

Combiner détection précoce et interception – modèles théoriques et pratiques

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Liens d'intérêt

Suzette Delaloge

Research support (to my institution)

AstraZeneca, MSD, BMS, Sanofi, Taiho, Novartis

European Commission, INCa, Banque des Territoires, Fondation
Philanthropia

Honoraria for lectures and advisory boards (to my institution)

Astra Zeneca, Gilead, Novartis, Elsan, Besins, Sanofi, Exact Sciences, Lilly

Travel support

Novartis (SPDV)

Plan

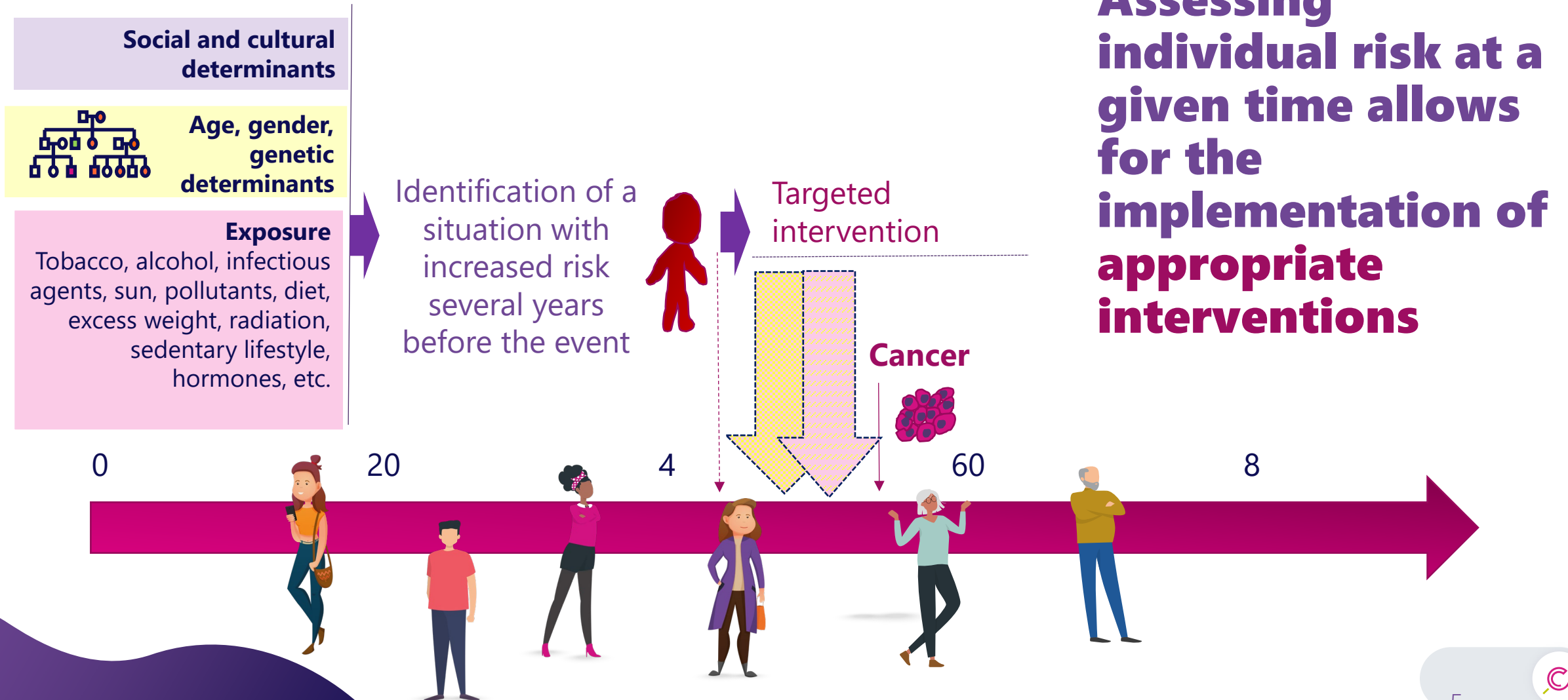
- Pourquoi combiner détection et interception
 - La carcinogenèse en cours est elle une bonne cible?
 - La détection par biopsie liquide est elle actionable
 - La prévention de précision aujourd'hui
 - Conclusions & perspectives

