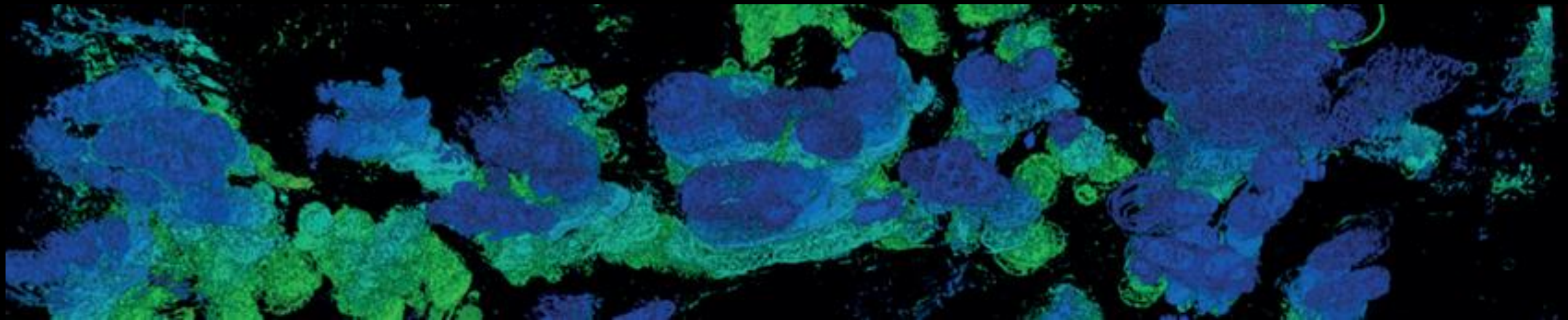


DOKTER, WAT IS HET VOOR DCIS WEER?

Jelle Wesseling

Antoni van Leeuwenhoek – Nederlands Kanker Instituut & Leids Universitair Medisch Centrum



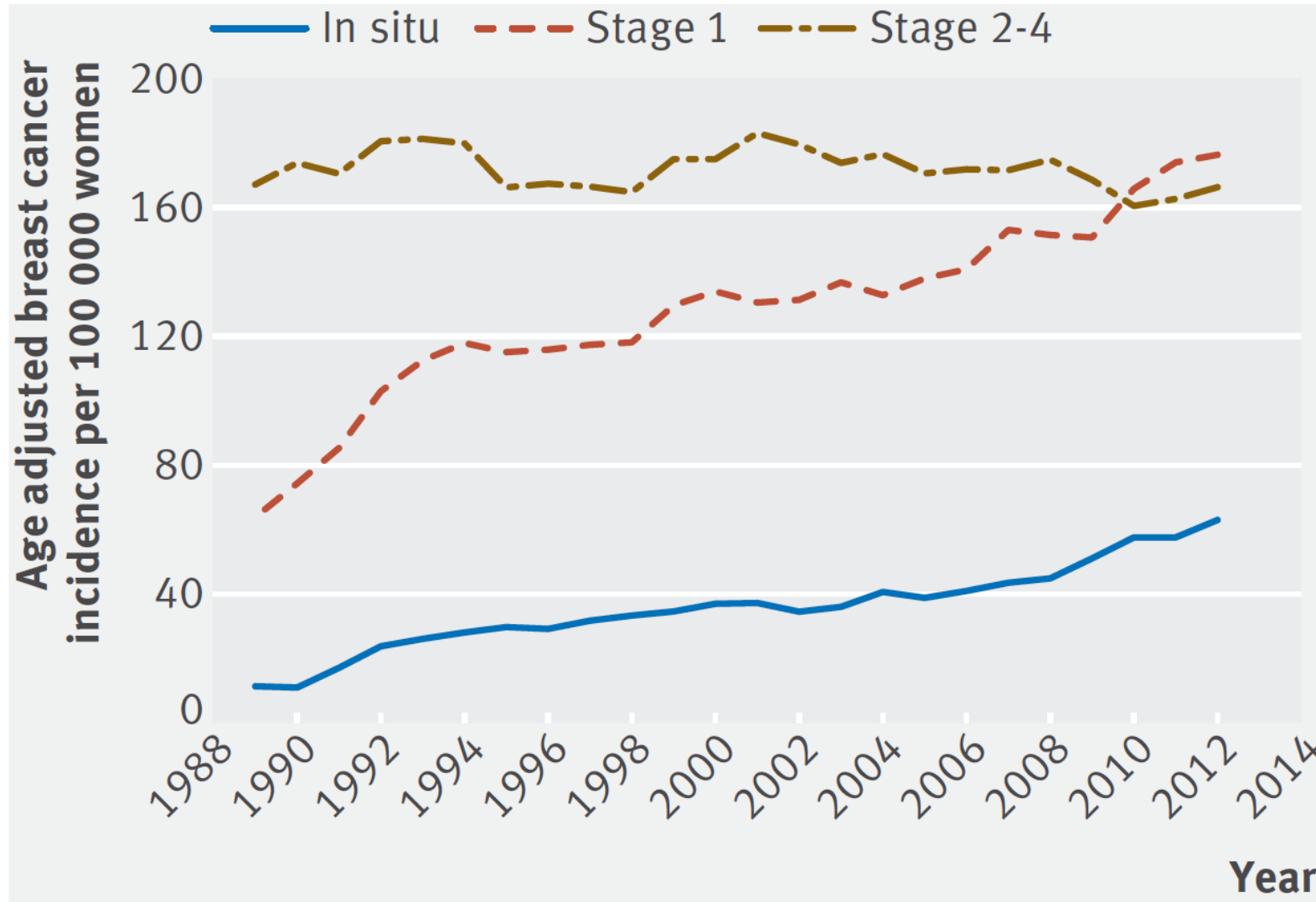


- 1. WAT IS HET PROBLEEM?**
- 2. WAT IS (SLECHTS) HET BEGIN VAN DE OPLOSSING?**
- 3. WAT IS DE OPLOSSING VAN HET PROBLEEM IN DE ECHE WERELD?**



1. WAT IS HET PROBLEEM?

HET GAAT OVER DE ONGEMAKKELIJKE WAARHEID VAN DCIS

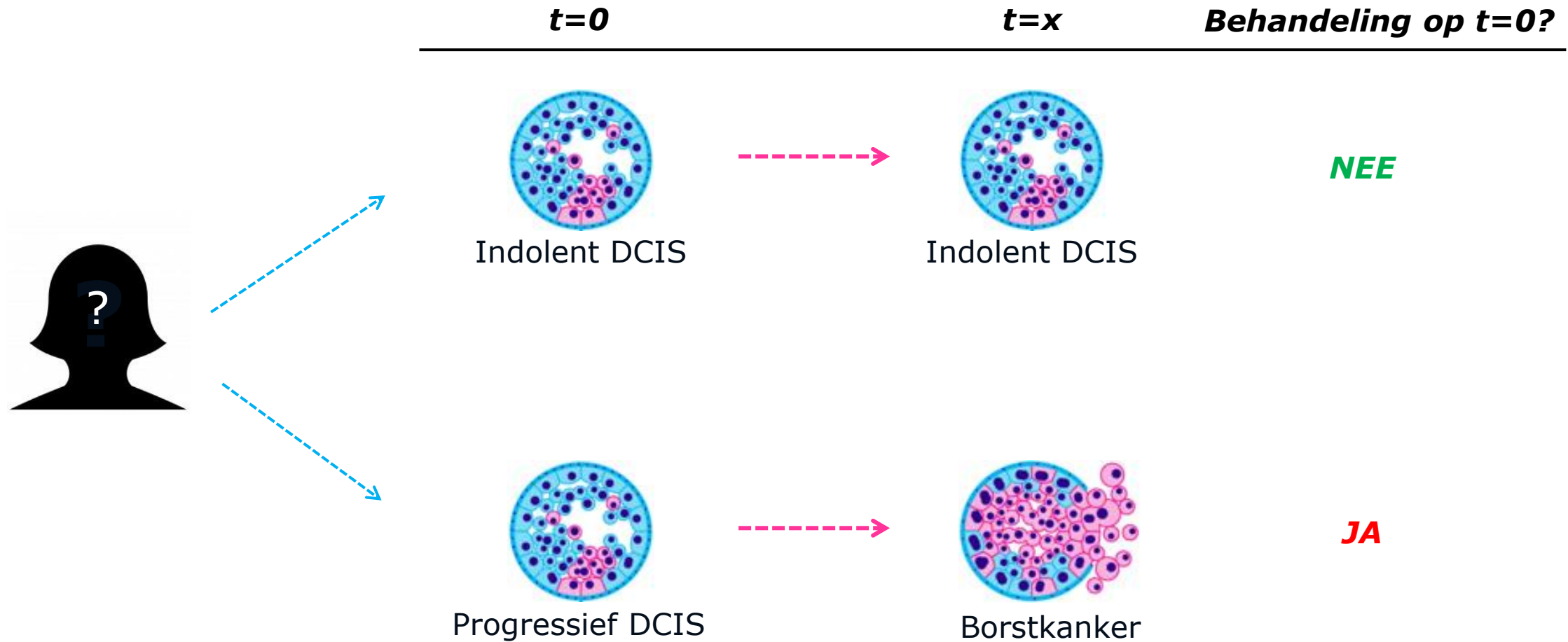


- Tot 25% van alle door screening gedetecteerde 'borstkankers'
- ~80% van alle DCIS is niet progressief en daarom ongevaarlijk
- DCIS zelf leidt niet tot overlijden
- Onmogelijk progressief van niet progressief DCIS te onderscheiden
- Bijna alle vrouwen met DCIS worden behandeld

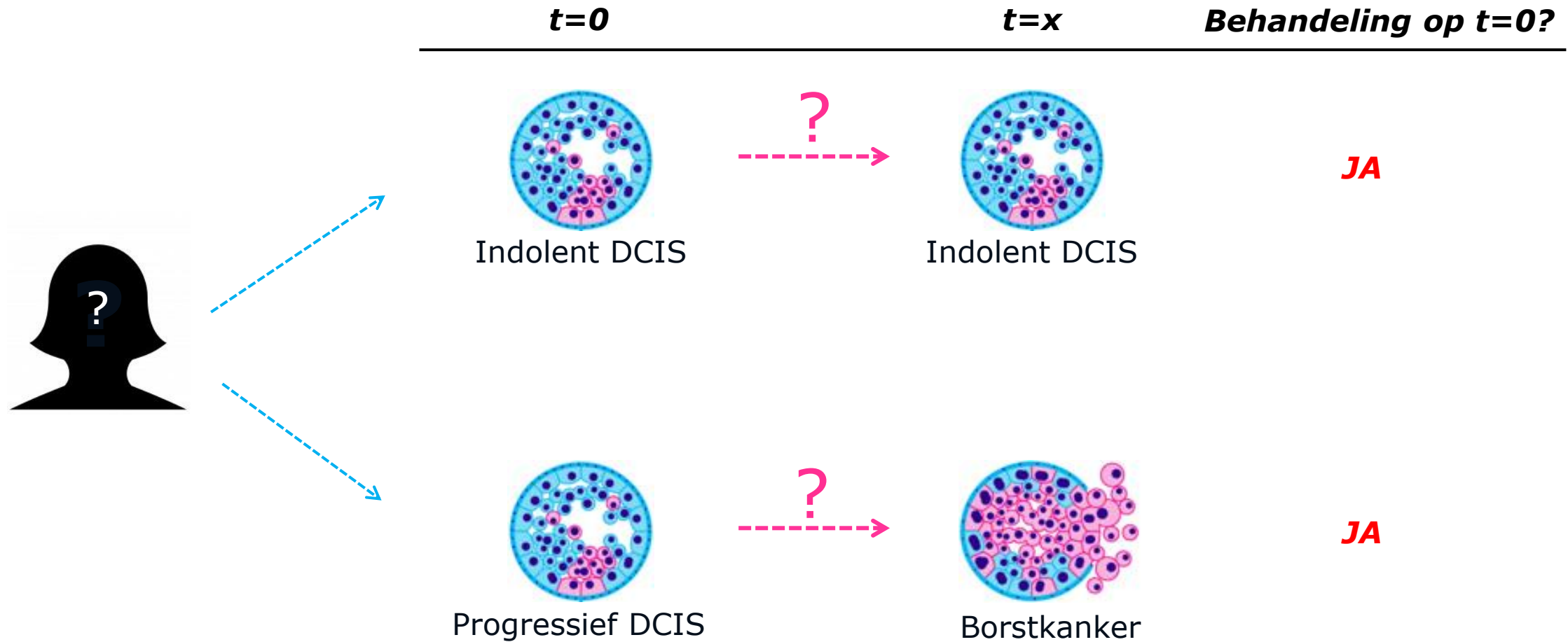
Autier et al. (2017), BMJ 359:j5224
Bleyer and Welch (2012), NEJM 367:1998-2005
Siegel et al. (2018), CA Canc. J. for Clinicians 68:7-30
American Cancer Society (2019)
Cancer Research UK (2020)
Elshof et al. (2018), Annals Surg. 267:952-958
Roses et al. (2011), Annals Surg. Oncol. 18:2873-2878
Ernster et al. (2000), Arch. Int. Med. 180:953-958
Ryser et al. (2019), JNCI 111:952-960
Grimm et al. (2017), Ann. Surg. Oncol. 24:3524-3540
Elshof et al. (2016), Breast Canc. Res. Treatm. 159:553-563
Rakovitch et al. (2013), Breast Canc. Res. Treatm. 138:581-590
Falk et al. (2011), Breast Canc. Res. Treatm. 129:929-938
Maxwell et al. (2018), Eur. J. Surg. Oncol. 44:429-435
Maxwell et al. (2022), Breast 61:145-155

Vele vrouwen met niet progressief DCIS dragen de last van zinloze behandeling

IDEALITER WIL JE HET BELOOP VAN DCIS ACCURAAAT VOORSPELLEN



HELAAS LEIDT ONZEKERHEID TOT OVERBEHANDELING INDOLENT DCIS



- Kleine series, korte follow-up, weinig 'events'
- DCIS zeer heterogeen
- Behandeling van DCIS is variabel
- Uitkomst niet uniform gedefinieerd
- Interobserver variabiliteit



