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PREvent ductal Carcinoma In Situ Invasive Overtreatment Now (PRECISION)
“When is Cancer Not Really Cancer”?
Welcome note from Jelle Wesseling

Dear Readers,

It is my immense pleasure to present our second PRECISION newsletter and share with you the scientific progress we have made since the beginning of this Grand Challenge Award in 2017, jointly funded by Cancer Research UK (CRUK) and the Dutch Cancer Society (KWF).

Ductal carcinoma in situ (DCIS) is a condition that can sometimes develop into breast cancer. Over 60,000 women are diagnosed with DCIS each year in the USA, more than 7,000 in the UK and over 2,300 in the Netherlands. Currently, which women with DCIS will develop breast cancer in the future is hard to predict. Therefore, women diagnosed with DCIS undergo hospital visits, surgery, and in many cases radiotherapy leading to needless stress and anxiety for the patients and their families. PRECISION aims to enable patients and clinicians to make informed, biology-based decisions to avoid unnecessary and burdensome treatment of indolent DCIS. The answer can only be found by synergistic collaboration between leading scientists, clinicians and patient advocates.

PRECISION has successfully collated large, comprehensive, clinically well-annotated DCIS cohorts (~ 85,000 primary DCIS patients) from the Netherlands, UK and USA. This series is unprecedented in size, data quality, and long-term follow-up. This is fundamental to discover when DCIS is not really cancer. Our in-depth molecular analysis suggest that 30% of subsequent invasive breast cancers after a diagnosis of DCIS are likely new lesions rather than recurrent lesions. If validated, this may greatly impact risk assessment after a diagnosis of DCIS. We are further building a classifier that can distinguish between non-progressive DCIS by subtype, without association of outcome. We have successfully established a pipeline for the generation of Patient Derived Xenograft (PDX) models from DCIS, resembling the original patient material in terms of pathological growth pattern and immune-histochemical features. Through advanced microscopy tech-
niques, we can now study the growth patterns of invasive and indolent DCIS in these models. Furthermore, we are now generating rat models that mimic in vivo progression of DCIS to capture how and when the initial primary DCIS lesion(s) become progressive or stay indolent.

There is a wide spectrum of DCIS ranging from low to high risk. “Low-risk” means it is more likely to be harmless and not progress to invasive breast cancer. “Low-risk” includes low and intermediate grades (1 and 2), as well as other physical and biological features which have a low potential for progression to a future invasive cancer. “Low-risk” DCIS differs greatly from “high-risk” DCIS which some research has shown to be faster growing and more closely associated with a future invasive breast cancer. We found only moderate agreement in DCIS grading among pathologists from UK, USA and the Netherlands. However, we report that high and low grade DCIS can be reliably distinguished by incorporating analysis of expression of markers like ER and HER2. Currently, active surveillance without surgery as a management strategy for low-risk DCIS (grade I/II) is being evaluated in three Randomized Controlled Clinical Trials (RCT), called the COMET (USA)- LORIS (UK)- and LORD (The Netherlands)-trial within PRECISION.

By integrating crucial biological and clinical information, PRECISION aims to establish a personalised DCIS management pipeline for each woman diagnosed with the condition i.e. whether to opt for breast conserving surgery followed by radiotherapy or choose active monitoring. This will ultimately save many women all around the world from the medical, economic and psychological burden of DCIS overtreatment.

For more information regarding our latest research and the clinical trials visit us at www.dcisprecision.org If you have questions feel free to write to us at precision@nki.nl

Prof. Dr. Jelle Wesseling
Senior Group Leader, The Netherlands Cancer Institute, Amsterdam, The Netherlands
Professor of Breast Pathology, Leiden University Medical Center, Leiden, The Netherlands

DCIS lesion surrounded by a stromal inflammatory infiltrate Picture Credit: Mathilde Almekinder’s (NKI)
## Precision Trials at a Glance

