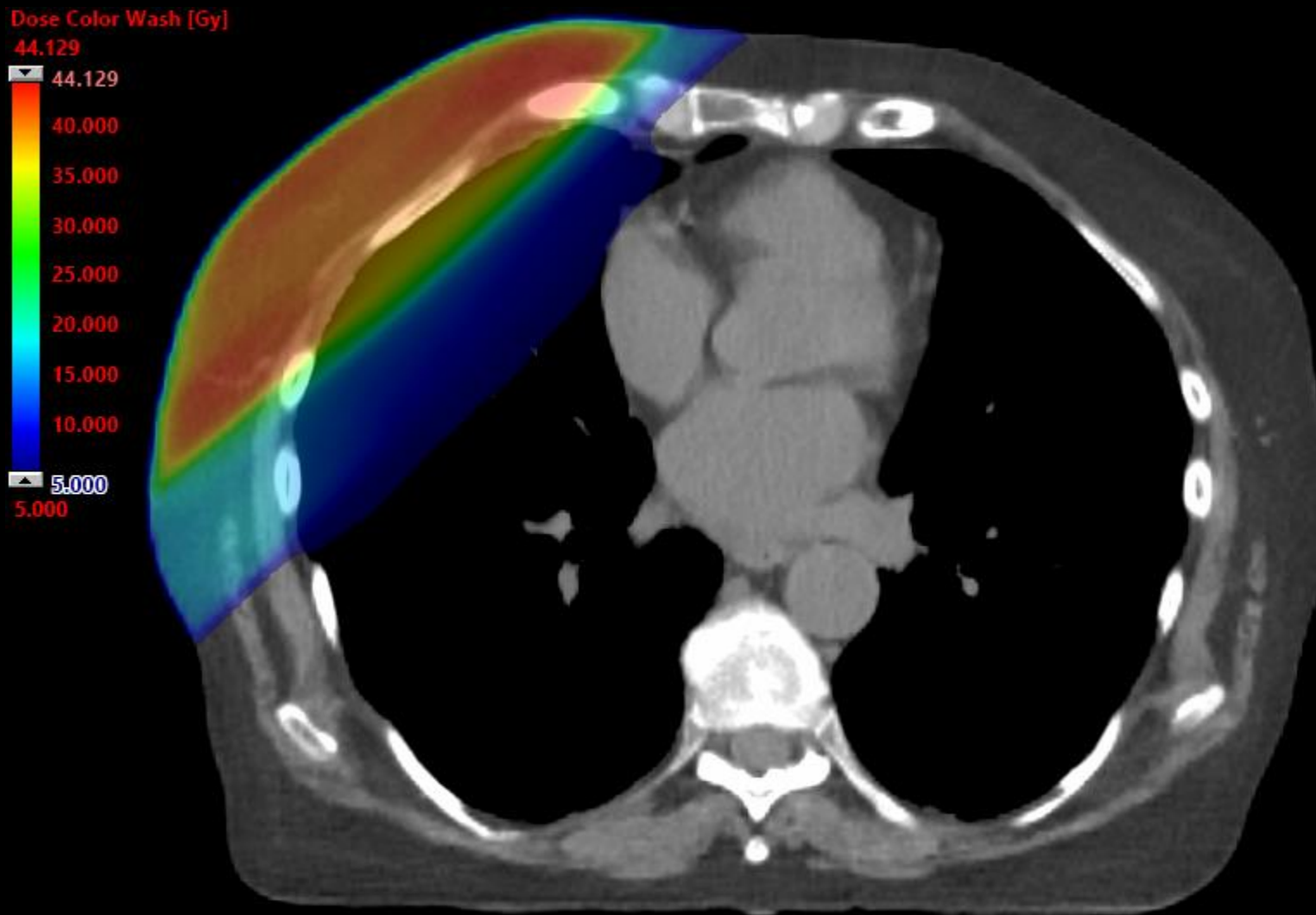
- Cardiac effects
- Respiratory effects
- Secondary cancer

