Team PRECISION

Impact Report

Funded 2017-2024 by

CANCER RESEARCH UK

KWF

The team that transformed our fundamental understanding of Ductal Carcinoma In Situ.

Challenge

Lethal versus non-lethal cancers

CANCER GRAND CHALLENGES

Dare to think differently

What is Cancer Grand Challenges?

Founded by

CANCER RESEARCH UK

NIH NATIONAL CANCER INSTITUTE

"Cancer Grand Challenges funding enabled us to transform understanding of DCIS biology and develop new approaches that could aid risk assessment to avoid overtreatment. We are empowering patients and clinicians to make more informed decisions about care."

Jelle Wesseling

PRECISION Team Lead, Senior Group Leader, The Netherlands Cancer Institute and Professor of Breast Pathology, Leiden University Medical Center.

Cancer Grand Challenges is a global initiative that is building a pioneering, interdisciplinary community to take on and solve cancer's most complex problems.

Co-founded by the two largest funders of cancer research in the world, Cancer Research UK and the National Cancer Institute in the US, Cancer Grand Challenges aims to accelerate high-impact research and translate discoveries for public and patient benefit by transforming how team science is conducted.

Through Cancer Research UK, Cancer Grand Challenges is building a network of like-minded partners and individual donors around the world, all of whom share our aspiration to create change. Our work wouldn't be possible without their collective support. We are grateful to the Dutch Cancer Society (KWF) who co-funded the PRECISION team.

The challenge

In 2015, Cancer Grand Challenges set the lethal versus non-lethal cancers challenge. After a rigorous selection process, led by our Scientific Committee of world-leading experts, the PRECISION team was chosen to tackle the challenge and distinguish between cancers that need treating, and those that don't. PRECISION focused on ductal carcinoma in situ (DCIS) of the breast.

At the time, the condition was generally considered as a precursor to invasive breast cancer, resulting in widespread overtreatment, as up to 80% of cases would never actually progress. In addition, since the introduction of population-based screening for the early diagnosis of breast cancer, the detection of DCIS had increased around seven-fold. However, it was not possible for clinicians to discriminate between harmless forms and the 20% that pose a real threat. Everyone diagnosed with DCIS was advised to undergo breast-conserving surgery or mastectomy, often followed by radiotherapy and sometimes also supplemented with hormone therapy. All for a condition that may never do them any harm.

When the team was funded by Cancer Research UK and the Dutch Cancer Society (KWF) in 2017, knowledge about the biology of DCIS was limited, and there was no clear understanding of what drove or prevented its progression to invasive cancer. By delving deeply into the biology of DCIS, the team aimed to identify factors that could distinguish between aggressive forms and those posing no threat.

Meet team PRECISION

Led by Jelle Wesseling at the Netherlands Cancer Institute (NKI), PRECISION assembled a team of over 60 researchers and clinicians, from pathologists to molecular biologists and machine learning experts.

> "PRECISION revealed biological clues as to what makes DCIS transform into invasive breast cancer, paving the way for changes to clinical practice, which could potentially spare women worldwide from invasive overtreatment."

Gemma Balmer

Head of Research, Cancer Grand Challenges

Map Key

- United States
- United Kingdom
- Netherlands

Jelle Wesseling

PRECISION Team Lead, Netherlands Cancer Institute

$19.25m

Amount of funding awarded

47,695

Women included in the world's largest DCIS dataset

60

Number of publications to date

Jacco van Rheenen discussing with the team.

Shelley Hwang presenting to the team.

Tackling the lethal versus non-lethal challenge

The PRECISION team has become a leading international authority in the DCIS field, driving a fundamental re-evaluation of how the condition is defined and managed. The team's research has catalysed a crucial debate on treatment approaches and provided the evidence base for considering active surveillance ("watch and wait") as a safe and effective option for patients with low-risk DCIS. Clinical trials assessing the safety of this watch and wait approach for women with DCIS in the US, UK and the Netherlands are currently ongoing.