La synergie entre les champs de prévention doit être exploitée pour adresser les grands enjeux

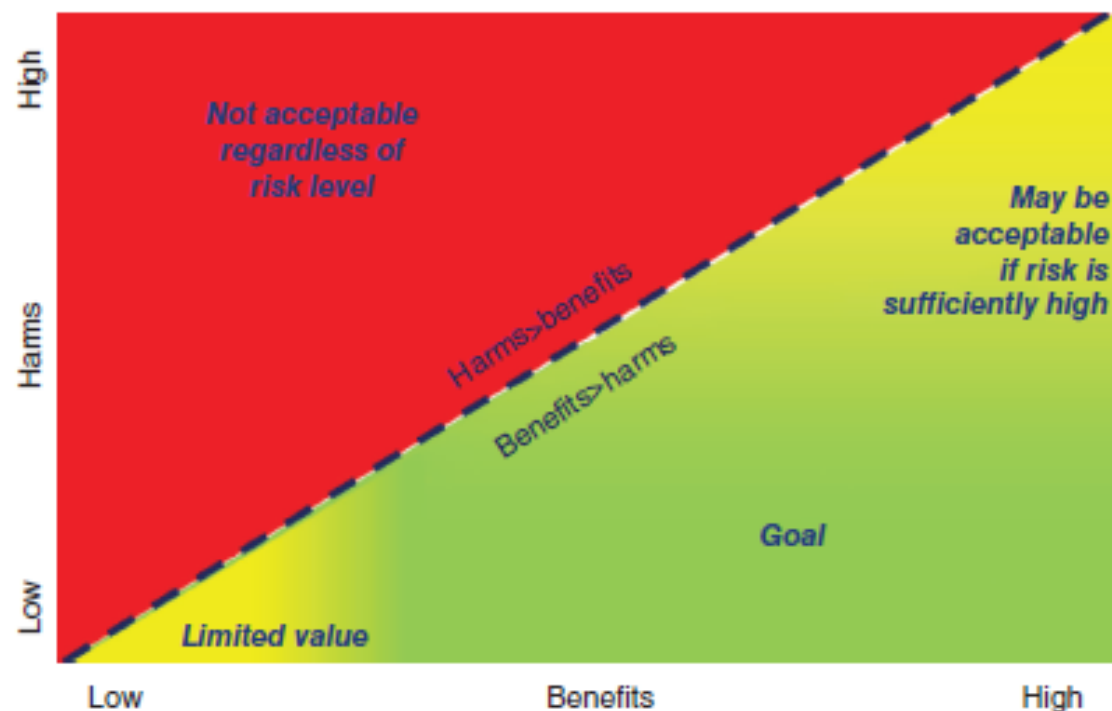
- Tackle the moving target of cancer epidemiology
- Transform our knowledge on carcinogenesis into efficient prevention strategies
- Reduce cancer-related health inequalities
- Build acceptable and desirable prevention strategies
- Build sustainable economical models
- Replace therapeutic strategies in the long run!

$$\frac{\lim_{n \rightarrow \infty} \frac{2^{2n} (n!)^2 \log 7}{(2n)! \sqrt{n}}}{\left| \int_0^\infty \frac{\sqrt{3} dt}{t^6 + 1} \right|^2 \left| \int_{-\infty}^\infty e^{-\pi t^2} dt \right| \left| \int_0^\infty e^{-t} t dt \right|} \left| e^{\frac{2^{2n} (n!)^2 \log 7}{(2n)! \sqrt{n}}} - e^{i \sum_{k=0}^\infty \frac{8}{(4k+1)(4k+3)}} \right| \int_0^\infty \frac{2t}{e^t - 1} dt = 50$$

Detecter précocement la carcinogenèse ou les situations à risque de cancer permet des actions multiples!