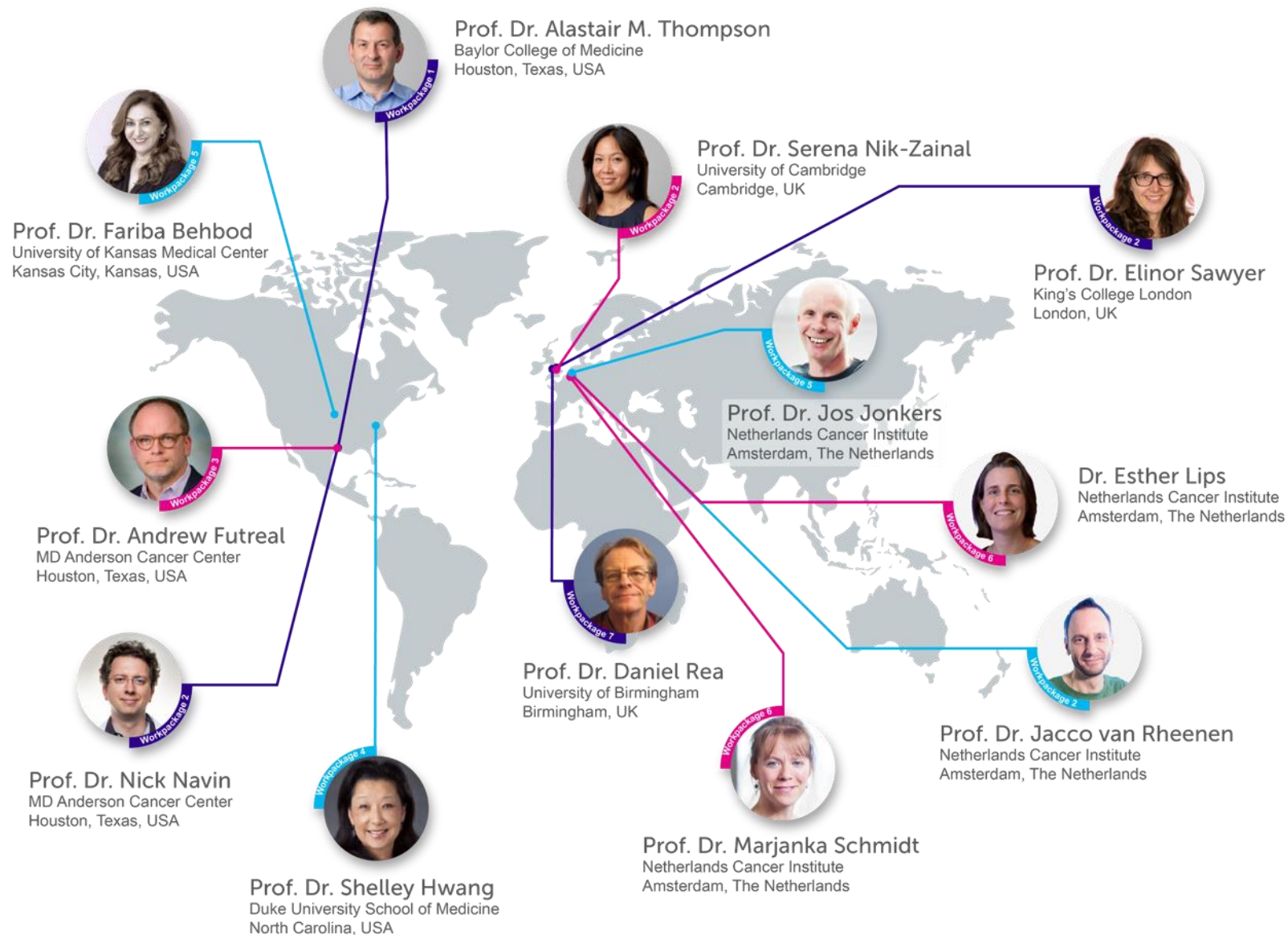
Wat nodig is om het beter te doen:

- Grote, a-selectieve series (n>10,000s)
- Details diagnose en behandeling
- Lange termijn follow-up (>10 jaar)
- Robuuste designs (case-control, etc.)
- Weefselblokjes
- Multidisplinaire experts en benadering



2. WAT IS (SLECHTS) HET BEGIN VAN DE OPLOSSING?

VOOR KLINISCHE IMPACT IS MULTIDISCIPLINAIRE SYNERGIE VEREIST



Project Lead

Prof. Dr. Jelle Wesseling, NKI

Project Manager

Dr. Proteeti Bhattacharjee, NKI

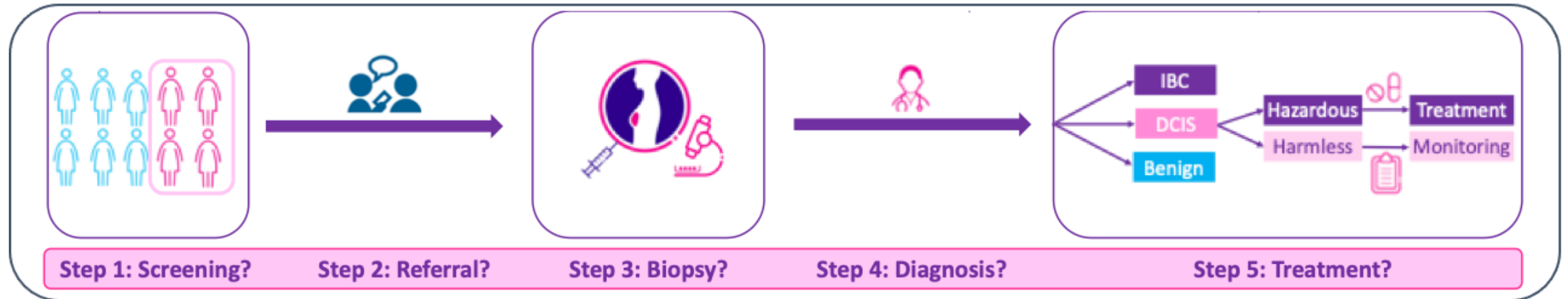
Collaborators

Prof. Dr. Joseph Lo, Duke University
Prof. Dr. Keith Rogers, University of Cranfield
Prof. Dr. Nick Stone, University of Exeter
Prof. Dr. Eveline Bleiker, NKI
Prof. Dr. Valesca Retel, NKI
Prof. Dr. Sarah Pinder, KCL
Prof. Dr. Lodewyk Wessels

Patient Advocates

Ellen Verschuur (NL)
Marja Oirsouw (NL)
Hilary Stobart (UK)
Donna Pinto (US)
Deborah Collyar (US)

DCIS MANAGEMENT VEREIST 'PRECISION' IN HET ZORGPAD



- Samengesteld cohort van meer dan 47.000 vrouwen met DICS uit VK, VS en Nederland
- Status sneevlak en grootte afwijking beperkt geassocieerd met risico op ipsilateraal borstkanker
- Slechts 3,2% risico op ipsilaterale borstkanker na 10 jaar

RESEARCH




OPEN ACCESS



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

Renée S J M Schmitz,¹ Alexandra W van den Belt-Dusebout,¹ Karen Clements,² Yi Ren,³ Chiara Cresta,¹ Jasmine Timbres,⁴ Yat-Hee Liu,¹ Danalyn Byng,⁵ Thomas Lynch,⁶ Brian A Menegaz,⁷ Deborah Collyar,⁸ Theresa Hyslop,³ Samantha Thomas,³ Jason K Love,⁹ Michael Schaapveld,¹⁰ Proteeti Bhattacharjee,¹ Marc D Ryser,^{5,11} Elinor Sawyer,⁴ E Shelley Hwang,⁶ Alastair Thompson,⁷ Jelle Wesseling,^{1,12,13} Esther H Lips,¹ Marjanka K Schmidt^{1,14}; on behalf of the Grand Challenge PRECISION consortium

Breast-CALcification Risk Evaluation (Breast-CARE)

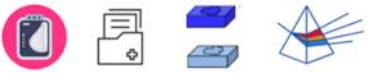
- **Population:**
 - Screen-detected breast calcifications only
 - 2010-2019
- **Methods:**
 - Registry-based cohort study
 - (AI-enabled) radiomics
- **Data:** 

Prognostic value of mammographic calcification descriptors


- **Population:**
 - DCIS presented as mammographic calcifications
 - 2000-2022
- **Methods:**
 - Systematic review and meta-analysis

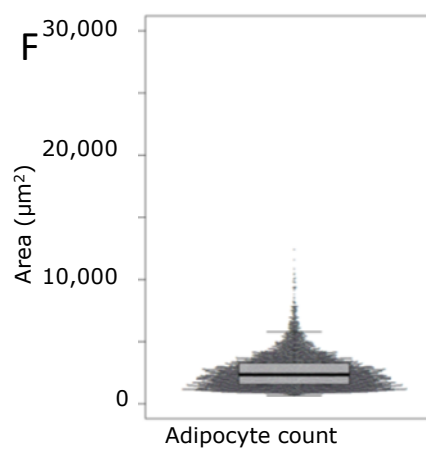
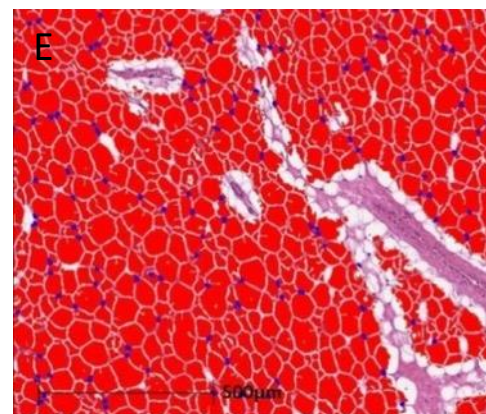
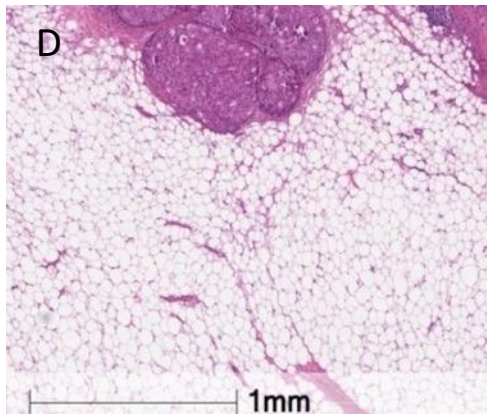
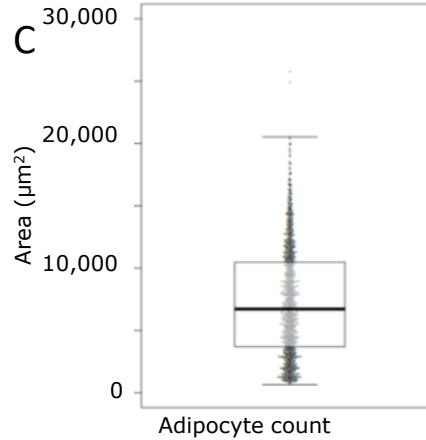
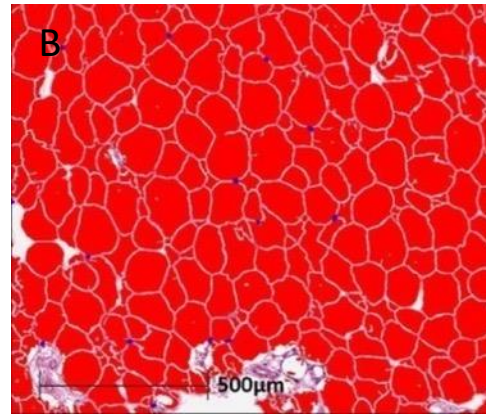
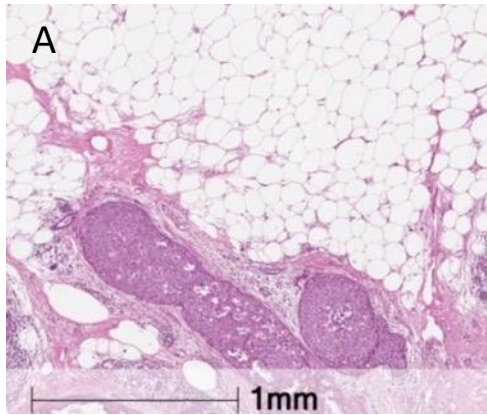
Common aim:
Distinguish high-risk from low-risk breast lesions to prevent unnecessary diagnostics and treatment

Characterization of high- and low-risk Benign Breast Disease (CharBBD)

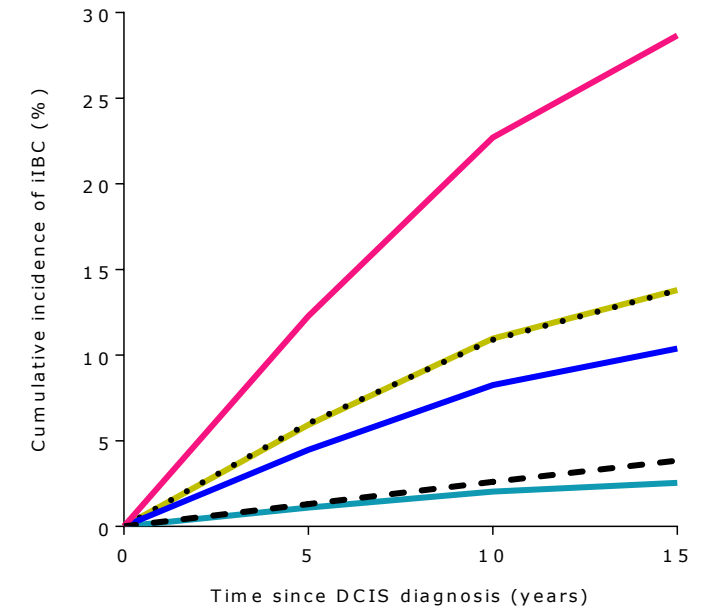
- **Population:**
 - Initially diagnosed benign BD (NKI)
 - 2006-2021
- **Methods:**
 - 1) Case-control study
 - 2) (AI-enabled) radiomics
- **Data:** 

DCIS & sentinel node positivity (SNOP)