*Prediction models for modern radiotherapy can only be created in the future.*

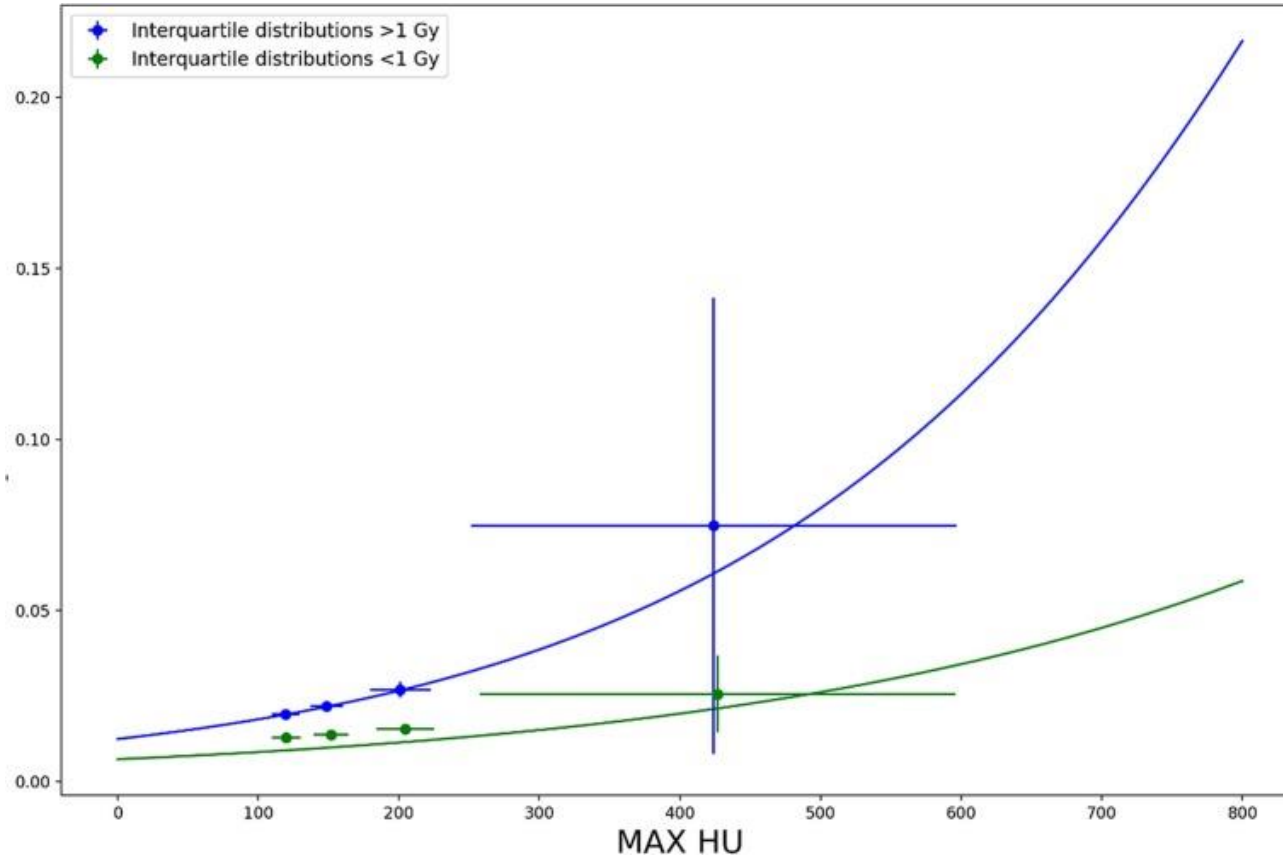
**Historical models will be tested in current cohort**

- **Basic risk scores**
- **Refined risk scores**

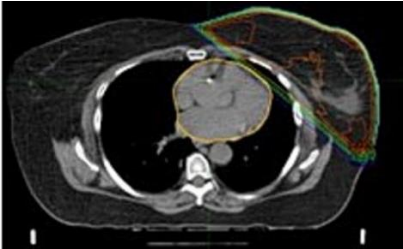
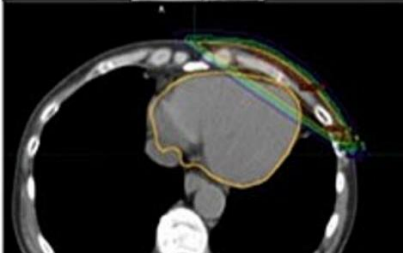
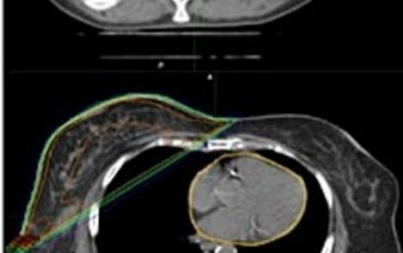
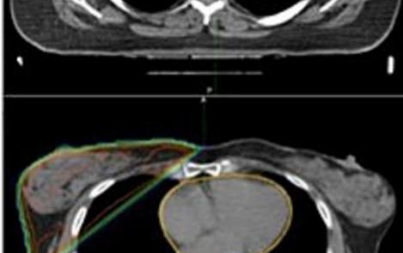
# A unique 3D dose distribution for each patient