The 3 clinical trials embedded in PRECISION – LORIS, LORD and COMET

<table>
<thead>
<tr>
<th>Country</th>
<th>LORIS</th>
<th>COMET</th>
<th>LORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;46</td>
<td>&gt;40</td>
<td>&gt;45</td>
</tr>
<tr>
<td>Standards of care</td>
<td>Standard local care</td>
<td>Guideline concordant</td>
<td>Standard local care</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>No</td>
<td>Possible</td>
<td>No</td>
</tr>
<tr>
<td>Time to Primary Endpoint</td>
<td>5 years</td>
<td>2, 5, 7, 10</td>
<td>10</td>
</tr>
<tr>
<td>Opened</td>
<td>2014</td>
<td>2017</td>
<td>2017</td>
</tr>
<tr>
<td>Sites open</td>
<td>47</td>
<td>82/100</td>
<td>35/40</td>
</tr>
<tr>
<td>Patients</td>
<td>181</td>
<td>&gt;500</td>
<td>59</td>
</tr>
<tr>
<td>Blood Samples collected</td>
<td>108</td>
<td>430; (440 tissue samples collected)</td>
<td>30</td>
</tr>
<tr>
<td>Accrual Target till 2020</td>
<td>188</td>
<td>1200 (900)</td>
<td>900</td>
</tr>
</tbody>
</table>

### Comments
- The LORIS Trial has now completed recruitment and all patients will be followed up for 10 years.
- *LORD changes design to Patient Preference Trial from randomized one in Q2 2020

### Summary of RCT for Low Risk DCIS

**Links:**
- [https://www.dcisprecision.org/clinical-trials](https://www.dcisprecision.org/clinical-trials)
- [http://www.COMETstudy.org](http://www.COMETstudy.org)
- [ClinicalTrials.gov](https://clinicaltrials.gov)
- [https://www.birmingham.ac.uk/research/crctu/trials/loris/index.aspx](https://www.birmingham.ac.uk/research/crctu/trials/loris/index.aspx)

Boris – LORIS mascot helping with histopathology
Patient Advocates in PRECISION

In line with CRUK's mission, we as a team are dedicated to communicate our research to the public and patients. Our patient advocates play a crucial role in highlighting the dilemmas of DCIS and creating awareness at various conferences, through blogs and several social media platforms. They work tirelessly to promote objectives of PRECISION and its clinical trials within the scientific and patient community. Their participation in DCIS and breast cancer activities and groups in national and international context has proven to be an effective model of patient advocate involvement in the setting of a basic research project like PRECISION. By writing, presenting and leading discussions online and offline about DCIS and PRECISION, the patient advocates have developed relationships with several breast cancer organizations who are now ready to help distribute information about PRECISION findings. They interact closely with the team of scientists, clinicians and PhD students in PRECISION by participating regularly in the topic-oriented teleconferences (TCs) which forms the backbone of our knowledge and collaborative exchange within the consortium. Patient advocates have been at the heart of the project since the beginning of PRECISION and they play a significant role in all phases of the project as described in the matrix on the next page:
### Role of Patient Advocates

<table>
<thead>
<tr>
<th>Phase of the project</th>
<th>Consult (1-way)</th>
<th>Advise (2-way)</th>
<th>Review or comment</th>
<th>Co-produce (shared responsibility)</th>
<th>Co-decide (shared ownership)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Concept</strong></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Writing Application</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Running the project</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Research and experimental design</td>
<td>I. Provide input at the level of steering committee</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Scientific Analysis of results</td>
<td>II. Interaction with individual Work Packages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Interpretation and implementation of scientific results from patient's point of view</td>
<td>III. Institute Visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV. Communication and outreach for internal and external stakeholders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dissemination of results</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Scientific articles</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>b. Review articles</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>c. Opinion paper/Per- spective paper</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. (Joint )Newsletter</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>e. Publication for patients, general public and policy makers</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Evolving role of patient advocates in PRECISION**