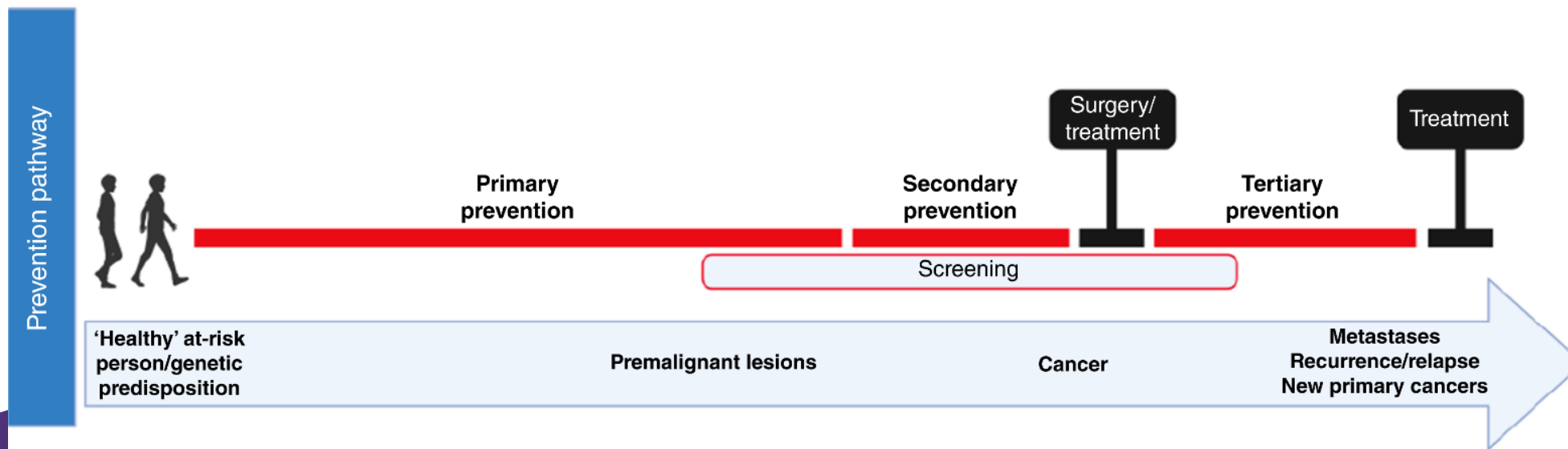
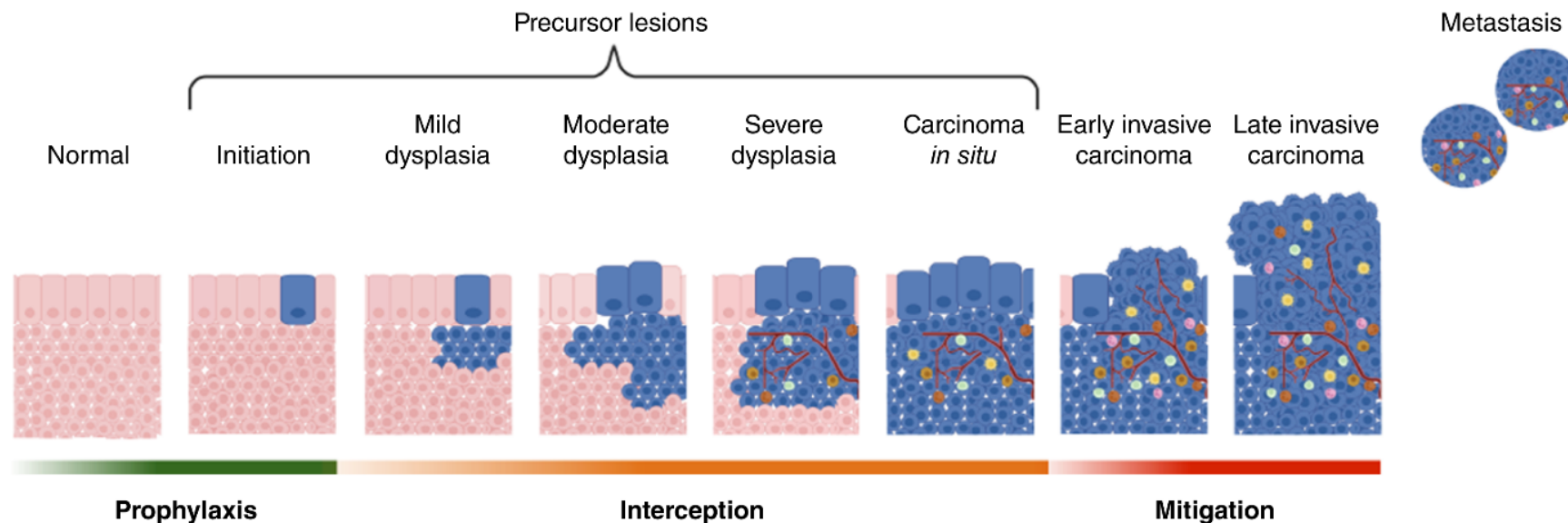
Precision prevention framework