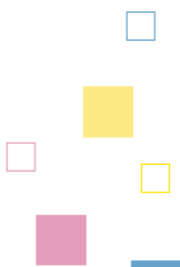


# Image-based biomarkers: cardiac calcifications

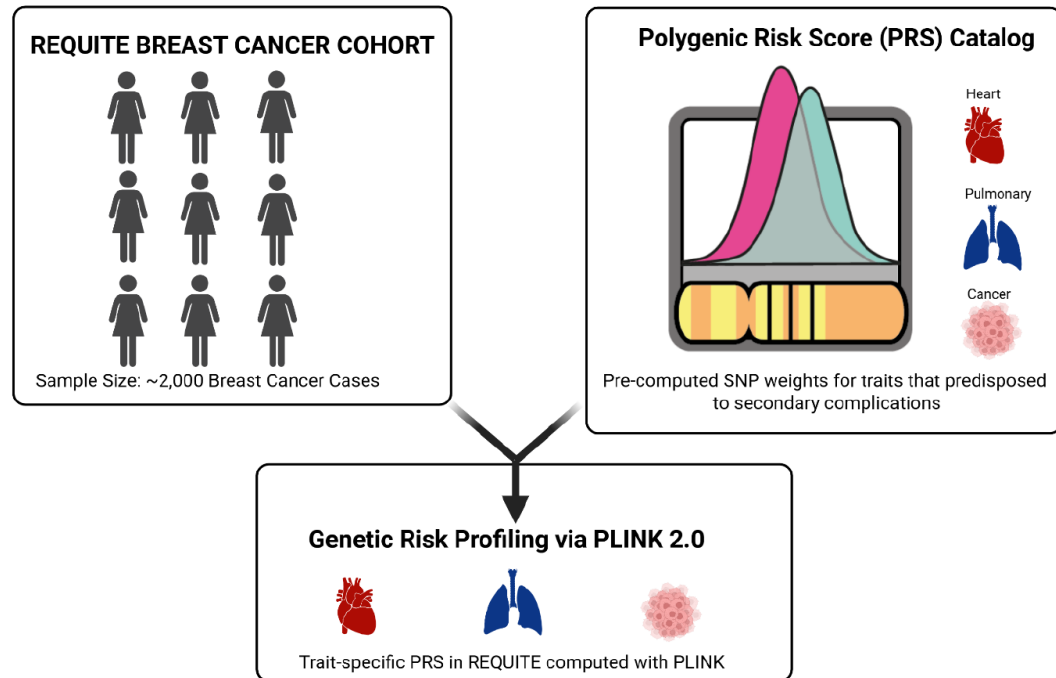
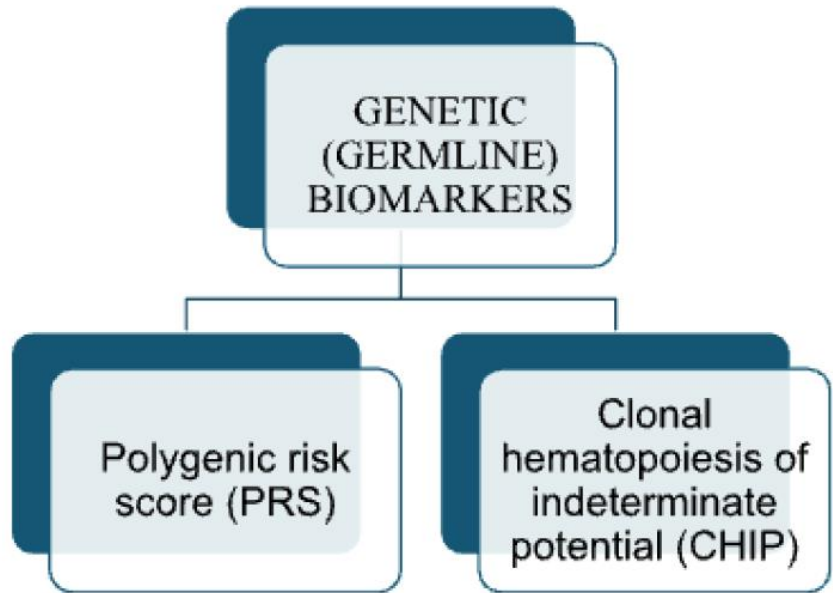