- Help foster and encourage teams to contribute better results for women with DCIS.
- Help design effective informational tools for providers, organizations, and the public.
- Understand international differences in health services, medical culture, and patient expectations.
- Recommend Improvements and harmonize global messages.
- Measure the value of patient Involvement in PRECISION.
- Communicate about ongoing research and (over)treatment.
- Develop international strategies to help implement findings from PRECISION that impact clinical care.
“Patient Advocates provide valuable insights into the translation of scientific discoveries in DCIS about the clinical importance of identifying when DCIS may not be so worrisome after all.”
Alastair Thompson, Breast Cancer Surgeon, Baylor College of Medicine

“PRECISION is a rich laboratory where international investigators and advocates have the opportunity to exchange and implement ideas to maximize engagement from the community. This engagement is essential when working on an initiative that challenges the status quo.”
Shelley Hwang, Breast Cancer Surgeon, Duke University

“The involvement of Patient Advocates in our PRECISION projects has encouraged a focus on the potential clinical applications of our research in the future, and how further work could be guided into a patient facing setting.”
Sarah Gosling, PhD student, Cranfield University

“Patient partners provide “real-time” feedback that can lead to important adjustments in study activities. For example, patient partners can advise researchers on recruitment plans and materials, data collection instruments and procedures, challenges with study implementation, interpretation of study findings, and plans for disseminating study results to meet the needs of various stakeholder groups.”
Ellen Verschuur and Marja Oirsouw, Patient Advocates, The Netherlands
Communicating Our Research through Publications and Posters

The impact of patient characteristics and lifestyle factors on the risk of an ipsilateral event after a primary DCIS: A systematic review
Sena Alaeikhaneshir, Ellen G. Engelhardt, Freerike H. van Duijnhoven, Maartje van Seijen, Patrick A. Bhairosing, Donna Pinto, Deborrah Collyar, Elinor Sawyer, Shelley E. Hwang, Alastair M. Thompson, Jelle Wesseling, Esther H. Lips, Marjanka K. Schmidt on behalf of PRECISION
Breast 2020 Apr; 50: 95–103.
doi: 10.1016/j.breast.2020.02.006

Calcification Microstructure Reflects Breast Tissue Microenvironment
Sarah Gosling, Robert Scott, Charlene Greenwood, Pascaleine Bouzy, Jayakrupakar Nallala, Iain D. Lyburn, Nicholas Stone, Keith Rogers

Ductal carcinoma in situ: to treat or not to treat, that is the question
Maartje van Seijen, Esther H. Lips, Alastair M. Thompson, Serena Nik-Zainal, Andrew Futreal, E. Shelley Hwang, Ellen Verschuur, Joanna Lane, Jos Jonkers, Daniel W. Rea and Jelle Wesseling
on behalf of the PRECISION team
doi: https://doi.org/10.1038/s41416-019-0478-6
 Prediction of Upstaged Ductal Carcinoma in situ Using Forced Labeling and Domain Adaptation

Rui Hou, Maciej A. Mazurowski, Lars J. Grimm, Jeffrey R. Marks, Lorraine M. King, Carlo C. Malley, E. Shelley Hwang, and Joseph Y. Lo

Predictors of an Invasive Breast Cancer Recurrence after DCIS: A Systematic Review and Meta-analyses

Lindy L. Visser, Emma J. Groen, Flora E. van Leeuwen, Esther H. Lips, Marjanka K. Schmidt, and Jelle Wesseling

Cancer Epidemiology, Biomarkers and Prevention doi: 1055-9965.EPI-18-0976

Genomic analysis of paired DCIS and subsequent recurrence to assess clonal relatedness in screen detected DCIS


SloneSteering Committee, CRUK Grand Challenge PRECISION Team,

Kings College London, London, UK; MD Anderson Cancer Center, Houston, TX; Public Health England, Birmingham, UK; Baylor College of Medicine, Houston, TX
One of the goals of PRECISION is to investigate the molecular and structural composition of the DCIS soft tissue and associated calcifications. Difficulty in discerning harmless DCIS lesions from potentially invasive ones can lead to overtreatment of this condition in many patients. We hope that a better understanding of how DCIS is formed will lead to tests (biomarkers) which will help to distinguish which DCIS has the potential to become invasive breast cancer and which does not.