By working collaboratively across borders the team assembled the largest-ever international DCIS collection of data and tissue samples – from 47,695 women in the UK, US and the Netherlands. Using this unique resource, the team found that clinical-pathological factors used when grading DCIS do not hold sufficient prognostic value to predict which women might be suitable for less invasive treatment strategies. PRECISION went on to reveal that differences in DCIS size, growth patterns and HER2 status could potentially be used to discriminate between harmless and hazardous lesions, as well as a combination of COX-2 levels and adipocyte size in the microenvironment. The PRECISION team also developed AI-based algorithms to analyse mammograms and tissue slides, with the goal of automated risk prediction. The team is now working to validate the most promising potential biomarkers and prediction tools and is exploring their translation into the clinic, with the hope of revolutionising DCIS management.

Uncovering the biology that drives DCIS progression

Crucially, PRECISION has made significant advances in understanding the biological mechanisms of DCIS evolution. Only through uncovering the biology of progression can we truly know which DCIS cases need treatment—and how to treat them most effectively. By studying the clonal and spatial relationships between seemingly normal breast epithelium adjacent to pre-cancerous DCIS lesions, the team saw that cells first spread to a field of mutant cells, which predisposes the tissue to lesion formation. Through genomic analysis of DCIS recurrence after surgery, the team made the surprising discovery that around 20% of subsequent invasive breast cancers were entirely unrelated to the initial DCIS. This suggests that DCIS is not only a precursor to invasive breast cancer but is also a risk factor for developing new primary breast cancers. This important breakthrough has wider implications for breast cancer screening and subsequent follow-up.

Changing the clinical perception of DCIS

As part of the LORD clinical trial, the team reported that when women with perceived low-risk DCIS were given a choice between active surveillance versus conventional treatment, a striking 76% opted for active surveillance. This illustrates the shift in perception around DCIS as a precursor to invasive breast cancer and demonstrates the real-world impact of the team's work.

Timeline

Tackling the challenge

2015

Lethal versus non-lethal challenge set

2017

PRECISION awarded $19.25m in funding

2019

JULY 2019

Ductal carcinoma in situ: to treat or not to treat, that is the question
BRITISH JOURNAL OF CANCER

2020

MAY 2020

De-Escalating Breast Cancer Surgery for Low-Risk Ductal Carcinoma in Situ
JAMA ONCOLOGY

2021

MARCH 2021

Breast adipocyte size associates with ipsilateral invasive breast cancer risk after ductal carcinoma in situ
NPJ BREAST CANCER

Microenvironmental factors as predictors of progression

PRECISION uncovered that features of the breast microenvironment are associated with whether DCIS progresses to invasive breast cancer. The team showed that larger adipocytes surrounding DCIS lesions, together with high COX-2 expression, markedly increases the risk of subsequent invasive disease by 28% (around 1 in 4 chance). To enable large-scale validation, the team developed a fully automated algorithm to measure adipocyte size and COX-2 levels, paving the way for these factors to be used as predictive biomarkers in DCIS management.

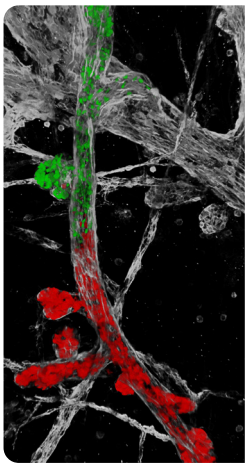


Image credit: Colinda Scheele

MAY 2021

Variability in grading of ductal carcinoma in situ among an international group of pathologists
THE JOURNAL OF PATHOLOGY: CLINICAL RESEARCH

ER and HER2 assessment improves DCIS grading

International analysis of DCIS grading revealed only moderate agreement among pathologists, highlighting the need for standardised assessment. The team found that incorporating ER and HER2 evaluation, which is now implemented in active surveillance clinical trials, improves diagnostic consistency and supports confident selection of low-risk DCIS candidates for non-invasive management.