RISK AND BENEFITS TO HARMS RATIO AS ORGANIZING PRINCIPLES FOR DEVELOPING AND IMPLEMENTING INTERVENTIONS

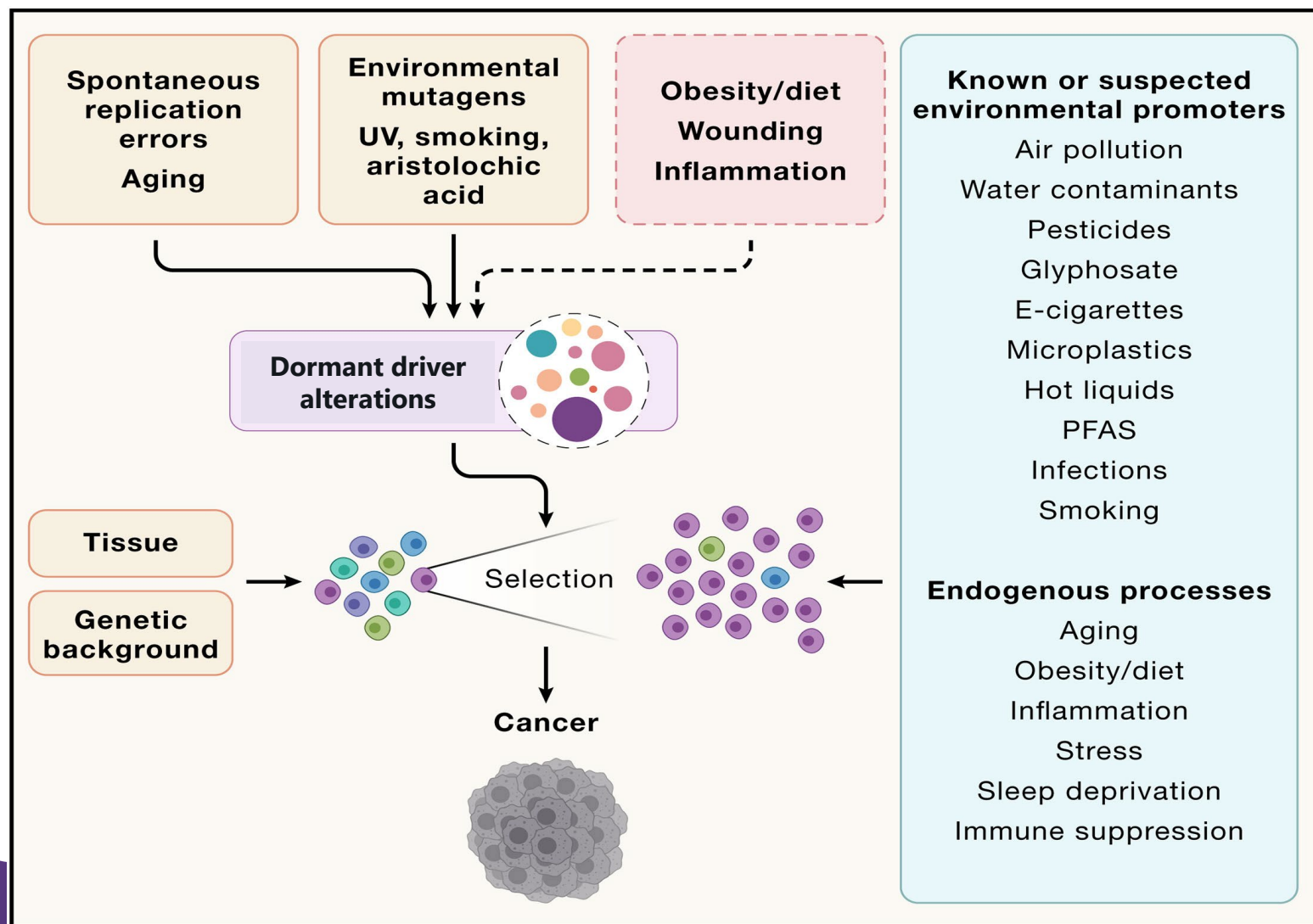
	Class of prevention		
Features	Prophylaxis	Interception	Mitigation
Cancer status	No evidence of cancer presence	Suspicion of cancer presence or knowledge of early precursor lesions	Early stage, curable cancer
Stage of natural history/carcinogenesis impacted	Prevent initiation and the development of precursor	Prevent progression of early biological changes and precursors to invasive cancer	Prevent cancer from causing death; optimize quality of life
Target population	General, at-risk population with no indication that events leading to cancer have occurred	Populations in which there is evidence that progression toward invasive cancer may have started	Population that may have early-stage cancer
Identification	General population, individuals at risk due to family history genetic susceptibility, exposures, etc.	Demographics (e.g., age), lab test (e.g., screening/ diagnostic test or procedure; genetic testing)	Lab test (e.g., screening/ diagnostic test or procedure; genetic testing)
General strategy	- Vaccination - Avoidance of exposure and behavioral modification	- Vaccination - Screening - Behavioral modification - Preventive agents	Tailor interventions to specific symptoms, medical manifestations, or behavioral/psychosocial needs
Examples	- HPV vaccination - HBV vaccination - Smoking prevention - Preventive surgery	- Smoking cessation - Screening & early detection - Daily aspirin use	Cancer early detection; monitoring low-grade cancer (e.g., low-grade prostate cancer)