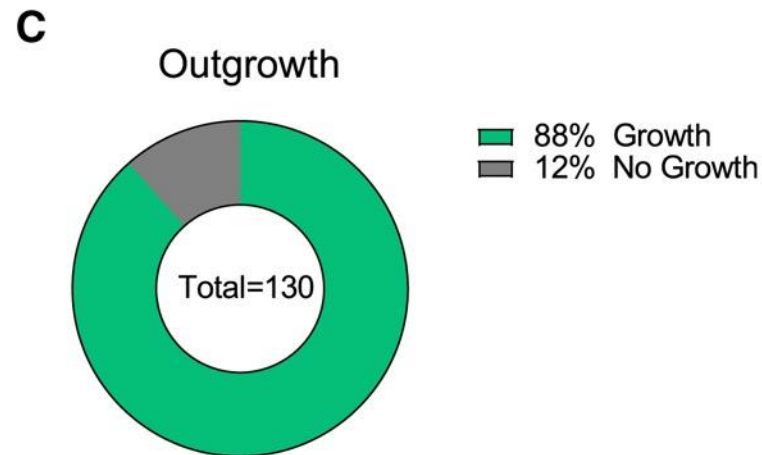
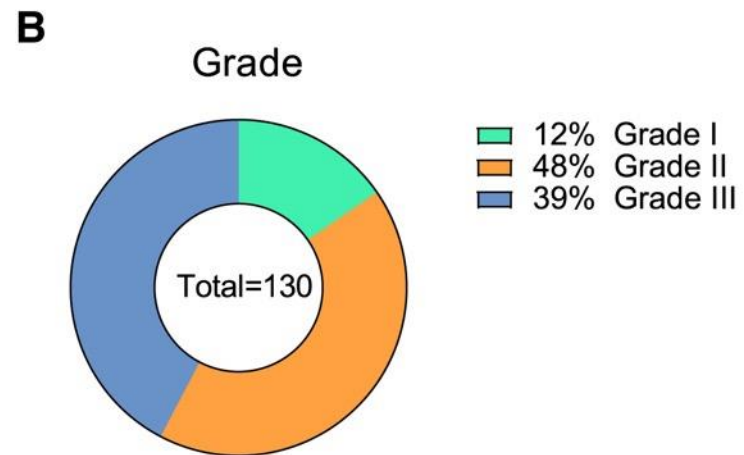
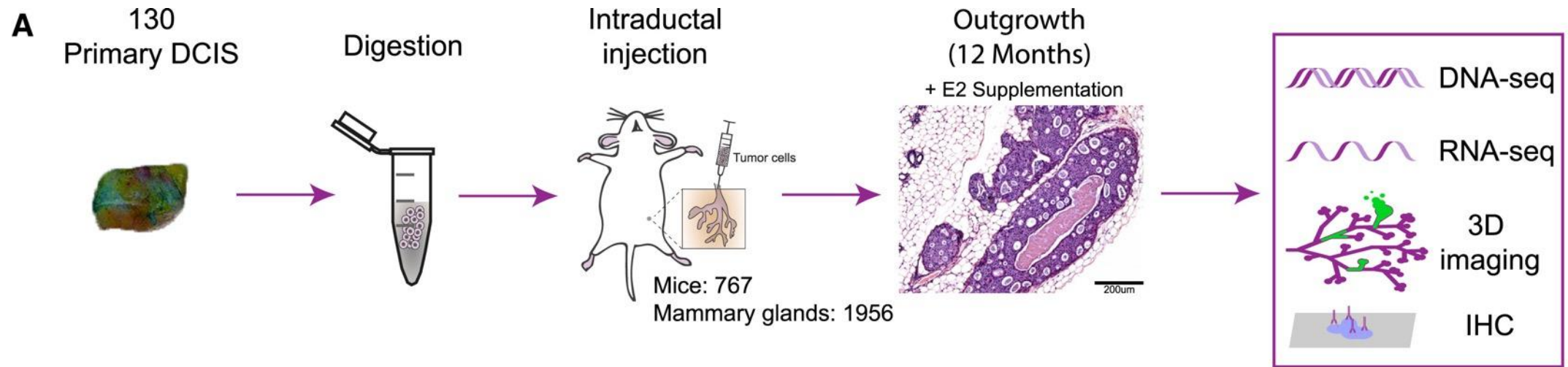
- **Population:**
 - Registered DCIS SN+ cases
 - 2005-2020
- **Methods:** National registry-based cohort study
- **Data:** 

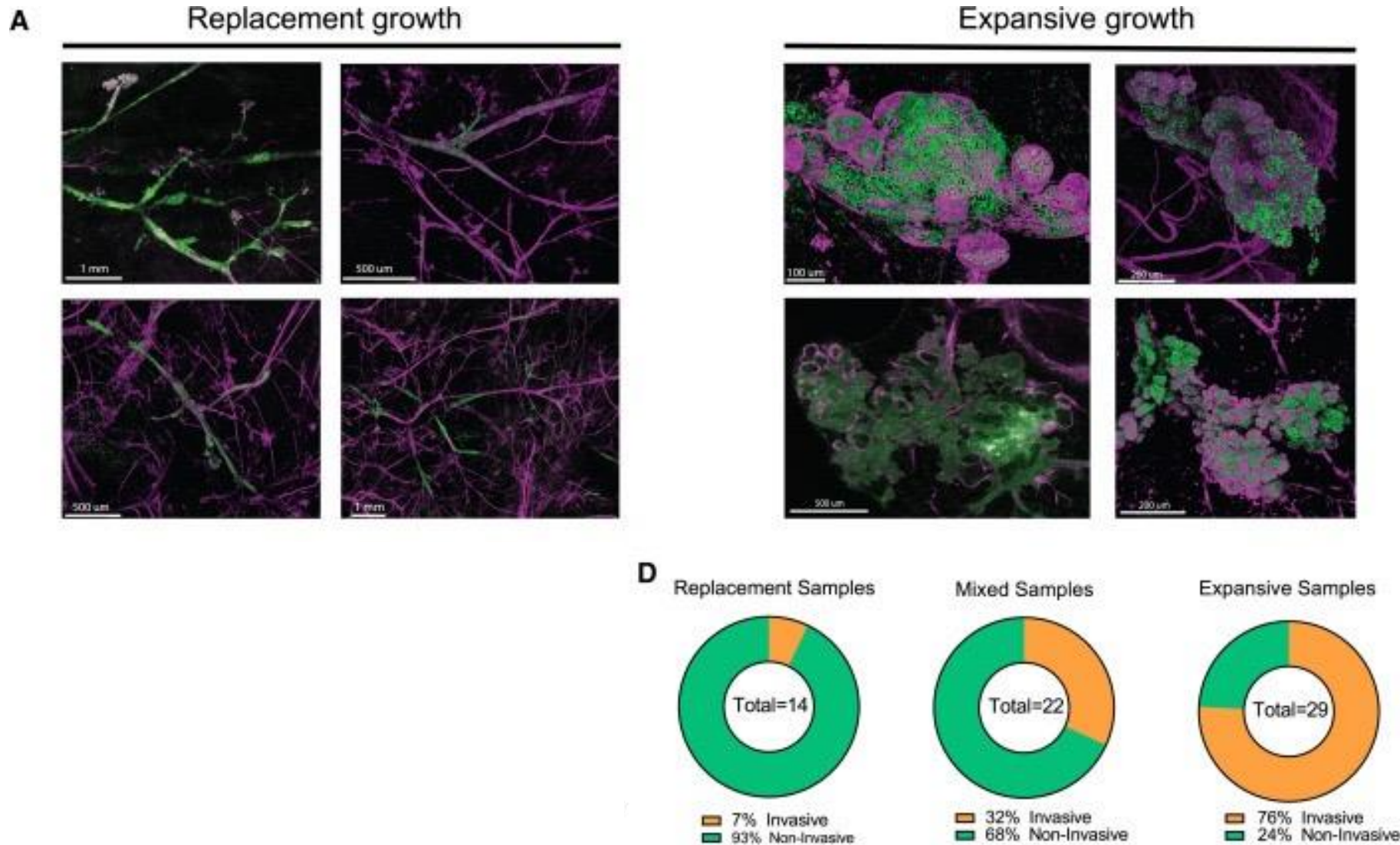


	Adipocyte area ^{75th} /COX-2	10-year (%)	15-year (%)
••••	Overall cumulative incidence	10.9	13.8
—	Area ^{75th} q4/COX-2 high	22.7	28.7
—	Area ^{75th} q4/COX-2 low	8.3	10.4
—	Area ^{75th} q1-3/COX-2 high	11.0	13.8
—	Area ^{75th} q1-3/COX-2 low	2.0	2.6
—	General population	2.6	3.9



PREKLINISCHE MUISMODELLEN LATEN PROGRESSIE DCIS LIVE ZIEN

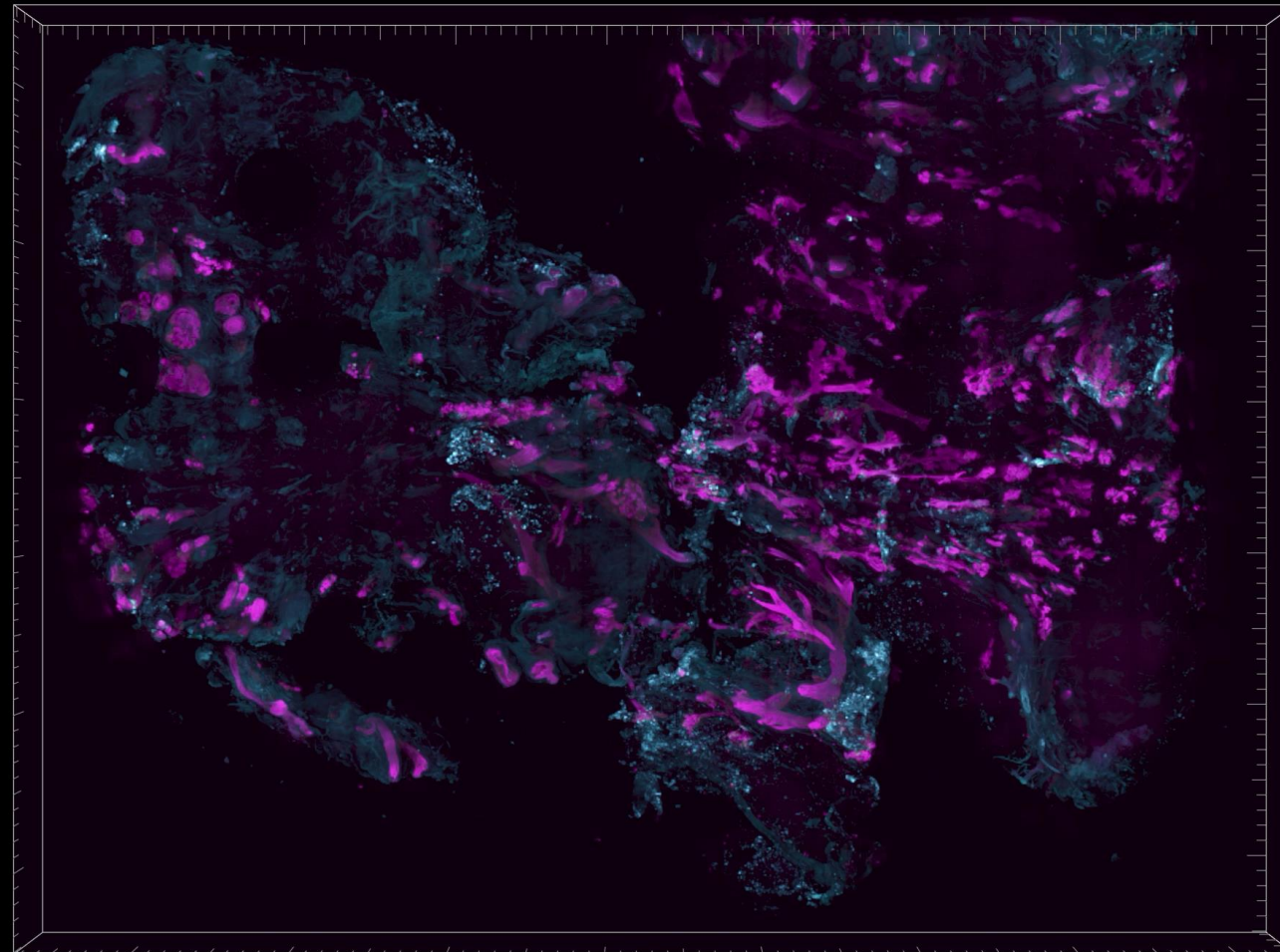




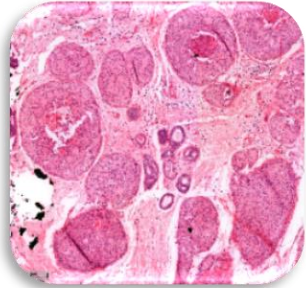
ZIEN WE DAT IN 3D OOK BIJ VROUWEN MET DCIS?



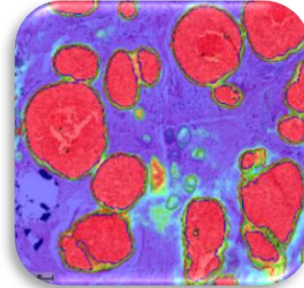
Resection DCIS
(local excision)



KUNNEN WE DIT VERTALEN NAAR 'GEWONE' COUPES IN DE KLINIEK?