OCTOBER 2021

Mouse-INtraDuctal (MIND): an in vivo model for studying the underlying mechanisms of DCIS malignancy
THE JOURNAL OF PATHOLOGY

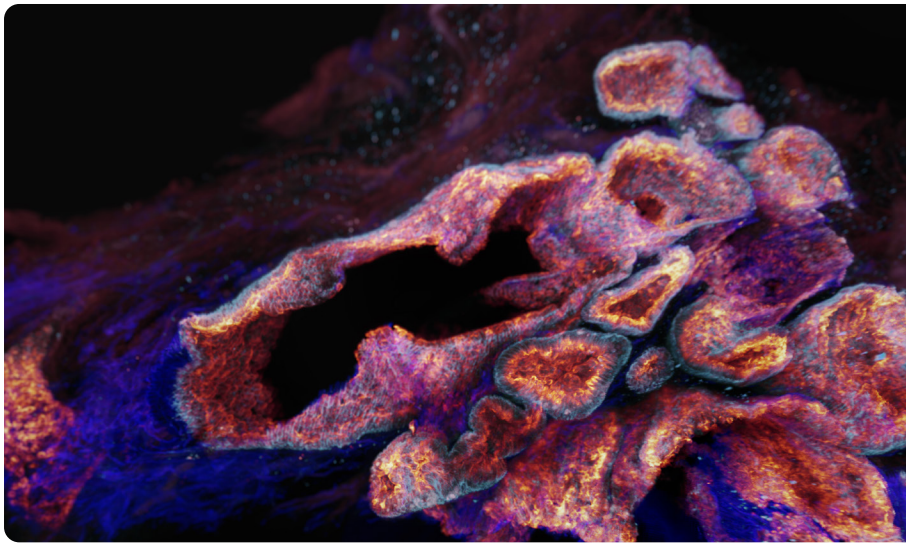


Image credit: Hendrik Messal and Jacco van Rheenen

Uncovering the bigger picture

Timeline Key:

- Stimulating a global debate
- Modelling DCIS *in vivo*
- Mammography models for risk stratification
- Redefining early breast cancer evolution
- AI-based risk prediction models

2022

APRIL 2022

Prediction of Upstaging in Ductal Carcinoma in Situ Based on Mammographic Radiomic Features
RADIOLOGY

MAY 2022

A multi-modal exploration of heterogeneous physico-chemical properties of DCIS breast microcalcifications
ANALYST

AI-driven mammography models for risk stratification

Mammograms are one of the first points at which DCIS is detected. PRECISION harnessed the power of mammographic imaging and AI to transform how DCIS could be assessed at diagnosis. By pooling over 1,500 mammograms from international cohorts, the team developed radiomics-based models that accurately predict DCIS upstaging and outperform current clinical criteria. These models were robustly validated across multiple datasets and are now being tested in active surveillance clinical trials (COMET, LORD, LORIS). Complementary deep learning tools were also created to automatically detect microcalcifications, advancing the precision of breast imaging. Together, these innovations pave the way for AI-driven decision support that could safely identify women suitable for active surveillance, potentially marking a major shift in DCIS management.

JUNE 2022

Genomic analysis defines clonal relationships of ductal carcinoma in situ and recurrent invasive breast cancer
NATURE GENETICS

DCIS is an independent risk factor for invasive breast cancer

PRECISION genomically profiled 95 paired DCIS lesions and their invasive recurrences to reconstruct the clonal architecture of DCIS and subsequent invasive cancers. The team revealed that while 75% of recurrences were true, clonally related tumours, 18% were genomically unrelated, representing independent primary cancers. This landmark work demonstrates that DCIS is not only a direct precursor to invasive breast cancer but also a marker of elevated future risk to developing new, independent cancers. These insights fundamentally shift how DCIS is understood and inform strategies for risk assessment, surveillance and treatment.