The Interception opportunity!



Our revised view of carcinogenesis fuels precision prevention

Adapted from Swanton et al Cell 2024,



- Major role of the microenvironment
- Deleterious exposures with risky clonal expansion
- Possibility of reprogramming tissue at risk

Prevention
>> Target cancer drivers or some of their modifiers



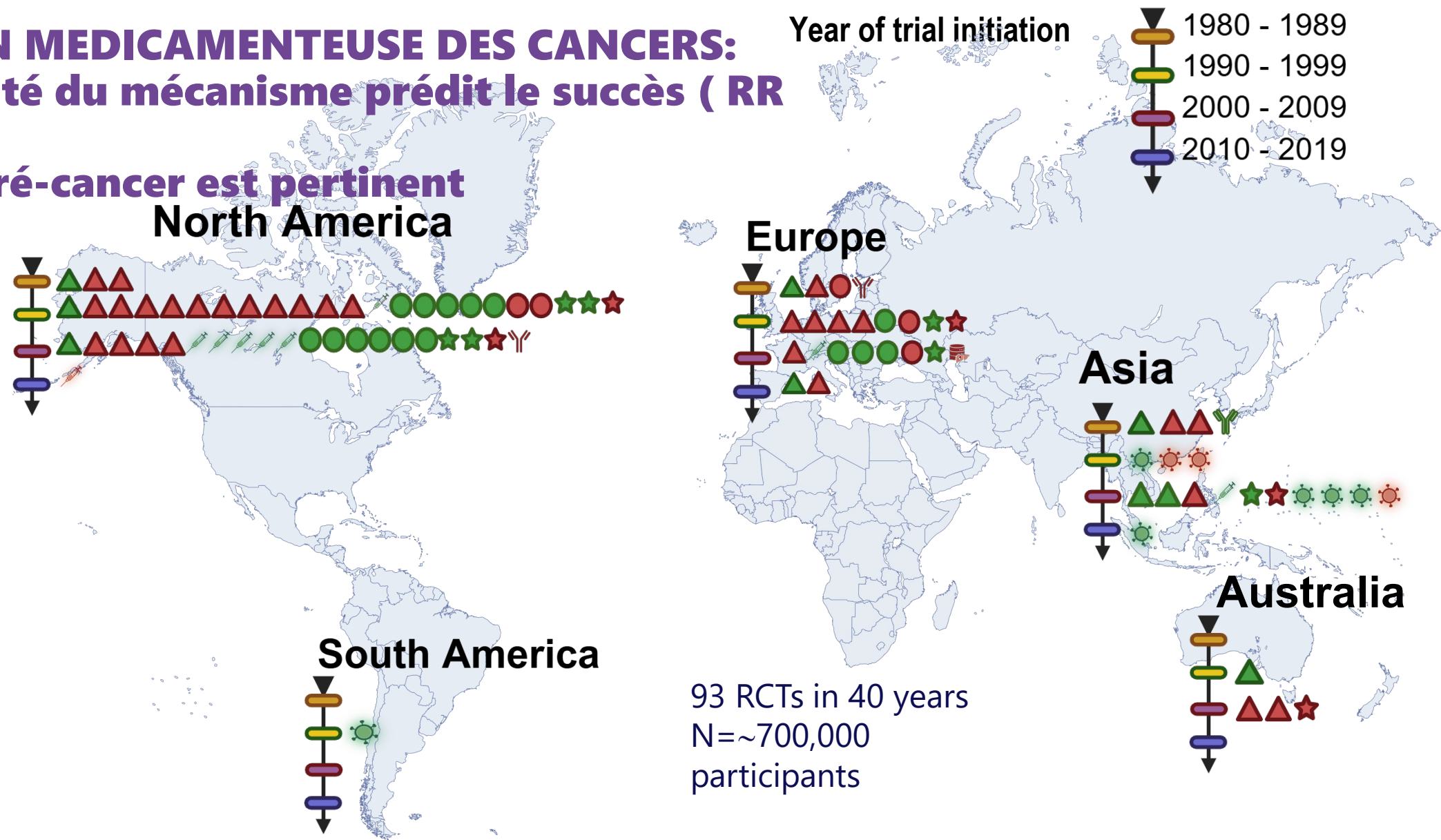