H&E coupes

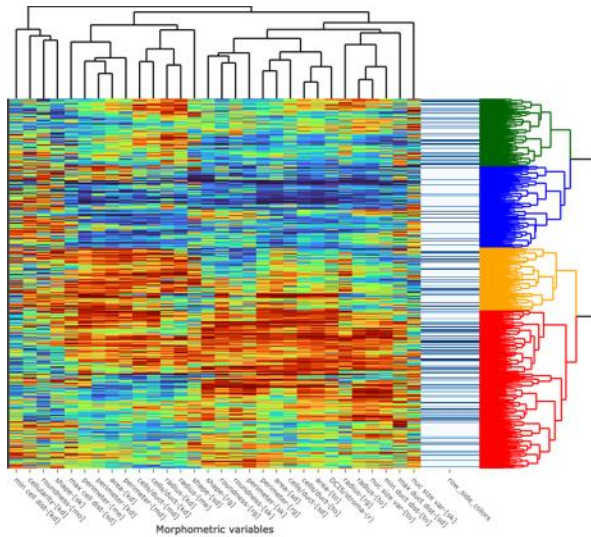


DCIS gedetecteerd

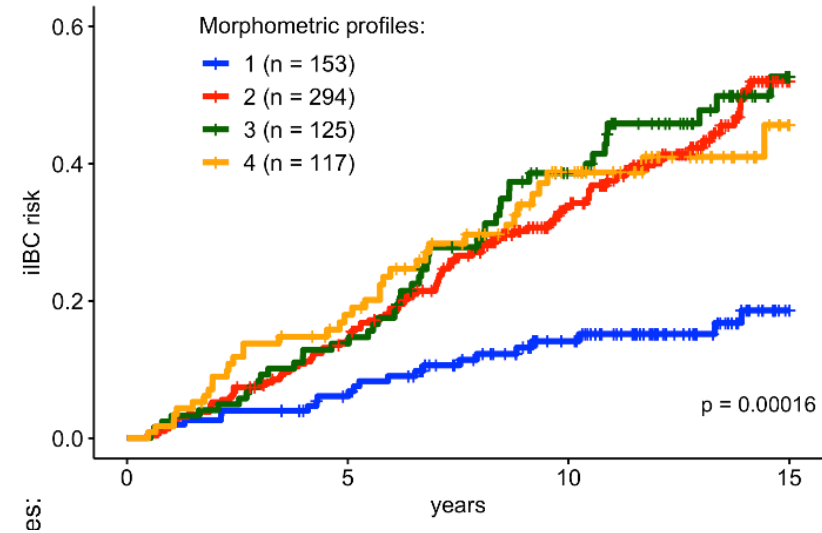


	Y0	X1	Y1	X2	
0.000	0	1212.031	255	1235.259	0
0.596	0	1154.259	255	1176.295	0
1.191	0	1119.119	255	1141.155	0
1.787	0	1051.221	255	1079.809	0
2.382	0	1013.699	255	1034.544	0
2.978	0	983.919	255	998.809	0
3.574	0	942.228	255	961.882	0
4.169	0	910.065	255	926.147	0
4.765	0	889.220	255	897.558	0
5.360	0	830.256	255	861.823	0

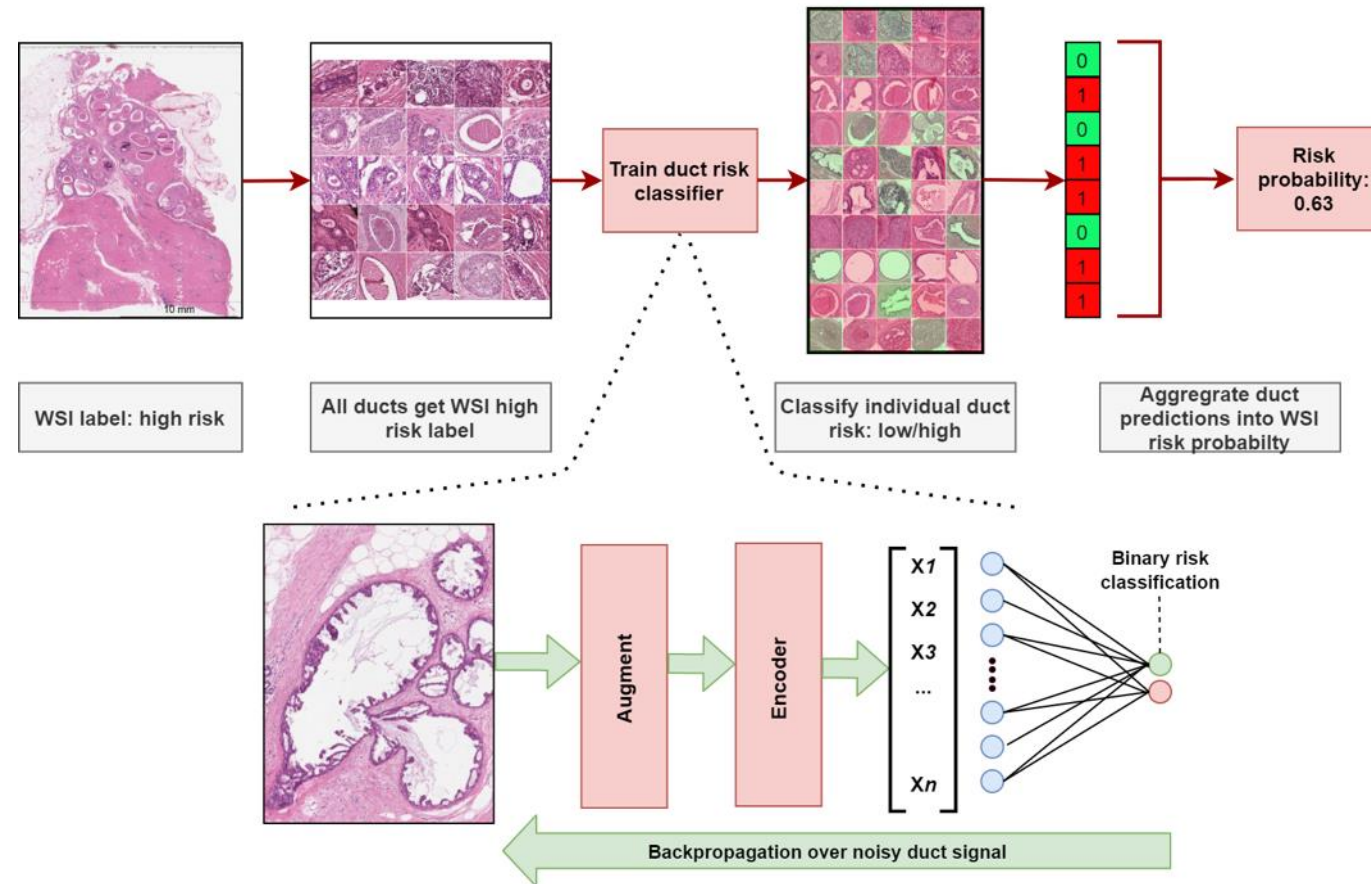
Morfologische metingen



Clusteren morfologische kenmerken



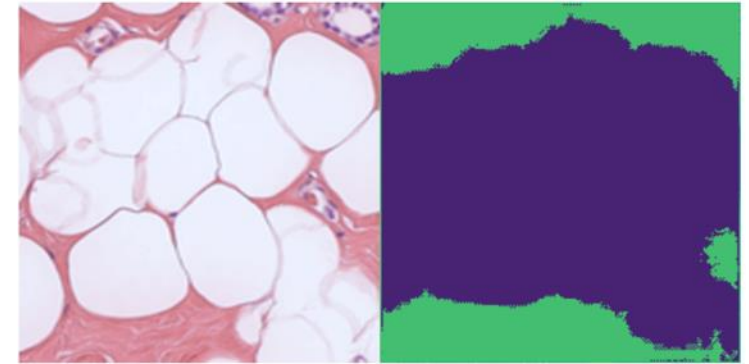
Blauwe lijn is laag risico DCIS



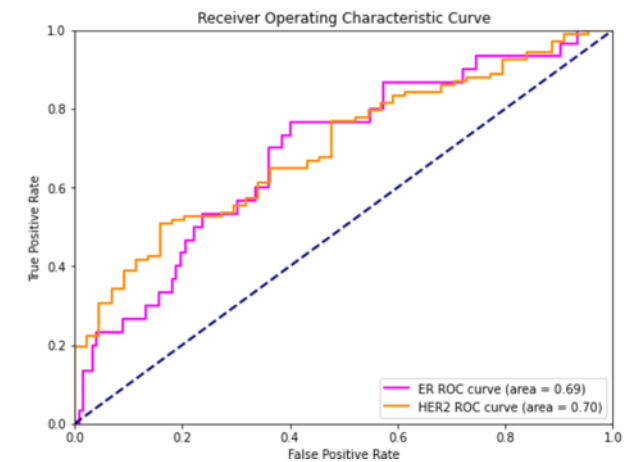
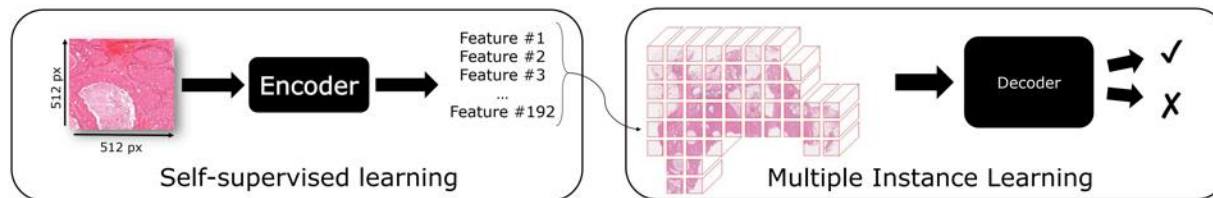
1. Voorspellen of er invasief mammacarcinoom ontstaat met een AUC van 0.78
2. Onafhankelijke validatie gepland

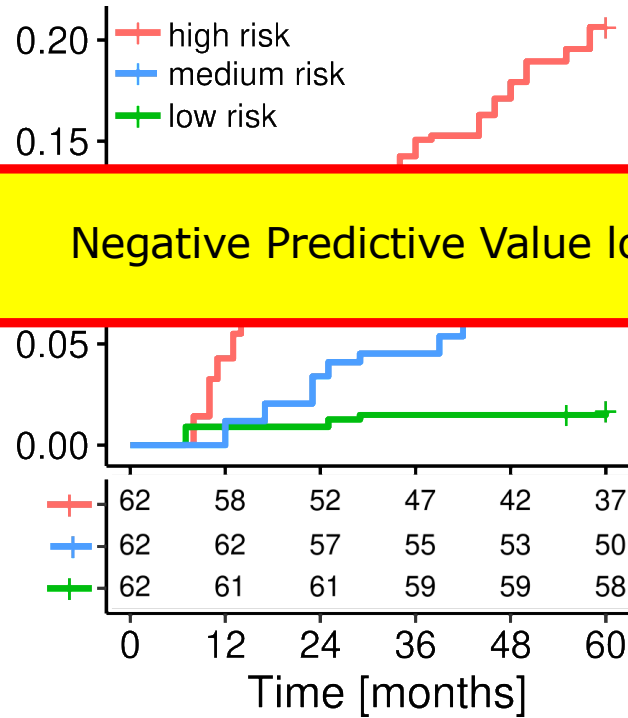
Verbeteren segmentatiemodellen

- Als je het beeld draait, dan zou de segmentatie ook moeten draaien
- Werkt dit ook voor segmentatie van de ducten?

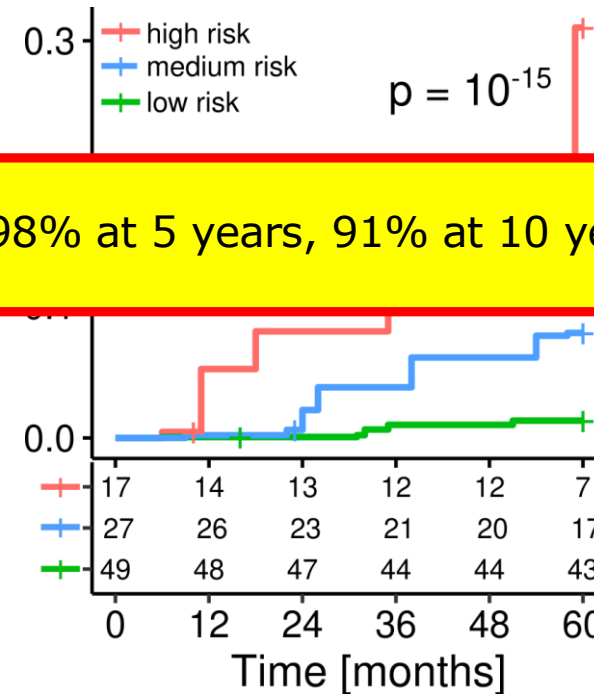


Kan je zo biomarkers voorspellen o.b.v. hele coupes?