SEPTEMBER 2022

AACR Special Conference: Rethinking DCIS

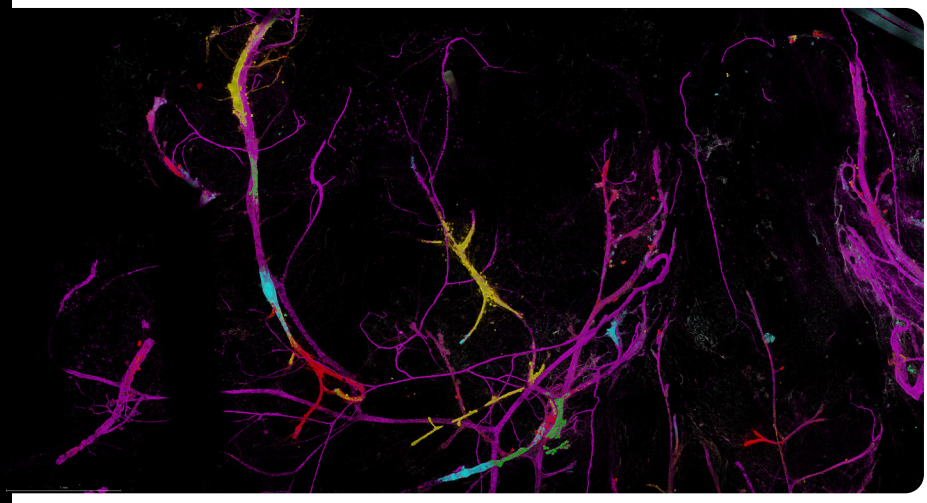


Image credit: Colinda Scheele

2023

MAY 2023

A living biobank of patient-derived ductal carcinoma in situ mouse-intraductal xenografts identifies risk factors for invasive progression
CANCER CELL

JUNE 2023

Microcalcification crystallography as a potential marker of DCIS recurrence
SCIENTIFIC REPORTS

AUGUST 2023

Archival single-cell genomics reveals persistent subclones during DCIS progression
CELL

Modelling DCIS *in vivo* uncovers biological factors to predict invasive risk

PRECISION developed the first models of DCIS, creating a living biobank of patient-derived DCIS mouse-intraductal (MIND) models, readily available to all the research community, enabling the study of DCIS progression *in vivo.* The team characterised 115 models spanning the full spectrum of patient DCIS and identified multiple factors associated with invasive progression. These include high grade, HER2 amplification, high burden of copy number aberrations and expansive 3D growth patterns. The team also discovered two distinct growth patterns — replacement growth, which preserves duct architecture, and expansive growth, which disrupts ducts and correlates with invasiveness — highlighting intrinsic differences between indolent and high-risk lesions. Importantly, 19 of these models are propagatable, providing a resource to accelerate research into DCIS biology and risk stratification.

From archives to insights: single-cell genomics reveals DCIS evolution

Formalin-Fixation and Paraffin-Embedding (FFPE) is the standard way hospitals have been storing patient tissue samples-preserving them for decades, yet rendering them intractable to many molecular biology techniques. To overcome this, PRECISION developed Arc-Well, a high-throughput single-cell DNA sequencing method compatible with archival FFPE tissue blocks up to 30 years old. Using Arc-Well, the team profiled thousands of single cells from 27 historic tumours, including DCIS samples with matched recurrences 2–16 years later. Analyses revealed key chromosomal aberrations in persistent subclones were associated with recurrence risk. Beyond DCIS, this technical breakthrough opens the opportunity to study the millions of archived clinical samples from across human diseases.

First author **Kaile Wang** is now a PI at the Shanghai Institute of Biochemistry and Cell Biology, China.

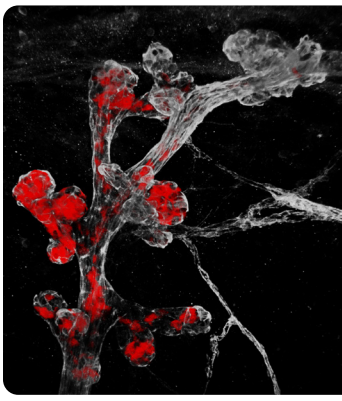


Image credit: Colinda Scheele

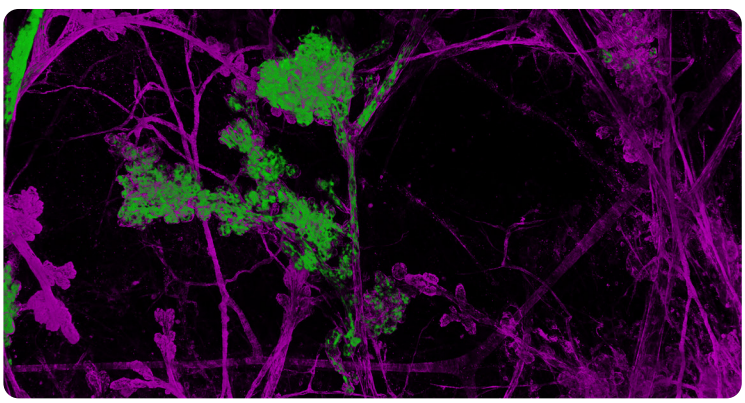


Image credit: Colinda Scheele

AUGUST 2023

Active surveillance versus treatment in low-risk DCIS: Women's preferences in the LORD-trial
EUROPEAN JOURNAL OF CANCER