Plan

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PREVENTION MEDICAMENTEUSE DES CANCERS:

1. la spécificité du mécanisme prédit le succès (RR 3.4)
2. cibler le pré-cancer est pertinent

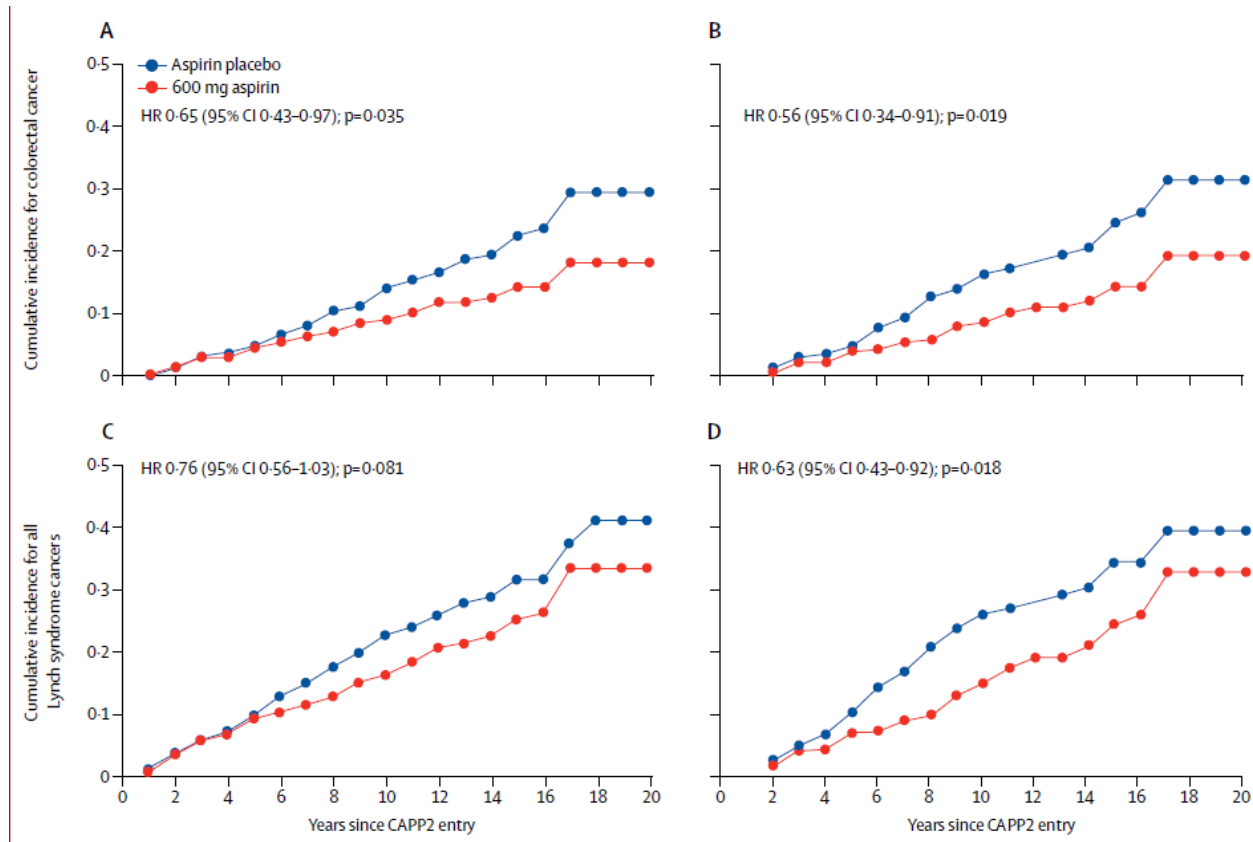
- △ Vitamins
- 📄 Vaccines
- Endocrine
- ☆ NSAID
- ☼ Anti-infectious
- Y Immune
- 📦 Metabolism
- Success
- Failure