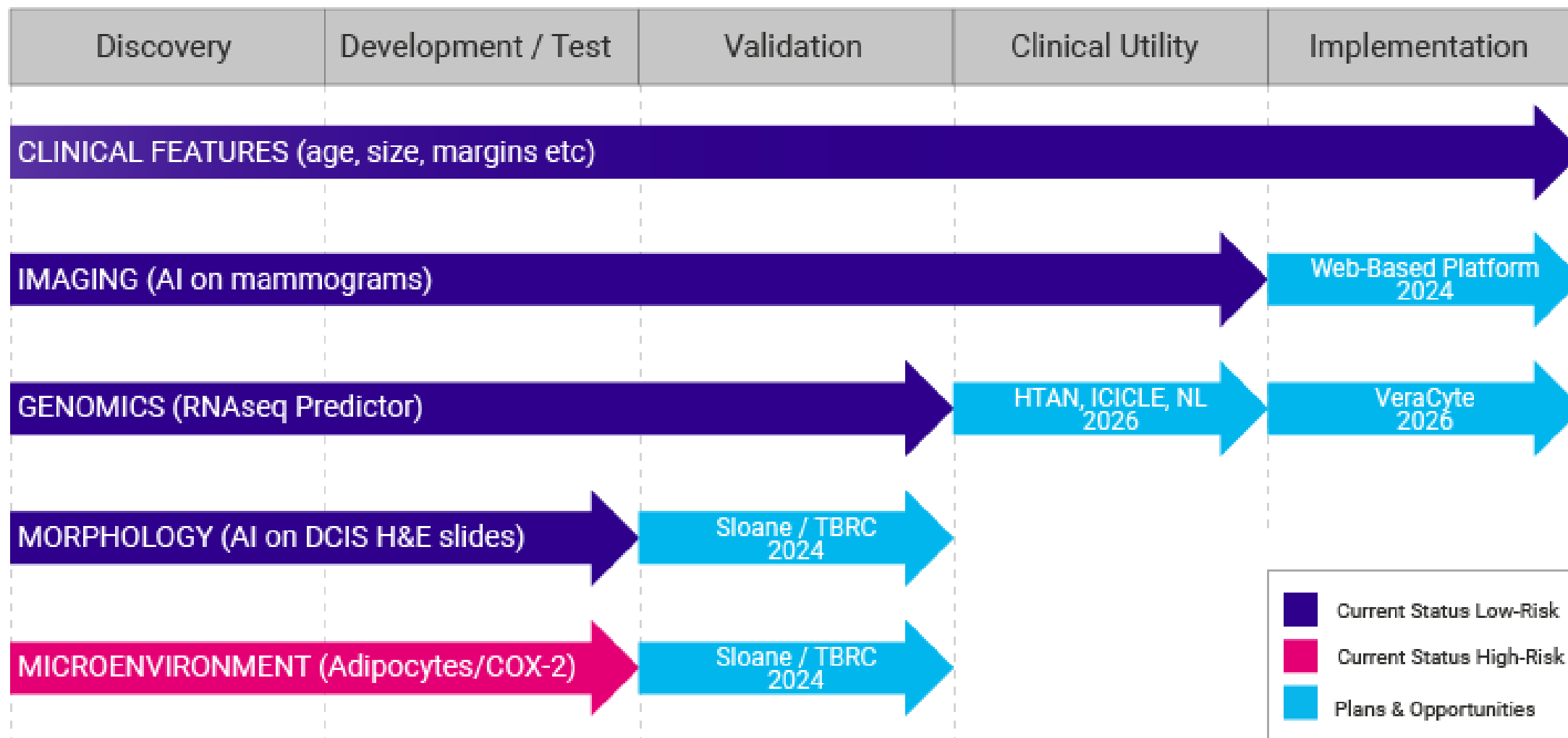


Negative Predictive Value low-risk group 98% at 5 years, 91% at 10 years



Developed on Dutch DCIS-cohort

Validated on UK-Sloane cohort



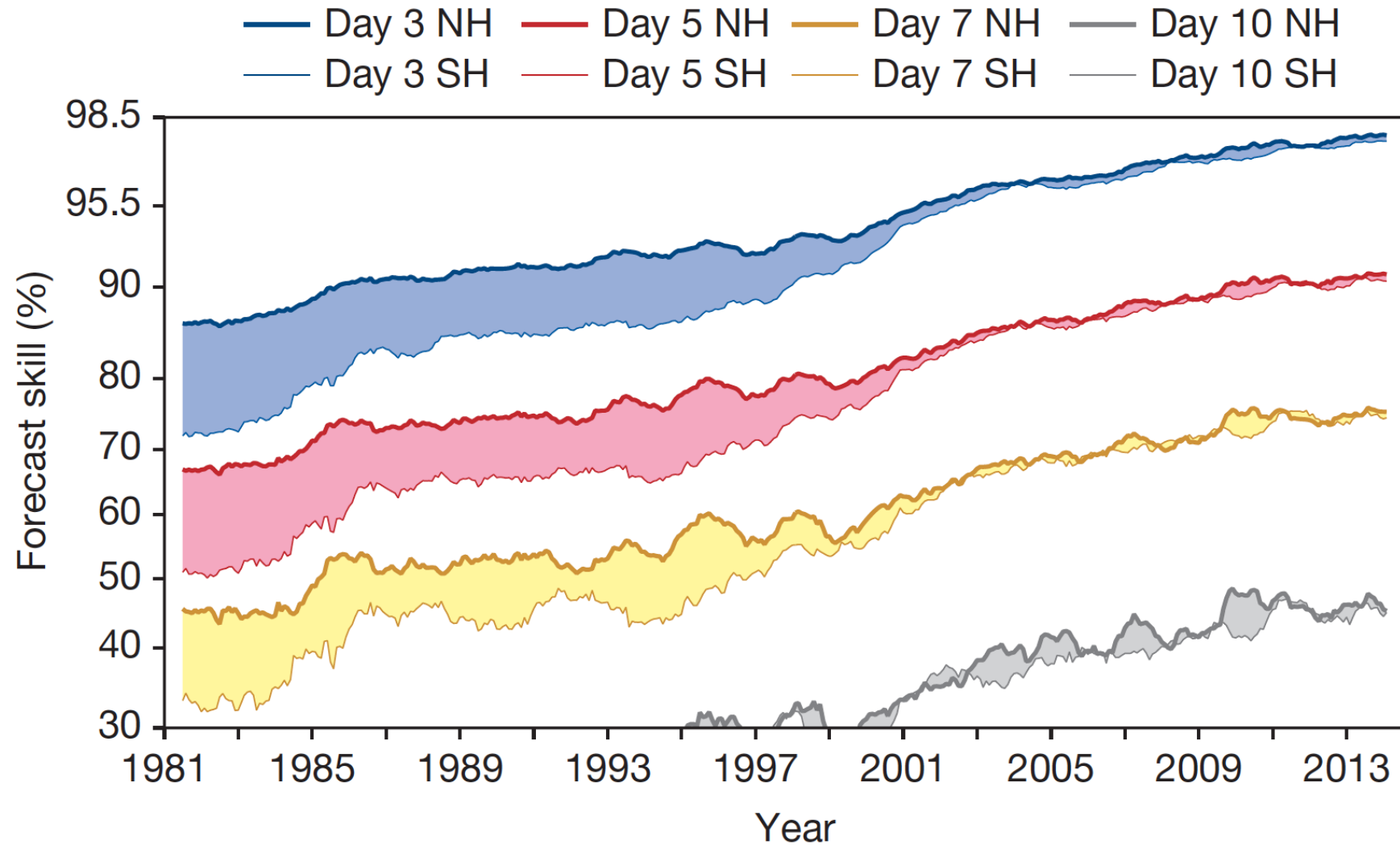
- DCIS is afwijking met een laag risico, dus weinig 'events'
- Weinig grote, goed gedefinieerde, niet selectieve series beschikbaar
- Cruciale inputwaardes veranderen met de tijd

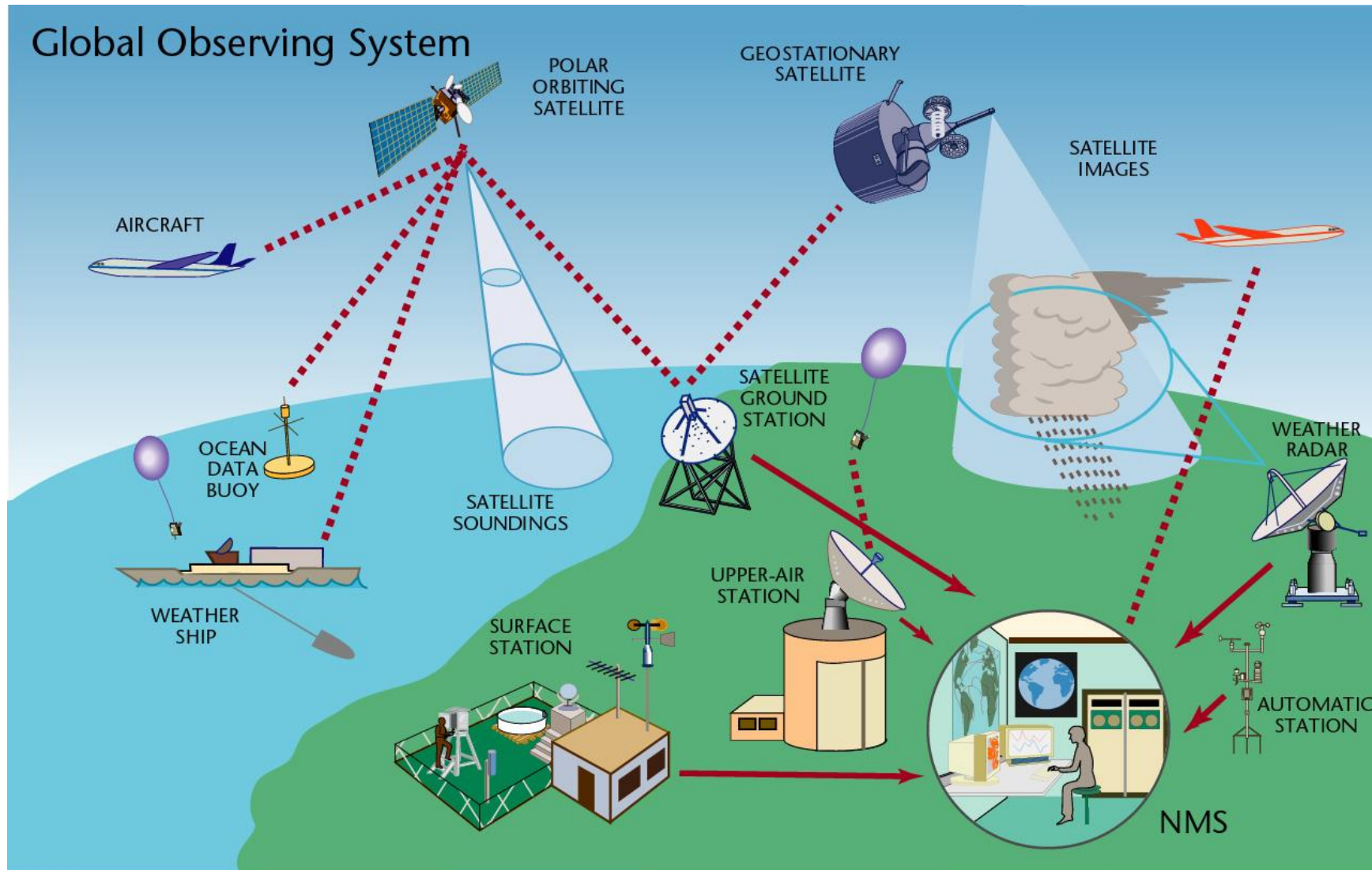




3. WAT IS DE OPLOSSING VAN HET PROBLEEM IN DE ECHE WERELD?

LEREN VAN HOE DE WEERSVOORSPELLING STEEDS BETER WORDT ...





- Geografische en historische data inzake weer en klimaat
- Recente waarnemingen en metingen (multidimensionele data)
- Modelleren m.b.v. AI en/of 'numerical weather prediction' (NWP)

Toegevoegde waarde

- Ontwikkelen model zonder voorafgaande training en/of prospectieve validatie
- Toevoegen nieuwe relevante variabelen 'on-the-fly'