Bellardo et al. Radiother Oncol. 2025;211:111098

	<b>Variable</b>	<b>Value</b>
	MHD >1Gy	Yes
	Max_HU	302
	Risk Probability	0.037
	<b>Variable</b>	<b>Value</b>
	MHD >1Gy	Yes
	Max_HU	113
	Risk Probability	0.022
	<b>Variable</b>	<b>Value</b>
	MHD >1Gy	No
	Max_HU	358
	Risk Probability	0.016
	<b>Variable</b>	<b>Value</b>
	MHD >1Gy	No
	Max_HU	104
	Risk Probability	0.008



# Genetic and transcriptomic risk factors



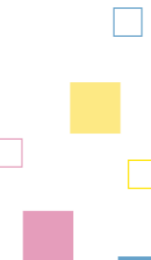
Genomics identifies genetic potential/predisposition, whereas transcriptomics shows which genes are active under specific conditions (revealing gene expression changes).

# Software tool to calculate and communicate risk scores

A tool calculating refined risk scores, tested in a large cohort, will meet the needs of patients and their doctors after therapy.

Reassurance where the risk is low.

Specific elevated risks can be anticipated and managed proactively.

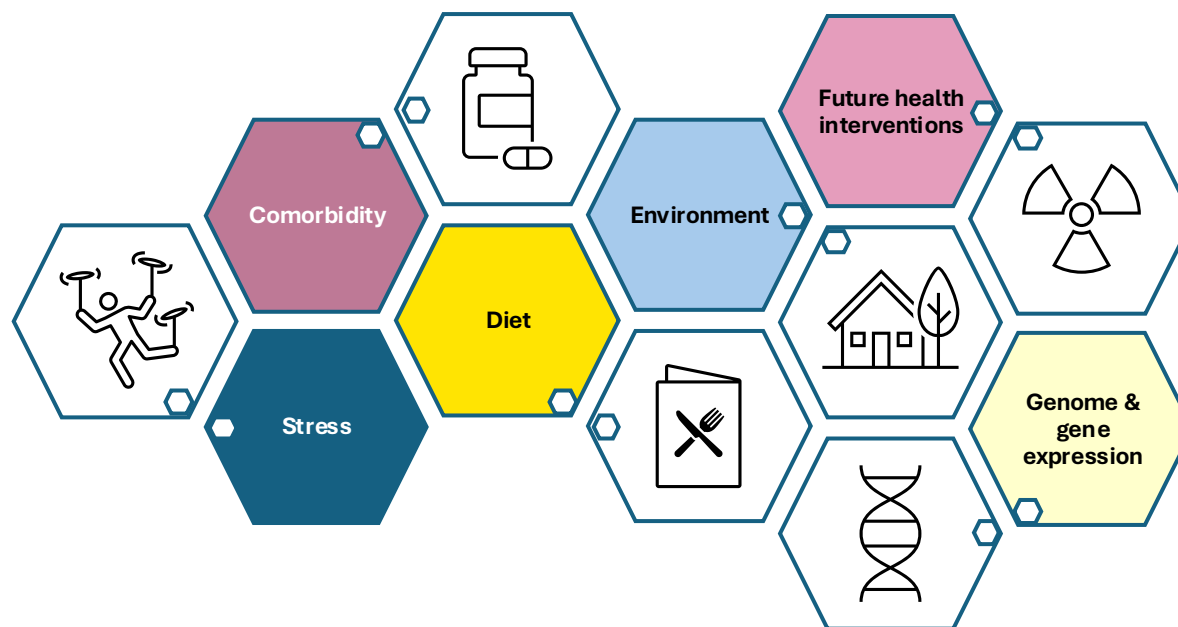


# Increasing the complexity

Current evidence packaged as regression models

- Validated and ready for clinical use
- Limited complexity

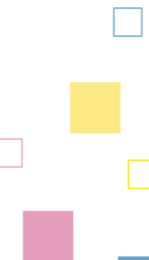
How to take into account the full spectrum of variables?



# Digital twins prototype

Prospective cohort of 250 patients  
with 3 years' follow up

- Full medical history
- Genomics
- Radiosensitivity
- Lifestyle questionnaires



## Digital twin approach

Patient-specific digital twins formulated as probabilistic graphical models integrating dose, imaging, omics, and lifestyle data. Enables representation, inference, and learning under uncertainty.

## High interpretability

Unlike black-box AI, the selected Bayesian framework provides transparent cause-effect relationships between radiotherapy, biology, and long-term outcomes.