Women favoured active surveillance for low-risk DCIS

The LORD clinical trial is investigating the safety of active surveillance for low-risk DCIS, recruiting women from 52 hospitals across the Netherlands. PRECISION reported on preferences of the women and their reasoning: 76% of 377 women chose active surveillance over conventional treatment. The main reason for choosing active surveillance was, "treatment is not (yet) necessary," while those opting for treatment were primarily motivated by "avoiding cancer worry."

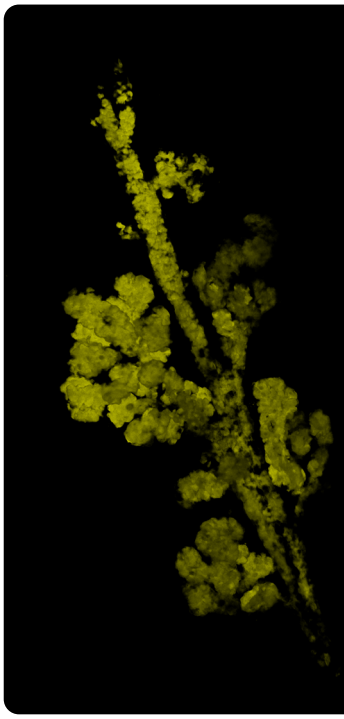


Image credit: Colinda Scheele

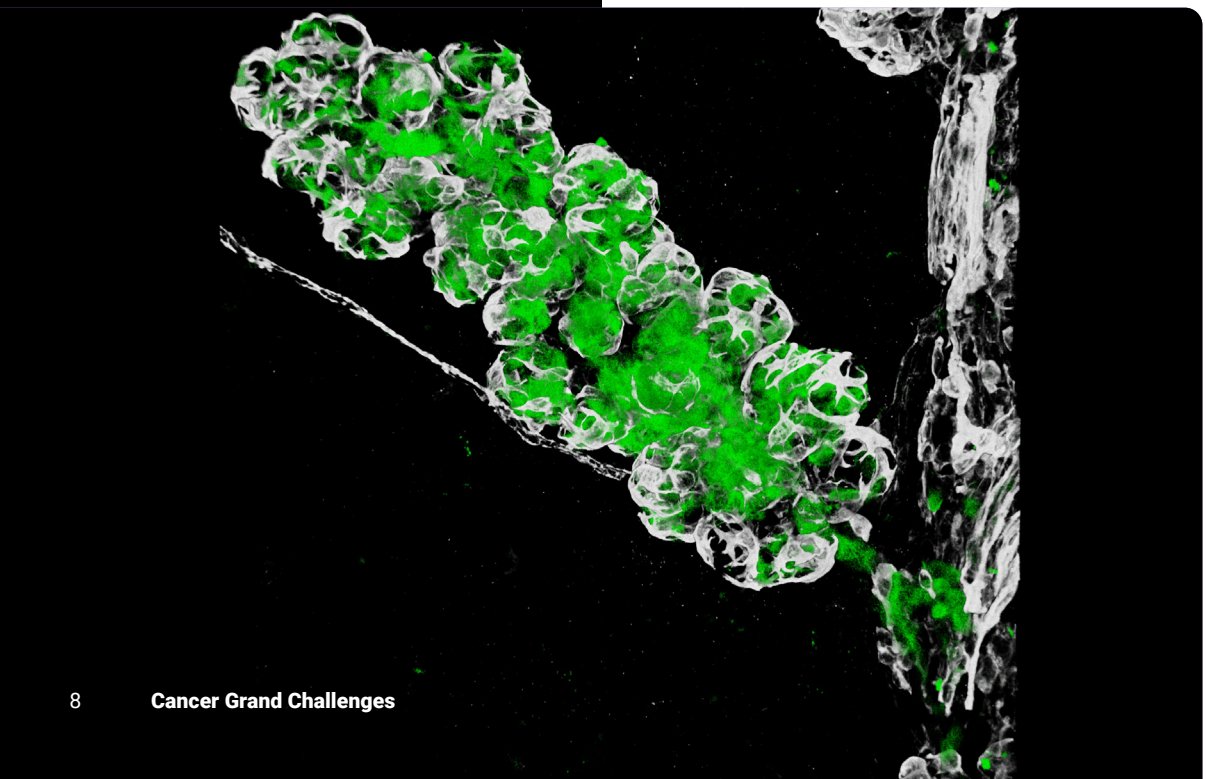
OCTOBER 2023

Association of DCIS size and margin status with risk of developing breast cancer post-treatment: multinational, pooled cohort study
THE BRITISH MEDICAL JOURNAL

Current clinical factors are insufficient for DCIS risk stratification

By studying over 47,000 patients from the UK, US and the Netherlands, PRECISION found that the 10-year risk of invasive cancer in the same breast after treatment is very low: 3.2%. While larger lesions and involved margins, i.e. cancer cells at the edge of the excised tissue, slightly increased risk, these clinicopathological factors alone could not reliably identify higher-risk patients. The study underscores the need for new, robust biomarkers to guide personalised DCIS management.

Image credit: Colinda Scheele



2024

MAY 2024

Ductal carcinoma in situ develops within clonal fields of mutant cells in morphologically normal ducts
THE JOURNAL OF PATHOLOGY

MAY 2024

Ductal carcinoma in situ of the breast: finding the balance between overtreatment and undertreatment
THE LANCET

SEPTEMBER 2024

Mechanisms that clear mutations drive field cancerization in mammary tissue
NATURE

Redefining early breast cancer evolution