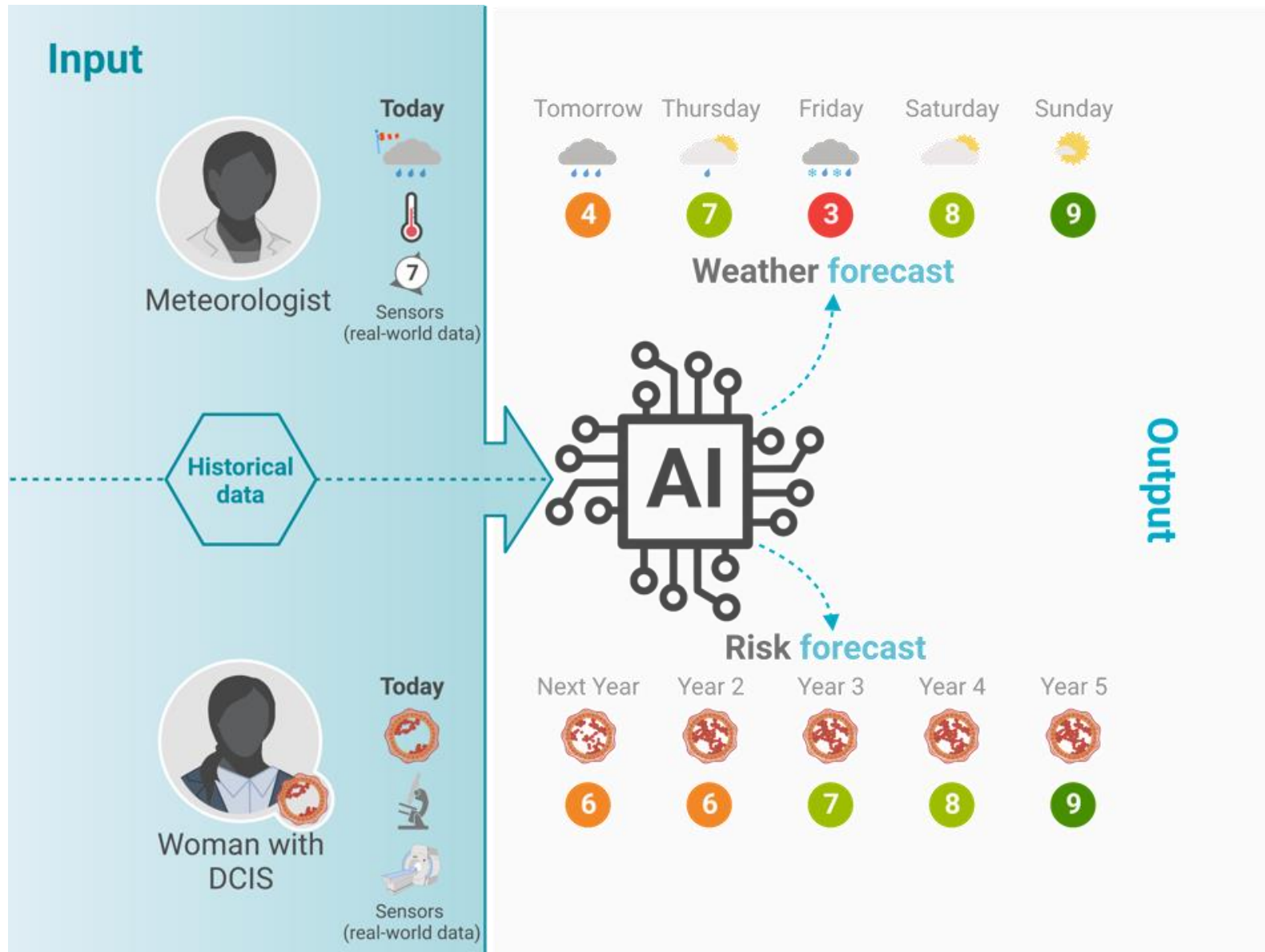
Beperking

- Modelleren weersvoorspelling gebaseerd op wetten in de fysica

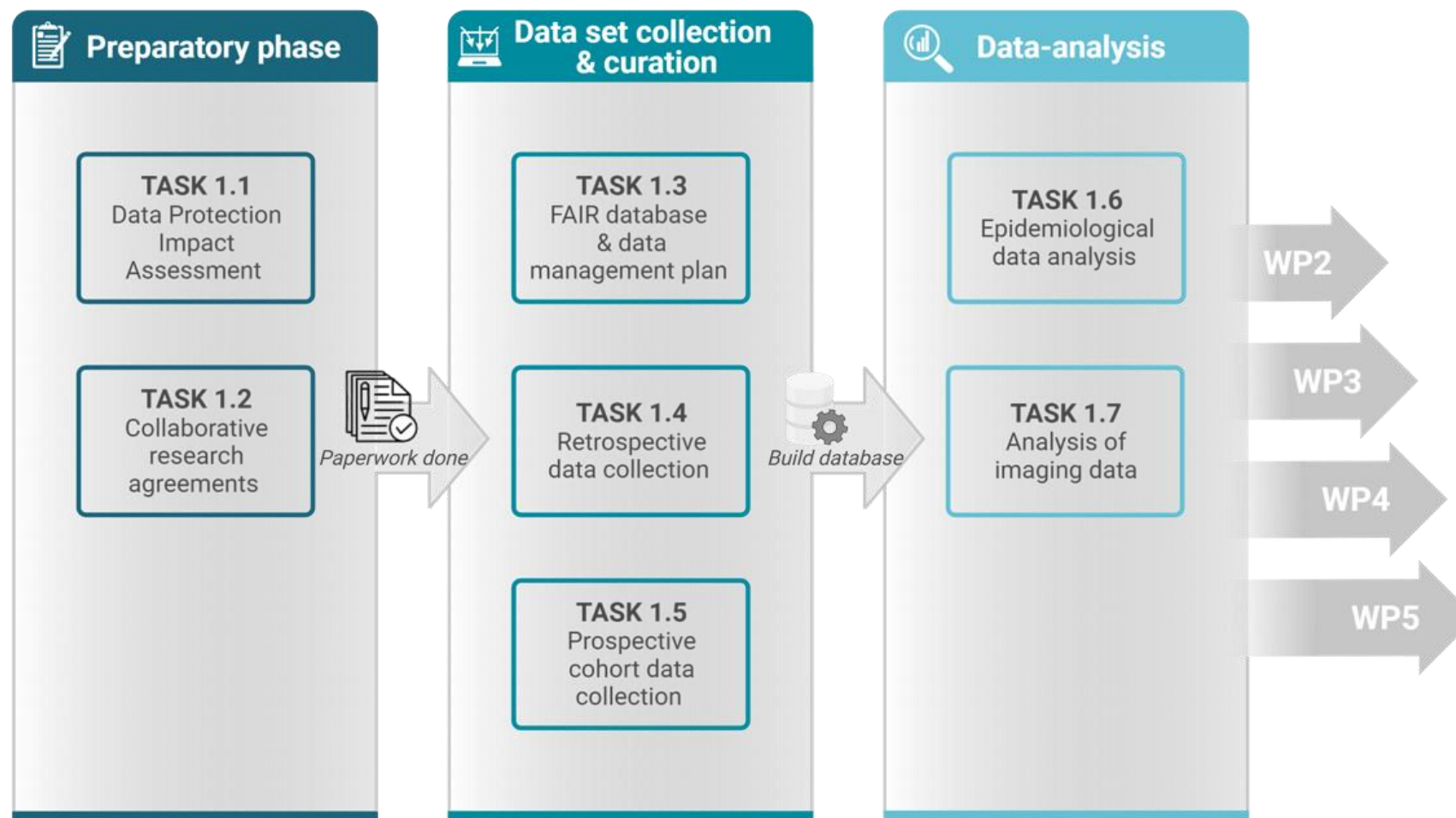
Absolute voorwaarde

- Excellente kwaliteit data vereiste om vergelijkingen/verbanden hieruit af te leiden

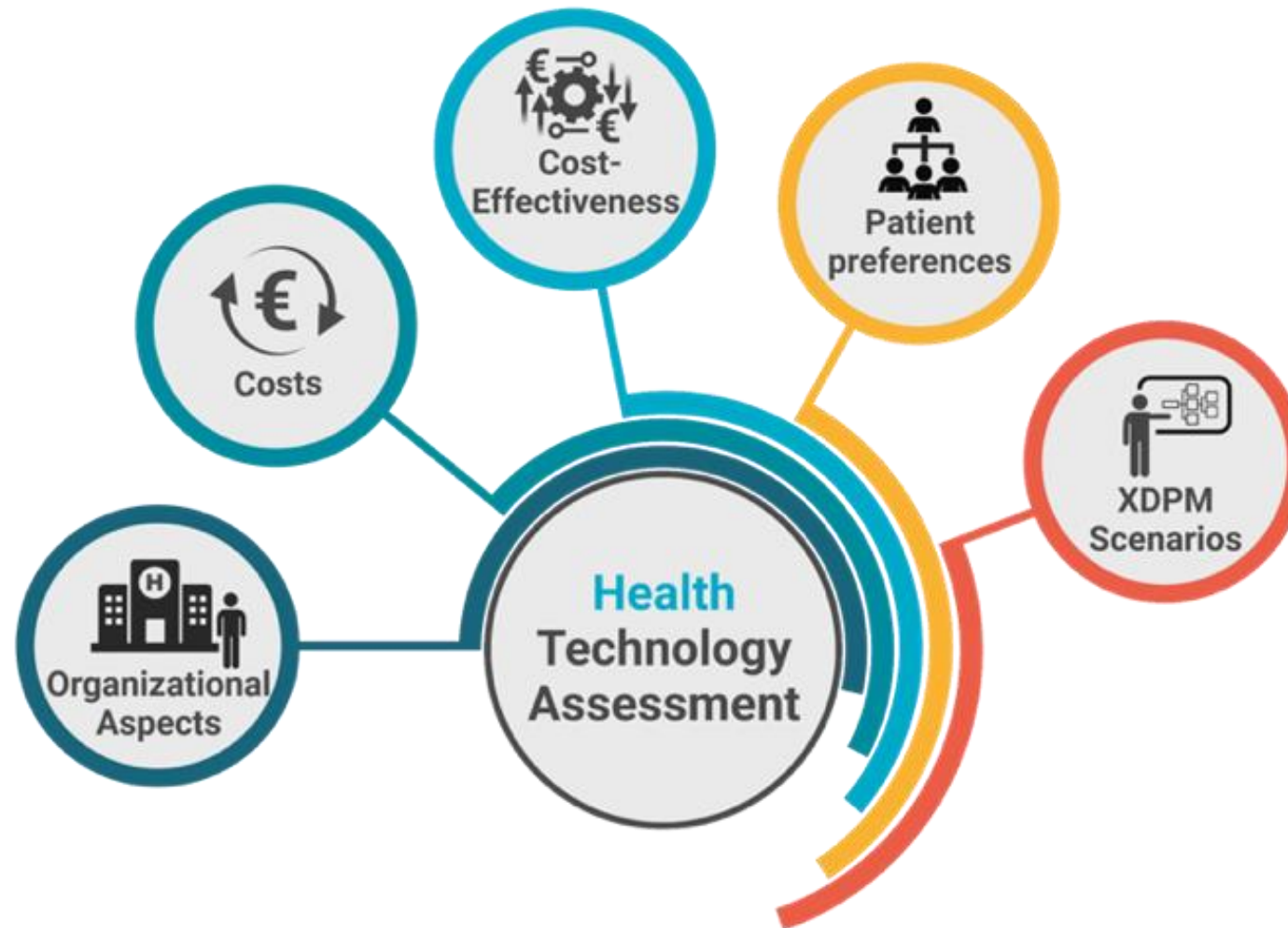
DIRECT DCIS OM OVERBEHANDELING TE VOORKOMEN



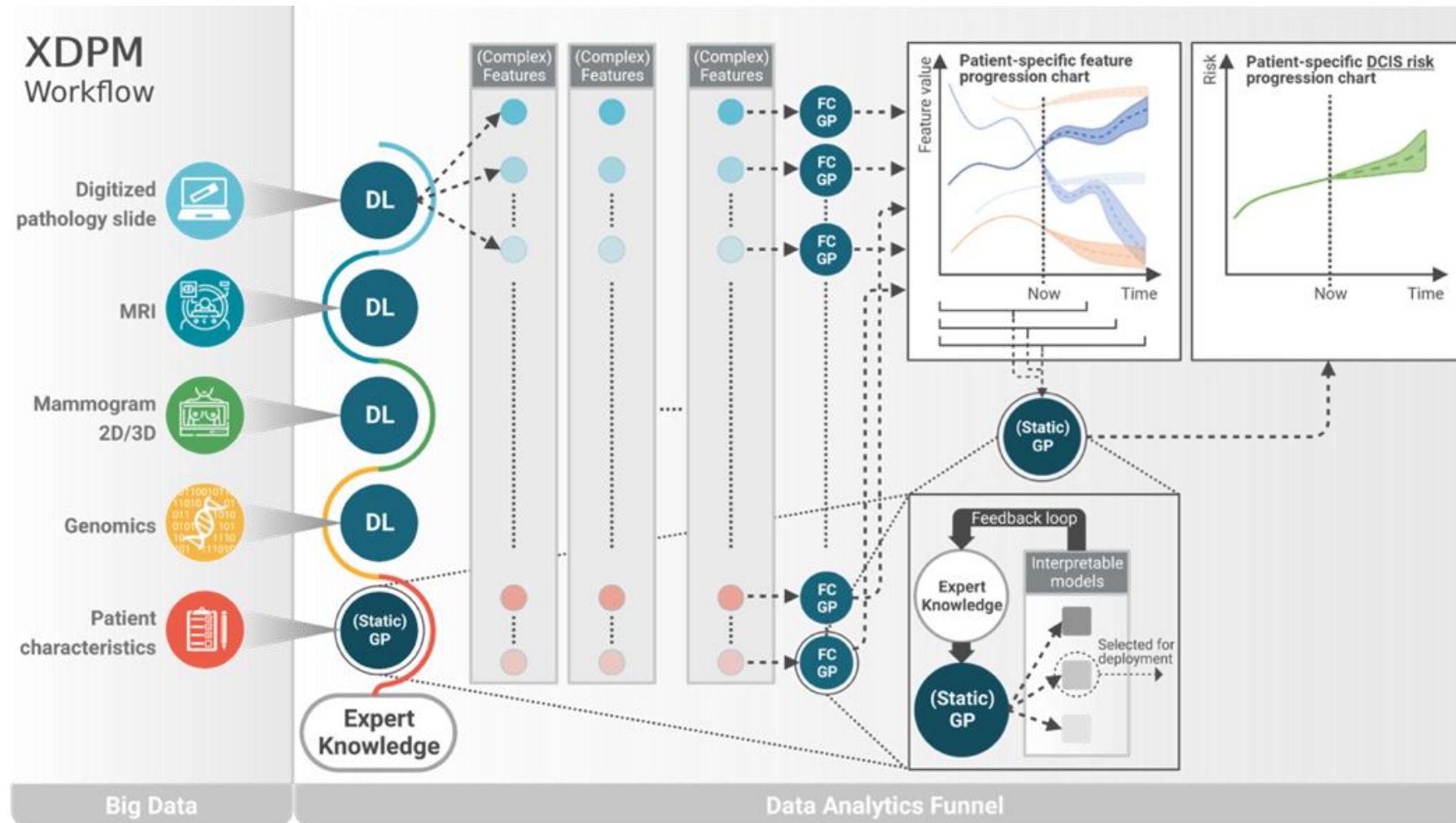
Leiding: Esther Lips (NKI)



Leiding: Valesca Retèl (NKI, EUR) & Esther de Bekker-Grob (EUR)



Leiding: Peter Bosman (CWI & TU Delft) en Tanja Alderliesten (LUMC)





Patient app

DIRECT-DCIS cohort have access to user-friendly UI to provide data and personal preferences, to review the personal real-time health status, the personalized 12 months care pathway, disease education and supporting programs (e.g. MyMentalhealth, MyMenu, MyFitness etc.)