Calcifications are deposits of calcium salts (crystals of hydroxyapatite) detected as white specks in mammograms of 80-90% of women diagnosed with DCIS. The size, shape and distribution of such calcium deposits are influenced by the microenvironment of the surrounding tissues.

Using three microscopy based molecular imaging techniques – X-ray diffraction, Infrared and Raman spectroscopy, PRECISION scientists are studying the detailed structural and molecular make-up of calcifications and their role in DCIS. The infrared and Raman techniques (which use the infrared and visible regions of light respectively) analyse the molecular bonds present in the sample and provide a unique ‘molecular fingerprint’ of the calcifications and the surrounding soft tissue. In complement, X-ray diffraction (which uses the X-ray region of light) determines the type and nature of calcifications by analysing their crystal structures in the order of 5 micrometers (at least 15-30 times smaller than thickness of a single human hair).

The molecular and structural information obtained from these techniques will be combined and processed by machine learning algorithms to identify ‘biomarkers’ that will inform which DCIS is harmless and which DCIS could progress to invasive breast cancer. A concept workflow of the process is shown in figure 1.
Different regions (histological features) of a DCIS breast tissue were identified based on the molecular and structural ‘fingerprint’ using infrared, Raman and X-ray imaging. The spectra extracted from each of these regions will be processed by machine learning algorithms to identify lethal cancer from non-lethal cancer.

A recent publication (Gosling et al, 2019) from the University of Cranfield and the University of Exeter shows how one of these techniques, X-ray diffraction has identified variability within the calcifications and importantly differences between calcifications in different DCIS grades. Thus, calcifications have the potential to become useful biomarkers for early stage diagnosis of breast disease.

Last year, PRECISION team members from Cranfield and Exeter Universities visited a National Synchrotron facility, the ‘Diamond Light Source’ near Oxford, in order to collect data from Duke University specimens. By shining high powered X-Ray beams on tiny fragments of tissue samples, fine crystal structures were investigated based on the pattern in which they scatter the X-Ray beam. Experiment time was allocated by Diamond in four consecutive 24-hour blocks and so data collection continued right through the nights. Four days of total beamtime meant engaging a large team of volunteers, both from PRECISION and from other members of Cranfield and Exeter Universities, in order to manage the workload and the lack of sleep! 50 samples were measured encompassing over 100 calcifications and 10,000 data files! This data is now being processed and analysed to identify differences in the crystal structure of calcifications.
Hilary Stobart, UK patient advocate for PRECISION was invited to join the scientists at the “Diamond Light Source” so she could see firsthand what the research involved. Hilary says, “I was impressed with the dedication of the team that stayed 4 days and nights, swapping samples in and out constantly and collecting data during that time. It served to remind me again of the pain-staking work that is necessary to make scientific breakthroughs.”

**Did You Know:**
Hilary explains: “The synchrotron is a large ring structure, half a kilometre in circumference, which accelerates a beam of electrons to almost the speed of light. As the electron beam is bent by large magnets, it creates bursts of energy in the form of X-rays, which can be directed towards the tissue samples. A detector is then used to detect how the X-rays scatter as they hit the molecules in the crystal.”

**Reference:**
**Calcification Microstructure Reflects Breast Tissue Microenvironment**
Sarah Gosling, Robert Scott, Charlene Greenland, Pascaline Bouzy, Jayakrupakar Nallala, Iain D. Lyburn, Nicholas Stone, Keith Rogers
In conversation with Rui Hou
PhD student in the Department of Electrical and Computer Engineering at Duke University

Supervisor: Prof. Joseph Y. Lo.
Interview by Scientific Project Manager of PRECISION, Proteeti Bhattacharjee

What is machine learning and how is it used in medical imaging?
Simply stated, machine learning involves training of computers to identify patterns in different datasets. In medical imaging, it is used to distinguish between healthy and diseased states by virtue of identifying particular features on digitally acquired images. The beauty of machine learning is that it can automatically learn to differentiate your targets with little human guidance, thus when applied to medical imaging problems it can help doctors in the process of clinical decision making.