PRECISION showed how multiple layers of protection exist to stop mutated clones from spreading within the breast. The work identified the molecular mechanisms behind why having fewer menstrual cycles is associated with decreased breast cancer risk. However, these mechanisms are a double-edged sword, which also drive field cancerisation, known as the "sick lobe" theory in the breast. In human samples, the team mapped the extent and dynamics of the spread of mutations, providing further evidence for the clinical significance of field cancerisation. The team developed game-changing imaging techniques that allowed the visualisation of the very early stages of tumour formation.

Lead author **Colinda Scheele** is now an Assistant Professor at the VIB KU Leuven Center for Cancer Biology, Belgium.

Co-first author **Hendrik Messal** is now a group leader at the NKI, NL.

DECEMBER 2024

An early economic evaluation of active surveillance for low-risk ductal carcinoma in situ
FUTURE ONCOLOGY

Economic evaluation of an active surveillance approach

PRECISION carried out an initial analysis on the economic impacts of DCIS care, finding that active surveillance for low-risk DCIS is a cost-effective alternative to surgery, with the potential to improve quality of life while maintaining survival. Incorporating biomarkers to identify low-risk women could further optimise outcomes, supporting a shift toward personalised, less invasive management of DCIS.

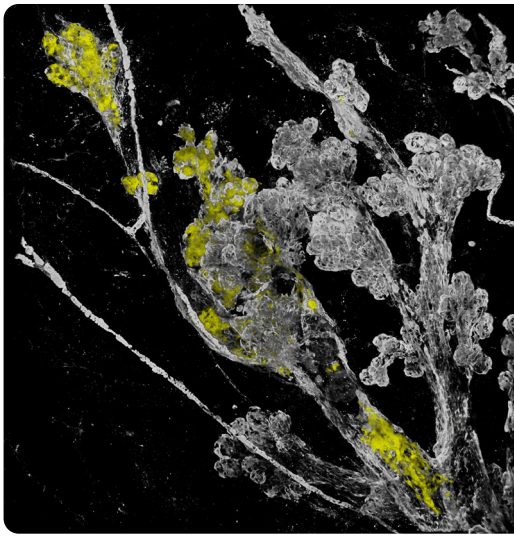


Image credit: Colinda Scheele

Image credit: Colinda Scheele

2025

JANUARY 2025

Conquering Overtreatment of DCIS: Lessons from PRECISION
CANCER DISCOVERY

JANUARY 2025

A morphometric signature to identify ductal carcinoma in situ with a low risk of progression
NPJ PRECISION ONCOLGY