DEARhealth Production Platform



Real time data analyses

for proven results of onboarded DCIS cohort (savings, HC consumption, health outcomes, satisfaction)

eXplainable dynamic predictive modelling XDPM

XDPM Data platform

Pseudonymized data

New DCIS data input

as result of XDPM Explainable AI and Machine Learning research

Clinical Evaluation



Clinical Evaluation

of XDPM results

Add the new validated XDPM data to DCIS medical model



Innovate Recommendations

by applying the validated XDPM results

In a MDR compliant *

*DEARhealth is MDR class II-a certified software as a medical device. Patient Safety First. No black box AI allowed

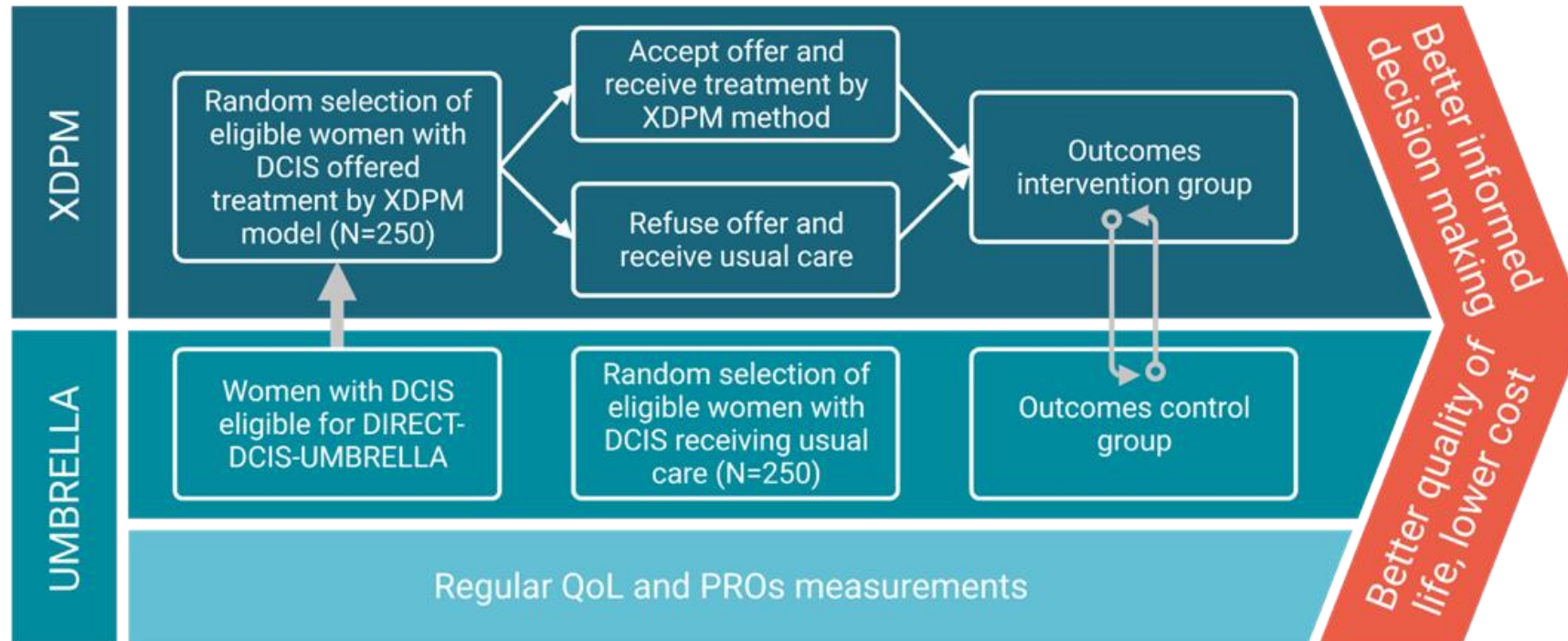


Leiding: Lenny Verkooijen (UMCU)



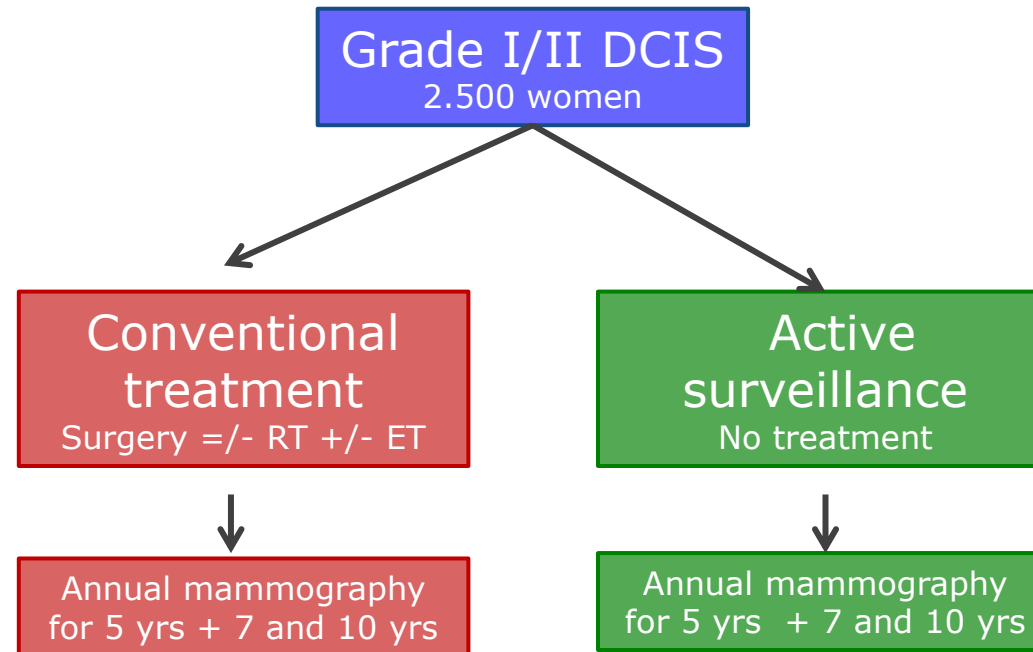
QoL and PRO vragenlijsten gedurende follow-up

Leiding: Lenny Verkooijen (UMCU)

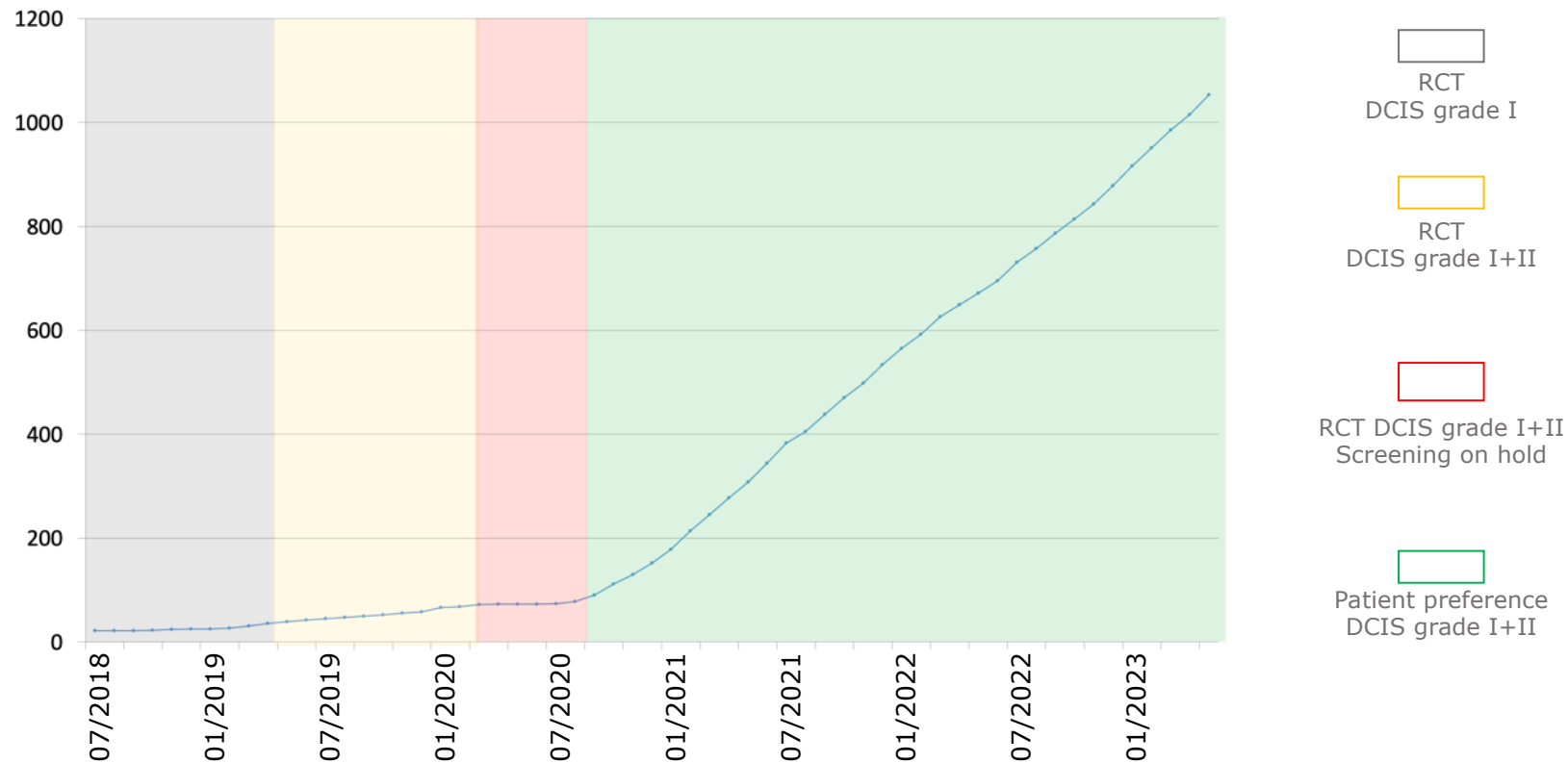


Trials within Cohorts (TwICs) design voor de DIRECT-DCIS studie

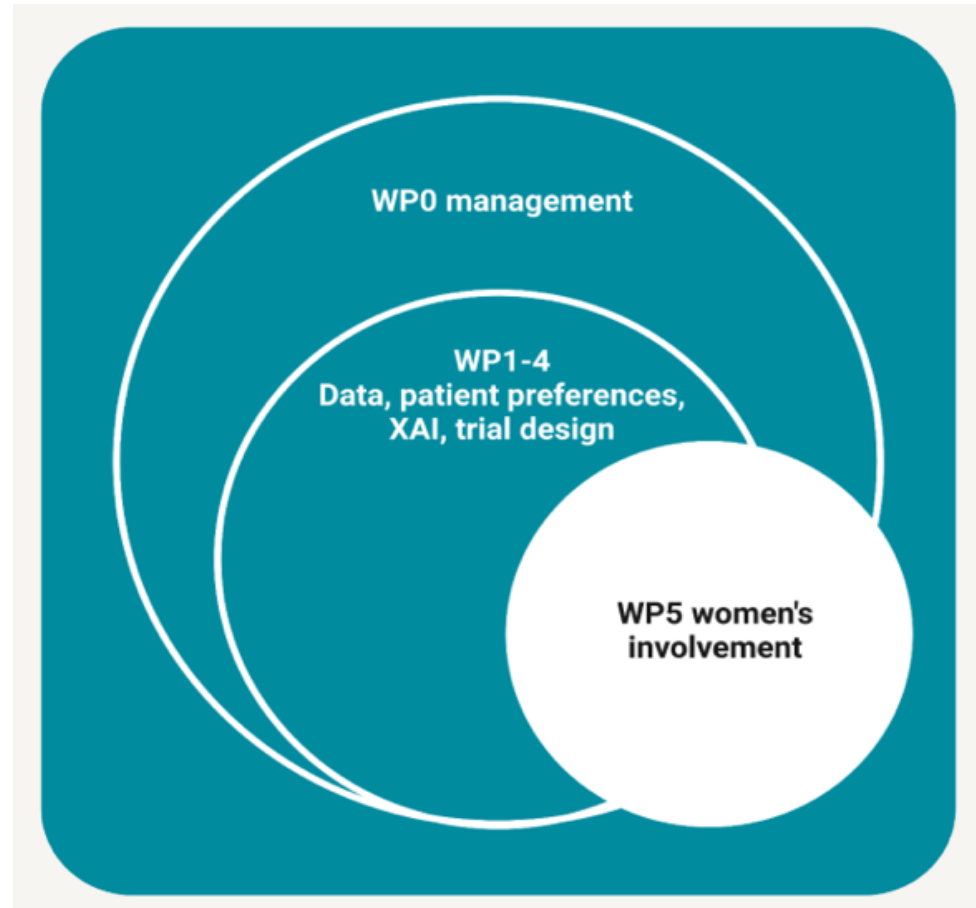
Is active surveillance veilig voor ER-positief, HER-negatief graad I/II DCIS gevonden op basis van bij screening gedetecteerde calcificaties in vrouwen ouder dan 45 jaar?



- Bijna 60% van alle vrouwen met ER+/HER2- graad I of II DCIS worden geïncludeerd in NL
- Bijna 80% kiezen voor 'active surveillance'