DO NOT POST



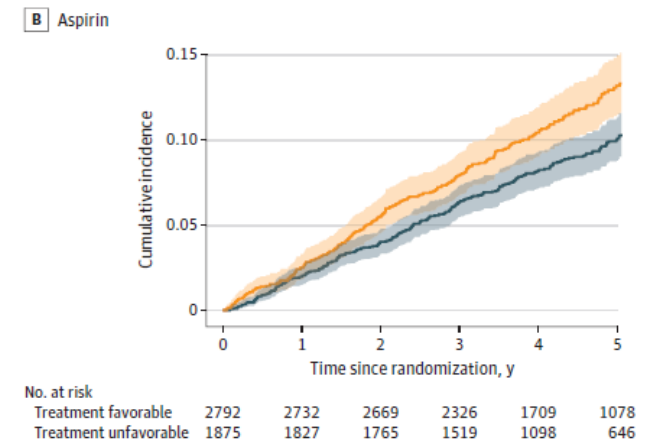
L'aspirine en prévention des cancers ne fonctionne pas.. Sauf sur le cancer du colon en cas de Sd de Lynch ou en cas de CHIP+?



Burn Lancet 2020

Group	No. (%) of participants	Participants with incident cancer (n = 1009)		HR (95% CI)
		No. (%) of placebo events	No. (%) of aspirin events	
All participants	9350 (100)	513 (25.3)	496 (24.4)	0.96 (0.85-1.09)
Treatment favorable	5529 (59.1)	307 (25.6)	267 (21.7)	0.85 (0.72-1.00)
Treatment unfavorable	3821 (40.9)	206 (25.0)	229 (28.6)	1.14 (0.95-1.38)