## Adaptive intelligence

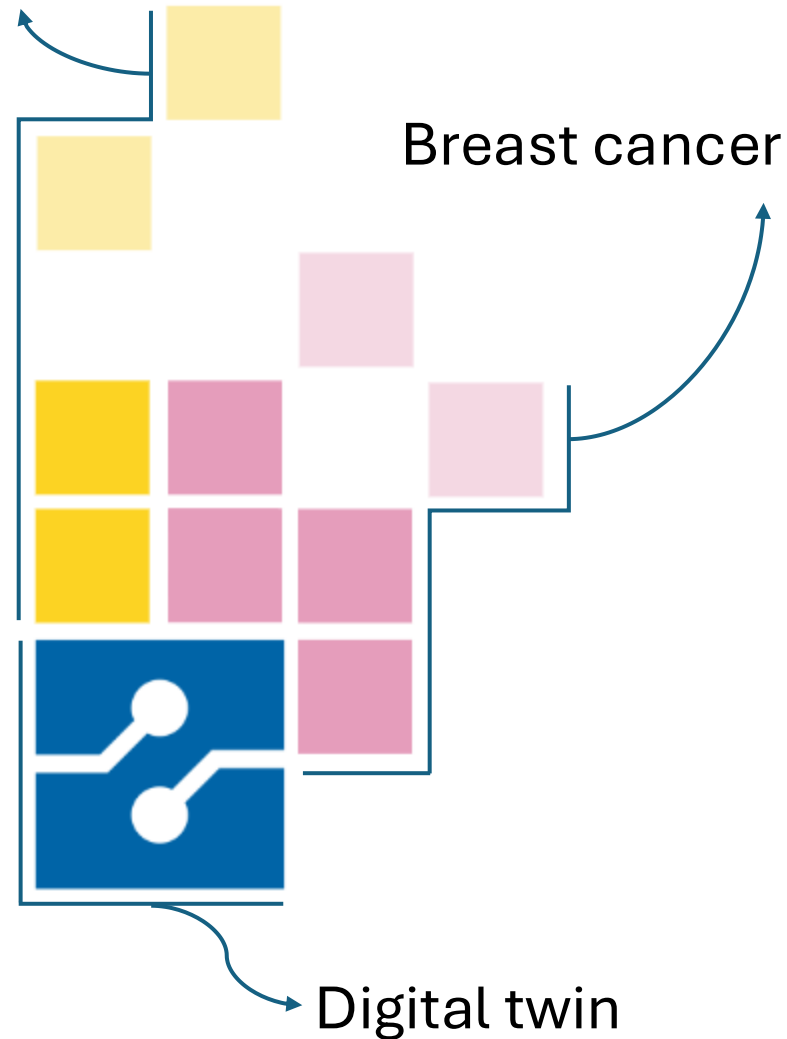
The twin evolves with patient data (follow-up exams, biomarkers), supporting data assimilation and feedback-loop learning.

## Clinical purpose

Simulate counterfactual scenarios (e.g., alternative lifestyles), to inform personalised radioprotection strategies.



Radiotherapy



PI: Tiziana Rancati

Stockholm TETRIS team:

Eva Onjukka, Filippo Schiavo, Giovanna Gagliardi,  
Mattias Hedman, Andri Papakonstantinou

Work package leaders:

Tiziana Rancati, Eva Onjukka, Claudio Fiorino, Sara  
Gutiérrez Enriquez, Ana Vega, David Gibon, Paulo  
Zunino, Sandrine Pereira

Scientific advisors:

Carolyn Taylor, Alfons Hoekstra

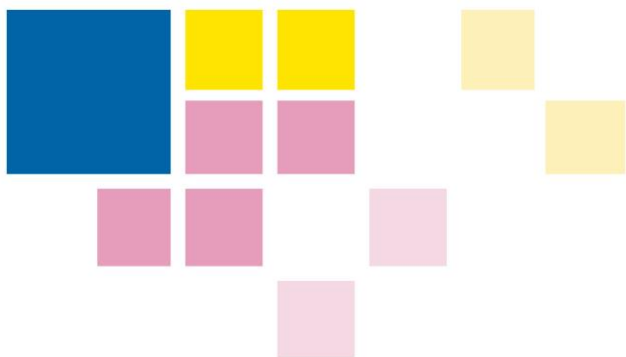
Patient representatives:

Amazona Stockholm, Europa Donna

# CENTRE CELLEX

5-117





# THANK YOU

TETRIS - Risk assessment *T*ools for severe side *E*ffects after *breasT* Radiotherapy:  
radiation safety through biological extended models and *digital twinS*

EU Grant Agreement n. 101166699



Follow us on social media