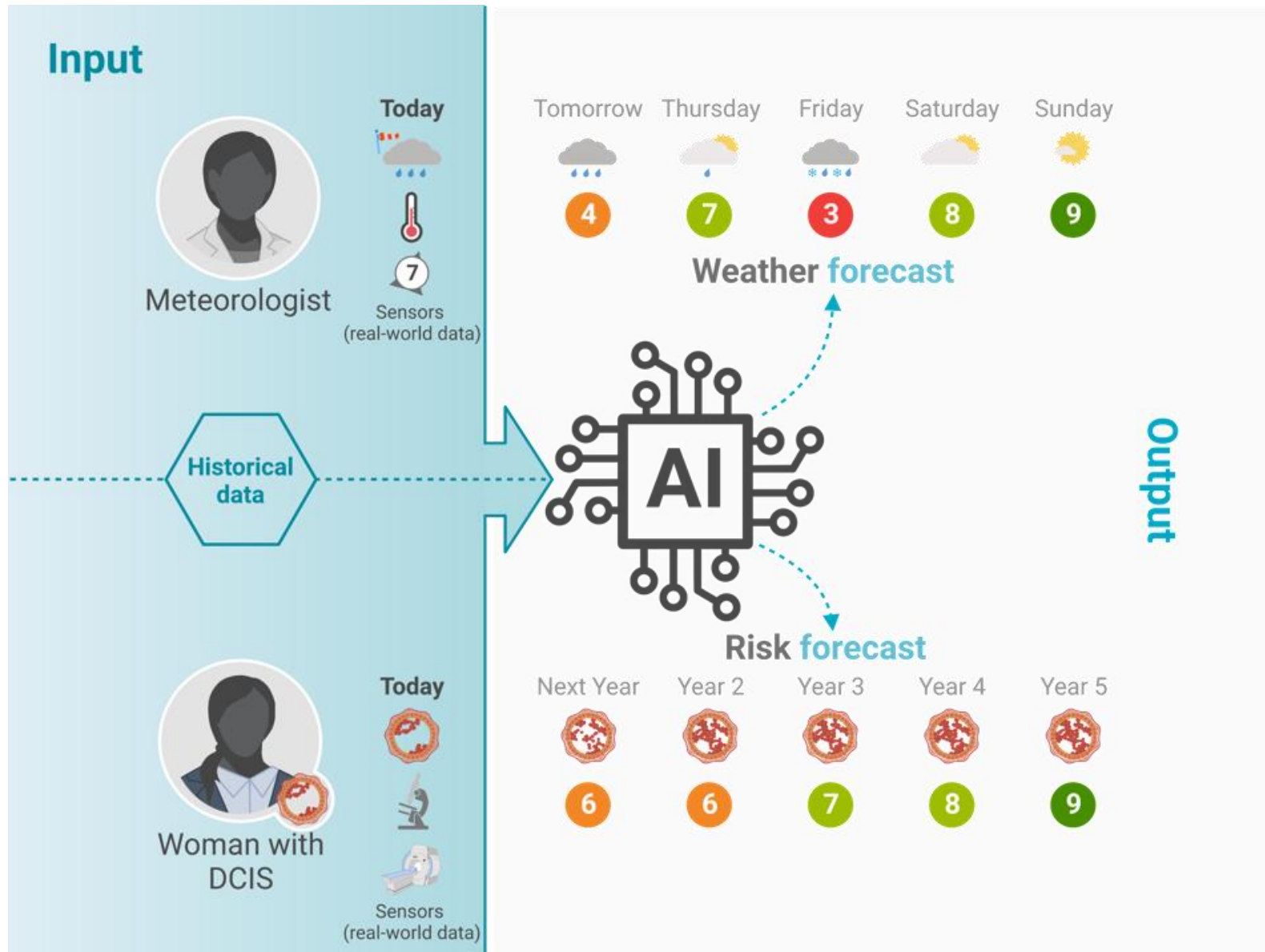


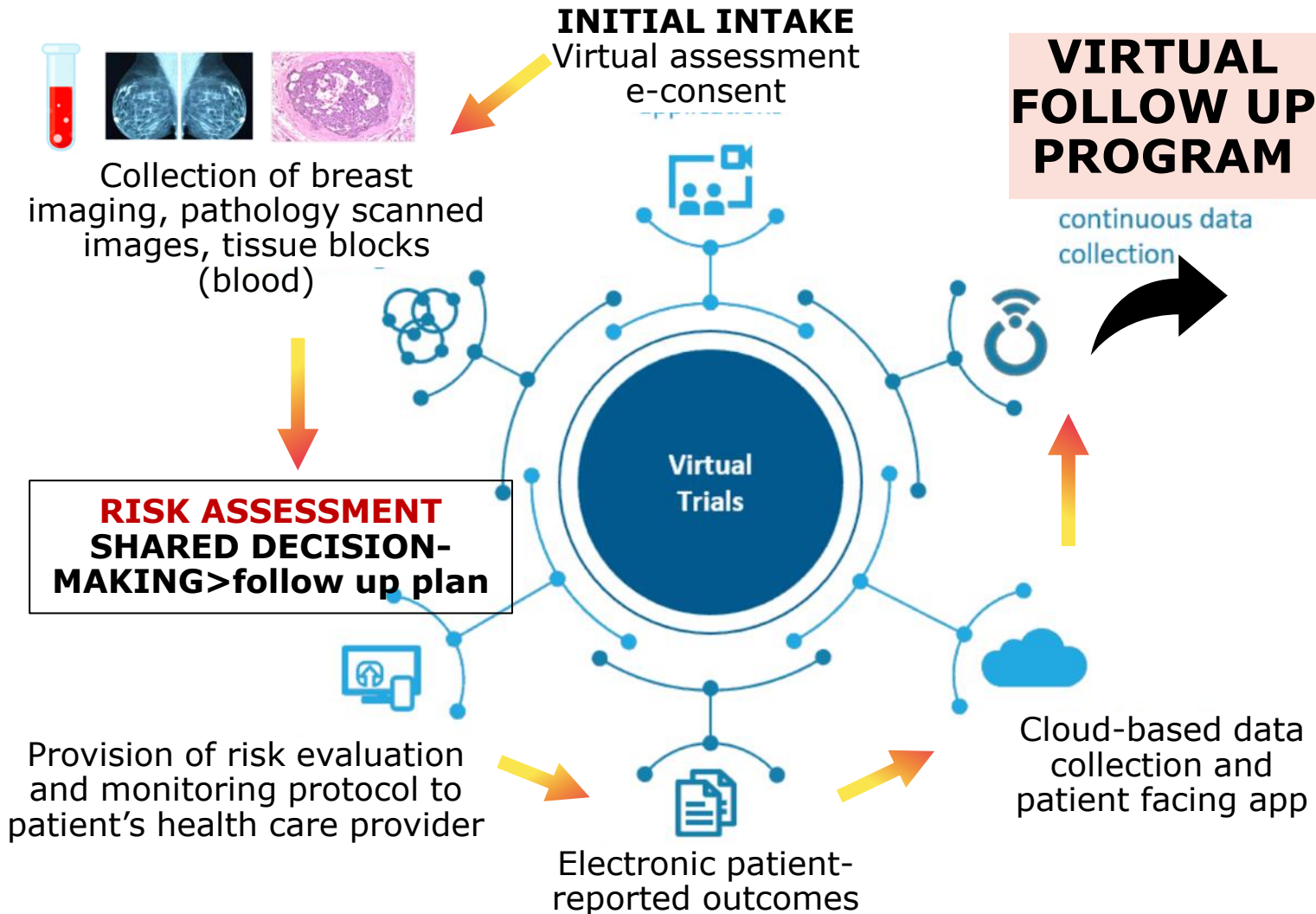
Leiding: Nanne Bos (NIVEL)

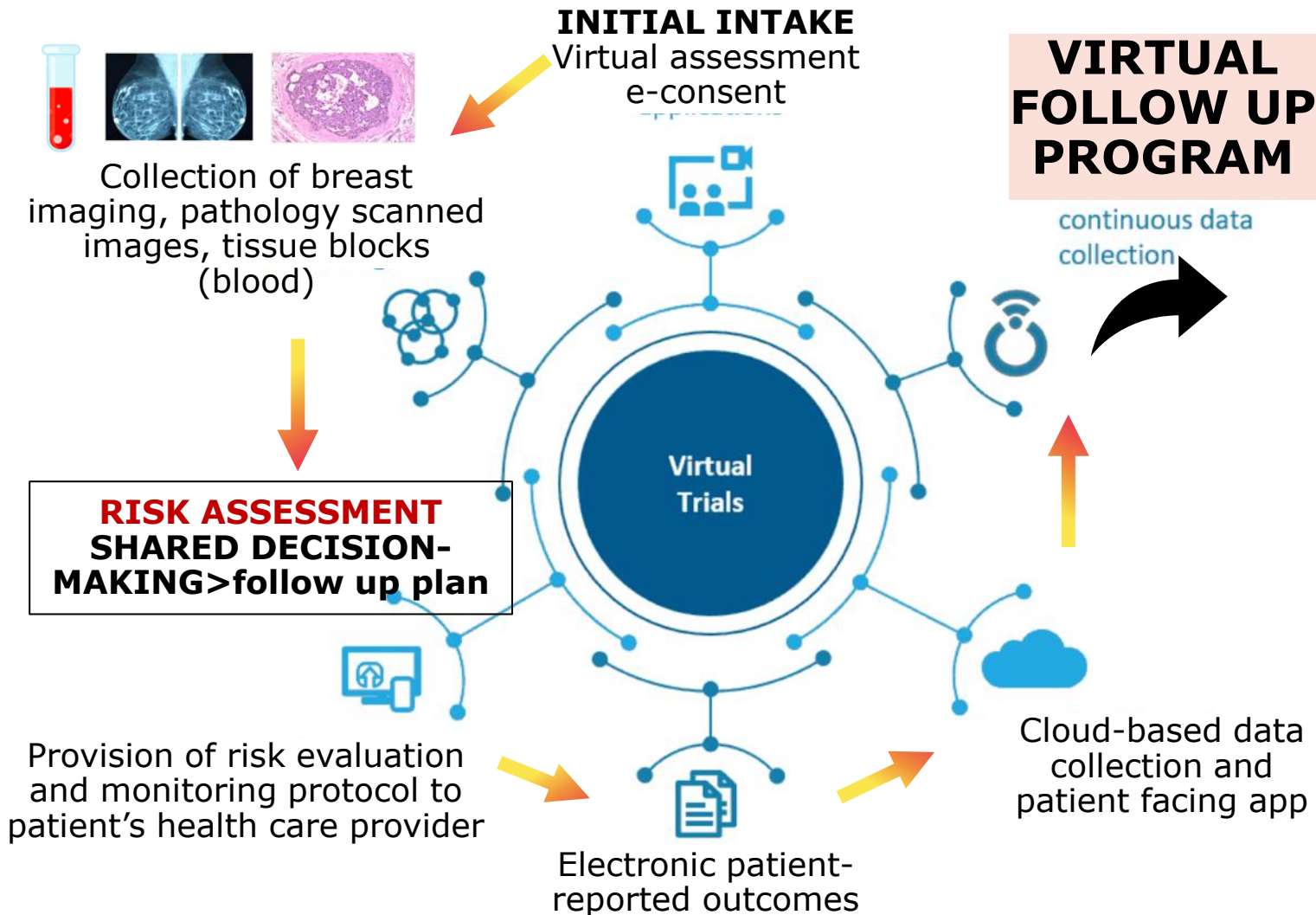


- Overbehandeling niet-progressief DCIS voorkomen
- Kwaliteit van leven behouden
- Besparen maatschappelijke en zorggerelateerde kosten

DIRECT DCIS OM OVERBEHANDELING TE VOORKOMEN







BENEFITS OF A VIRTUAL CLINIC

Cost effective



Project costs would include website management, virtual risk assessment and shared decision making, **24-hour help desk**

Increased patient enrollment



GLOBAL participation not limited by access to trial sites

Reduced patient dropouts



No additional physician visits, better patient follow-up through patient-powered engagement, access to help desk for general questions and support

INITIAL INTAKE
Virtual assessment
e-consent

**VIRTUAL
FOLLOW UP
PROGRAM**

BENEFITS OF A VIRTUAL CLINIC

Cost effective



Project costs would include virtual shared our

virtual
shared
our

Patiënt centraal
Laagdrempelig toegang tot active surveillance
Inschatting risico op borstkanker
Shared-decision making gebaseerd op risicoprofiel

ECHTE GEZONDHEIDSZORG & VALIDATIE MARKERS

**RIS
SHA
MAKI**

co

in visits,

Provision of risk evaluation and monitoring protocol to patient's health care provider



Electronic patient-reported outcomes

Cloud-based data collection and patient facing app

better patient follow-up through patient-powered engagement, access to help desk for general questions and support

Wesseling Group NKI-AVL

Associate Staff Scientist
Esther Lips

Project Management:
Proteeti Bhattacharjee

Postdocs:
Marcelo Sobral-Leite
Sandra van den Belt

PhD students:
Renée Schmitz
Merle van Leeuwen
Lot Mulder
Marte Liefwaard
Mathilde Almekinders
Sena Alaeikhanehshir
Shannon Doyle
Marek Oerlemans
Will Harley

Technical and data support:
Lennart Mulder
Petra Kristel
Shiva Vonk
Yat-Hee Liu

Molecular Pathology NKI

Hugo Horlings Group
Marjanka Schmidt Group
Jacco van Rheenen Group
Jos Jonkers Group

Imaging & AI NKI-AVL

Ritse Mann Group
Jonas Teuwen Group

Surgical Oncology NKI-AVL

Frederieke van Duijnhoven
Marie-Jeanne Vrancken-Peeters

Medical Oncology NKI-AVL

Gabe Sonke
Sabine Linn

Epidemiology, HTA & Psycho-Oncology NKI-AVL

Flora van Leeuwen
Eveline Bleiker Group
Valesca Rétel Group
Michael Schaapveld

Bioinformatics NKI-AVL

Tycho Bismeyer
Misha Sheinman
Lodewyk Wessels

Clinical Project Manager

Carine Sondermeijer

Alumni Wesseling Group

Lotte Elshof, Lindy Visser, Maartje van
Seijen, Emilie Groen
Marlous Hoogstraat, Bert van der Vegt,
Marnix de Roos

CFMBP & Biobank bvn NKI-AVL

Annegien Broeks, Dennis Peters, Ingrid
Hofland

Dutch National Pathology Data and Tissue Bank (PALGA)

Netherlands Cancer Registry
Numerous pathology labs!!!

Cancer Grand Challenge PRECISION

PRECISION Patient Voices, UK & US & NL
Alastair Thompson, BCM, Houston, US
Elinor Sawyer, KCL, London, UK
Sarah Pinder, KCL, London, UK
Serena Nik-Zainal, Cambridge University, UK
Helen Davis, Cambridge University, UK
Andrew Futreal, MDACC, Houston, US
Nicholas Navin, MDACC, Houston, US
Shelley Hwang, Duke University, Durham, US
Fariba Behbod, Kansas University, US
Nick Stone, Exeter University, UK
Keith Rogers, Cranfield University, UK
Daniel Rea, Birmingham University, UK
Matthew Wallis, Cambridge University, UK

DIRECT-DCIS PIs

Esther Lips, NKI, Amsterdam, NL
Esther de Bekker-Grob, Erasmus MC, Rotterdam, NL
Valescal Rétel, Erasmus MC Rotterdam & NKI-AVL, NL
Peter Bosman, CWI Amsterdam & TU Delft, NL
Tanja Alderliesten, LUMC, Leiden, NL
Helena Verkooijen, Sofie Gernaat, UMC Utrecht, NL
Nanna Bos, NIVEL, Utrecht, NL

DIRECT-DCIS Patient Representatives

Ellen Verschuur, BVN, Utrecht, NL
Marjolein Scholten, BVN, Utrecht, NL

DIRECT-DCIS Private Partners

Screenpoint Medical (Nico Karssemeijer)
DEARhealth (Katinka de Korte)
IQVIA - CTcue (Jacqueline Hartgerink)

Others

Joyce Sanders, Erik Hooijberg, Rianne van der Linden, Koen van de Vijver, National Pathology Database (PALGA), Dutch Cancer Registry (IKNL), Dutch screening organization (RIVM), Dutch Breast Cancer Study Group (BOOG), EORTC HQ



- Posters
- Co-auteur publicaties
- **Samenvattingen voor leken**
- Nieuwsbrieven
- Website

*Ik stel het belang van de patiënt voorop en eerbiedig
zijn opvattingen. Ik zal aan de patiënt geen schade
doen. Ik luister en zal hem goed inlichten. Ik zal
geheim houden wat mij is toevertrouwd.*

'Primum, nil nocere' (Hippocratic Oath at the entrance wall of Domus Medica, Utrecht, the Netherlands)