What is the goal of your research project in PRECISION?
The aim of my research is to use “computer vision techniques” to accurately identify tell-tale features in mammograms that can differentiate between pure DCIS and progressive or as we refer to as upstaged DCIS cases. As we still do not know how many of DCIS cases will eventually progress into invasive breast cancer, machine learning techniques can help in make good predictions which can further inform diagnosis and subsequent course of treatment. It can help in the guidance of performing active surveillance, and also avoid over-treatment and over-diagnosis.

Could you explain about your recently published work on “Domain Adaptation”?
In our recently published article in Transactions of Biomedical Engineering, we describe a technique called Domain Adaptation, where the machine learning model is not trained from DCIS itself, but trained from two related diseases, Atypical Ductal Hyperplasia (ADH) and Invasive Ductal Carcinoma (IDC). The relationships between these classes may be illustrated in the figure below. Our study targets, pure and upstaged DCIS, which exist in between ADH and IDC along the breast cancer spectrum. Pure and Upstaged DCIS are differentiated by the existence of invasive cancer, therefore upstaged DCIS may share characteristics with IDC, and pure DCIS may share certain characteristics with ADH, these two related cases can help in our problem. Our experiments showed that this achieved the best AUC performance on our initial study with 140 cases.

How will you proceed further with the insights gained from your above publication?
As an ongoing work, we’ve collected a lot more cases since the last study. We will validate this algorithm on a bigger dataset, and also across institution datasets, including NKI and OPTIMATE. I’ll also be exploring other types of deep learning techniques into this problem to improve the performance.

Reference: Prediction of Upstaged Ductal Carcinoma in situ Using Forced Labeling and Domain Adaptation
Rui Hou, Maciej A. Mazurowski, Lars J. Grimm, Jeffrey R. Marks, Lorraine M. King, Carlo C. Malley, E. Shelley Hwang, and Joseph Y. Lo
IEEE Transactions on Biomedical Engineering (Early Access)
doi: 10.1109/TBME.2019.2940195
Data and Material Sharing Across Borders

Collating, curating and sharing clinical data and tissue samples among the PRECISION partner institutes located mainly in the USA, UK and the Netherlands is no average feat! Brian Menegaz, Data Manager at Baylor College of Medicine in Houston, Texas, takes us through the challenges and opportunities of intra-consortium material and data sharing for a complex, interdisciplinary and international project like PRECISION.

Interview by Scientific Project Manager, Proteeti Bhattacharjee

What are the initial requirements to establish a material and data sharing pipeline for an international multi-partner project such as PRECISION?

At the outset, the collection, sharing and dissemination of clinical information and tissue series requires setting up of material transfer agreements (MTAs) and/or data transfer/data use agreements (DTAs/DUAs). In addition, secure, legally and ethically approved databases for the protection and management of all the samples and clinical data in the analysis pipeline of the consortium needs to be established right at the beginning of the project.

How many MTAs/DTAs does PRECISION have currently and how long does it take to prepare such documentation?

Currently, there are 70 agreements which enable material and data transfer in PRECISION. Setting up such agreements can take months or even up to a year in the case of complicated agreements due to different administrative and legal requirements and rules in different countries where the partner institutes are located. Therefore, the formalisation of MTAs/DTAs becomes an important rate-determining step in the overall progress of the project. The faster scientists have legal access to clinical data from national cohorts and biological material for performing experiments, the faster scientific discoveries can be made.

After a MTA/DTA is prepared; what are the next set of challenges?

As overarching data governance regulations like GDPR or country-specific rules may prohibit or limit the export of data, the choice of a data repository suitable for all partner institutes who are official signatories of an MTA/DTA becomes the next major challenge. The data repository should be flexible, accessible for data managers across all partner institutes, have an adaptable interface for regular data quality checks and allow dataset harmonisation as more information is fed into the repository over the course of the project.

Which data repositories are used for PRECISION?

We use REDCap (Research Electronic Data Capture) for tissue samples and OpenClinica for clinical data from national cohorts. The need for separate databases arose from the exact challenges listed above, where data governance rules required the consortium to be flexible based on the type of data and actual host location, but these data can ultimately be linked through a unique coded identifier.