Leading a global debate on DCIS management

The PRECISION team has stimulated an important debate around how a DCIS diagnosis is considered. The first ever conference fully focussed on DCIS prominently featured PRECISION researchers and spotlighted the team's discoveries. This global forum cemented PRECISION's role as global leaders in the field. In a review in The Lancet, Jelle Wesseling came together with other experts in DCIS to discuss how the field is moving away from considering DCIS as a precursor to invasive breast cancer and finding the crucial balance between its over - and undertreatment.

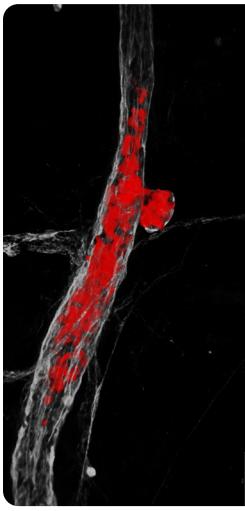


Image credit: Colinda Scheele

JUNE 2025

Deep learning for predicting invasive recurrence of ductal carcinoma in situ: leveraging histopathology images and clinical features
EBIOMEDICINE

NOVEMBER 2025

Cross-national radiomics validation using mammography to predict occult invasion in ductal carcinoma in situ
RADIOLOGY

AI-based morphology profiling to predict low-risk DCIS

PRECISION developed AIDmap, an AI-based morphology analysis pipeline for DCIS H&E tissue slides – hematoxylin-eosin, the standard staining method in pathology - to identify lesions with low risk of progression to invasive breast cancer. By analysing duct morphology across 689 Dutch cases, 226 of which went on to develop invasive breast cancer, the team identified a morphometric signature — small ducts, low cell numbers, and low DCIS to stroma ratio — associated with reduced recurrence risk.

The team went on to develop a DCIS risk and outcome prediction algorithm, also based on H&E slides. Trained on two large cohorts, totalling 558 cases with median 20-year follow-up, the models outperformed traditional clinical risk models, accurately stratifying patients into high - and low-risk groups without manual intervention.

Pending validation on large-scale external datasets, both promising tools have the potential to distinguish harmless DCIS and guide treatment decisions.

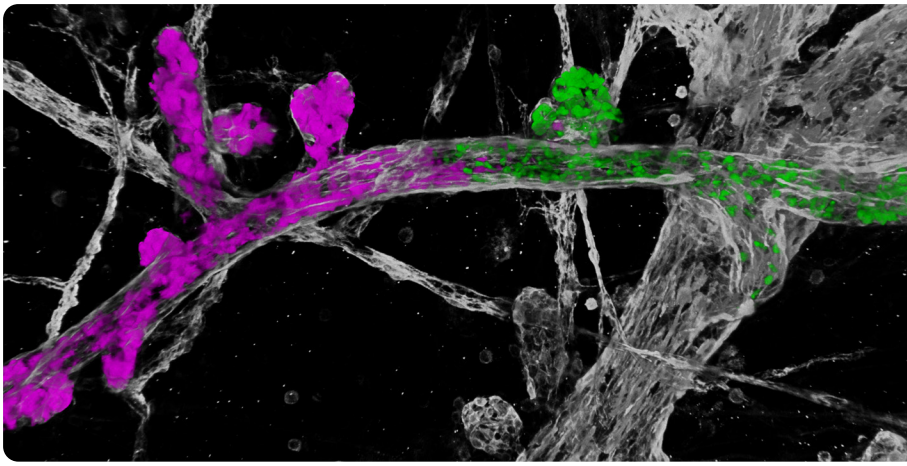


Image credit: Colinda Scheele

"PRECISION's research has led to a paradigm shift around DCIS as a precursor to invasive breast cancer and redefined care. Through funding the team, we are proud to help shape a future where cancer care is more precise, less invasive and tailored to each woman's unique needs."