What according to you ensures smooth collaboration through a seemingly complicated process of paperwork and bureaucracy?

Most importantly, keep it simple. Throughout the process manage risks and engage with stakeholders to facilitate a successful collaboration. Regular meetings with data managers and coordinators of all partner institutes are held twice a month where all technical challenges are addressed and best practice methods shared for the benefit of all. Ultimately, data and material management exists to facilitate research and improve patient lives, and keeping that goal in mind will ensure we overcome any obstacle on the way to reduce the overtreatment of DCIS.
Finally, the PRECISION consortium is incredibly fortunate to have a great working on data and materials management, including Jason Love (MD Anderson Cancer Center), Tom Lynch and Ilona Stashko (Duke), Karen Clements (Public Health England), and Liping Fu, Yat-Hee Liu and Sandra van den Belt (NKI) amongst many others.
An overview of PRECISION MTAs and DTAs
Sneak Peak:
The impact of DCIS grade and lifestyle factors on DCIS treatment

The ultimate aim of PRECISION is to enable DCIS patients make informed treatment decisions in consultation with their clinicians. This can be achieved by building a risk prediction model which can accurately distinguish the risk of DCIS from further progressing into an invasive disease or remaining benign. The consortium plans to integrate clinical, molecular and imaging data emerging from the current studies to develop a robust risk prediction model.

The first step towards developing such a model is to ensure that DCIS classification is concordant between different countries, pathologists, study-aides and observers. To investigate this in detail, Maartje van Seijen and colleagues performed an interobserver variability study where histological parameters of four retrospective DCIS cohorts (Dutch cohort, Sloane, MDACC cohort, Duke cohort) were compared. 425 slides were examined on nine variables by nine pathologists from three different countries (NL, UK, US). We observed that there is moderate agreement in grading of DCIS by different pathologists depending on the scoring method used. Since therapeutic decisions and inclusion in clinical trials partially rely on DCIS grade, there is a pressing need to reduce interobserver variability in DCIS grading. Additionally, incorporating ER and HER2 expression could be useful to distinguish high and low risk DCIS as indicated in our studies.

For accurate DCIS risk prediction, identification of prognostically relevant modifiable lifestyle factors is important. As this information could not be retrieved from our large DCIS cohorts, we performed a systematic literature review to study the effect of lifestyle factors on DCIS prognosis. In our recent publication, Sena Alaeikhanehshir demonstrated that younger age, positive family history of breast cancer, high BMI, a pre and perimenopausal status and a high breast density were predictors for a subsequent breast event. However, only few studies with small patient numbers were performed, indicating the need for large-scale high-quality studies regarding the influence of lifestyle factors on subsequent events after DCIS.

Expanding knowledge base for modifiable lifestyle factors and incorporation of ER and HER2 markers in active surveillance trials will immensely help women to avoid receiving aggressive treatment for DCIS unless truly necessary.

Reference:
The impact of patient characteristics and lifestyle factors on the risk of an ipsilateral event after a primary DCIS: A systematic review
Sena Alaeikhanehshir, Ellen G. Engelhardt, Frederieke H. van Duijnhoven, Maartje van Seijen, Patrick A. Bhairosing, Donna Pinto, Deborah Collyar, Elinor Sawyer, Shelley E. Hwang, Alastair M. Thompson, Jelle Wesseling, Esther H. Lips, Marjanka K. Schmidt on behalf of PRECISION
Breast 2020 Apr; 50: 95–103.
doi: 10.1016/j.breast.2020.02.006
Credits

i) Concept and Content Development: Donna Pinto and Proteeti Bhattacharjee

ii) Contributors: Alastair Thompson, Brian Menegaz, Claire Gaunt, Ellen Verschuur, Esther Lips, Hilary Stobart, Jayakrupakar Nallala, Jelle Wesseling, Maartje van Seijen, Marja van Oirsouw, Rui Hou, Sarah Gosling, Sena Alaeikhanehshir, Shelley Hwang, Thomas Lynch

iii) Design and layout: Mediaschip