Carla van Gils

Director of Dutch Cancer Society (KWF)
Co-funder of team PRECISION

10
Postdoctoral researchers trained

22
PhD students trained to date

3
Independent research groups established

3
Progression prediction algorithms developed

115
PDX-MIND Mouse models developed

Tools, techniques & models

Team PRECISION pursued an ambitious long-term strategy to address research gaps hindering progress in the field of DCIS. To this end, the team created innovative patient-derived DCIS intraductal mouse models (DCIS-MIND) and Arc-Well, a single-cell sequencing technology to analyse historically collected tissues, previously thought to be incompatible with this kind of analysis.

The team meticulously developed techniques to allow the stochastic induction of mutations in just a few cells throughout the breast in mice and follow their behaviour using lineage tracing. This approach more accurately reflects the natural situation, where cells acquire mutations at random over time whilst being surrounded by otherwise normal tissue, as opposed to mutating entire tissues or model organisms. The team then developed advanced 3D imaging approaches to scan the whole breast to find and then study these mutated cells.

PRECISION has also developed multiple AI-based algorithms to aid the prediction of which DCIS will progress, based on mammograms or H&E tissue slides. These tools could readily be deployed worldwide with relatively limited cost. These resources, tools and models, which are available to the scientific community, will pave the way for further advancements in the DCIS field and beyond.

Future leaders impact

PRECISION's future leaders drove the development of the innovative technologies that the team created, changing how DCIS is studied. The scope, scale and duration of PRECISION provided opportunity for trainees from different disciplines and countries to gain experience beyond a typical PhD or postdoctoral project. Through interactions between junior, mid-career and senior researchers, via regular Zoom meetings, annual face-to-face meetings and international lab visits, they have built a network that will help them in their future scientific endeavours.

Cancer Grand Challenges funding enabled the team to train 10 postdoctoral researchers and 22 PhD students as well as support the development of junior faculty. Over the course of the funding, Colinda Scheele transitioned from a PhD student to an independent group leader at VIB KU Leuven Center for Cancer Biology, Belgium, where her lab investigates mammary tumour initiation employing the cutting-edge techniques developed as part of PRECISION. Her lab has already published ground-breaking work showing the role of the menstrual cycle in regulating the response to chemotherapy in breast cancer patients.

Advocacy impact

Patient advocates are embedded into Cancer Grand Challenges teams and are important members of the teams we fund to address cancer's toughest challenges.

PRECISON had five patient advocates from the Netherlands, UK and US: Deborah Collyar, Donna Pinto, Hilary Stobart, Ellen Verschuur and Marja van Oirsouw. They worked with each of the low-risk DCIS trials, supporting funding applications and the generation of patient materials, newsletters and information to increase enrolment. The patient advocates also developed resources to aid communication about DCIS and treatment options, explaining the risks of future invasive cancer. The patient advocates and researchers plan to continue to work together to raise awareness of DCIS to clinicians, patients and the public, and remain committed to creating decision aid tools for women with DCIS.

Looking ahead

The PRECISION team has transformed our fundamental understanding of the biology of DCIS.

It is yet to publish its whole genome sequencing data, the most comprehensive analysis of the genomic landscape of DCIS to date.

PRECISION has driven a critical re-examination of how DCIS is defined and treated. With clinical trials across the UK, US and the Netherlands testing active surveillance reading out in the coming years, the team has a unique opportunity to study the natural evolution of DCIS and validate its findings. PRECISION hopes its work will ultimately lead to a change in international clinical guidelines and that its predictive risk tools will aid patients and clinicians in making better-informed decisions. The team is also working to develop dynamic risk prediction models, which continuously update an individual's breast cancer risk based on new clinical, pathological, and imaging data - similar to weather forecasting, where predictions evolve as new information becomes available.

The resources generated, along with the biological insights and predictive algorithms developed, hold promise for future strategies to prevent the overtreatment of DCIS. These advancements have the potential to improve the lives of thousands of women diagnosed with the condition each year worldwide – sparing many from undergoing the stress, anxiety and physical side effects of unnecessary and invasive treatment.

Funded institutes:

Baylor College of Medicine
Duke University
King's College London
Netherlands Cancer Institute
University of Birmingham
University of Cambridge
University of Kansas
University of Texas MD Anderson Cancer Center