Test for heterogeneity: P = .02



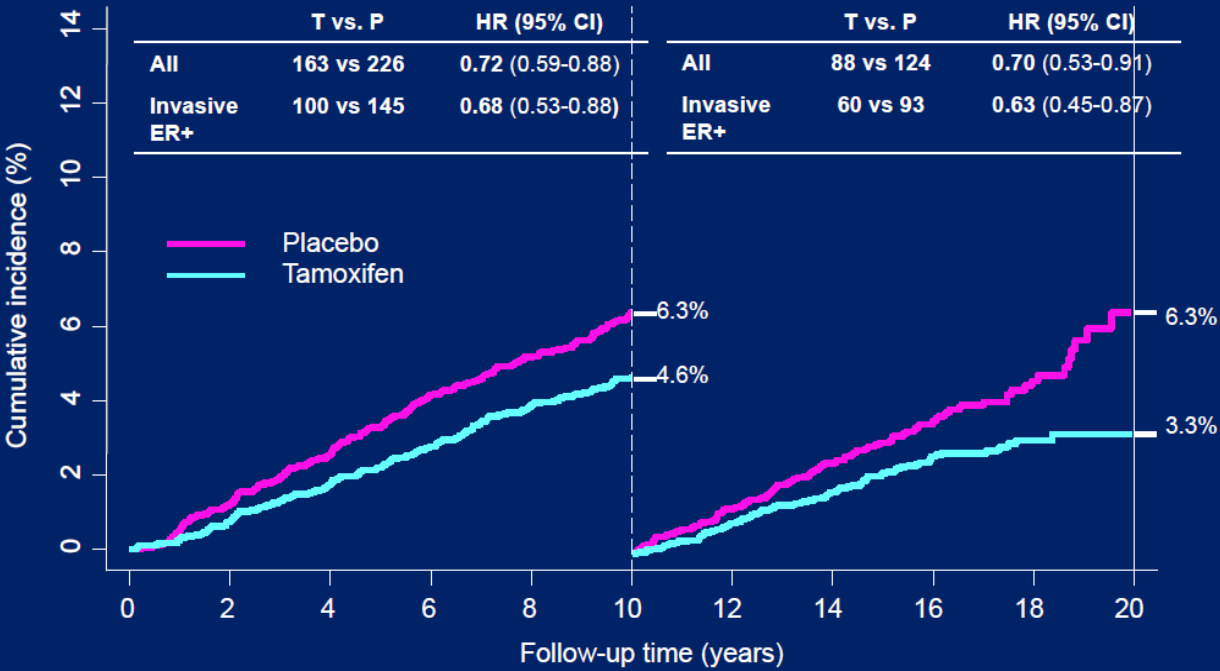
Thi Phuong Tao JAMA Oncol 2025



A MODEL FOR BREAST CANCER INTERCEPTION: LONG-TERM EFFECT OF 5 YEARS OF TAMOXIFEN IN THE IBIS-1 STUDY

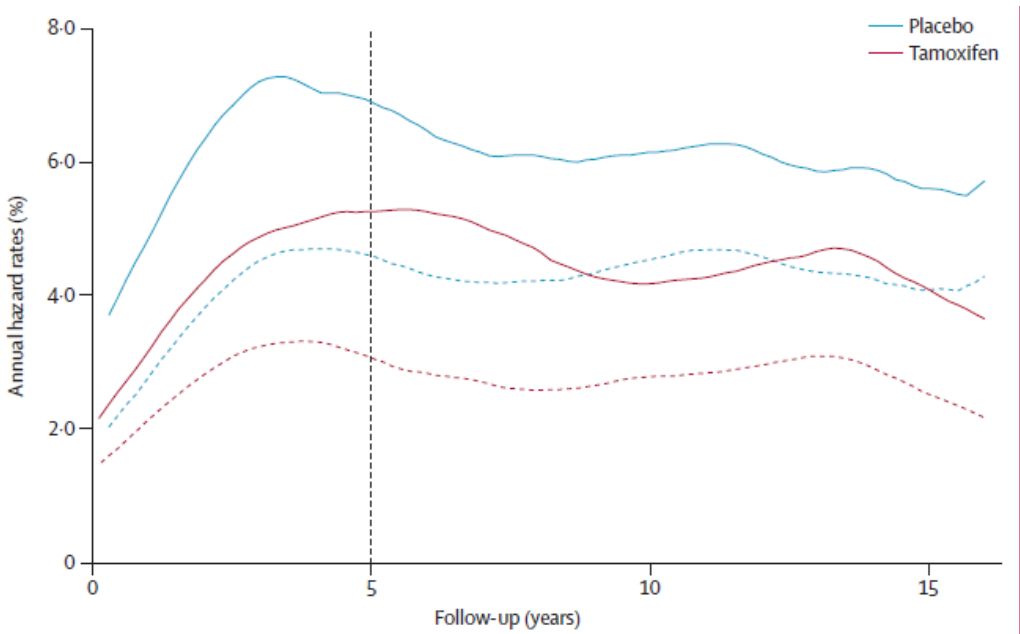
Tissue reprogramming may be allowed by **limited term interventions**

Cumulative incidence for all breast cancer



Number at risk											
Placebo	3575	3527	3474	3410	3358	3296	3239	2850	1901	725	165
Tamoxifen	3579	3542	3495	3446	3385	3344	3293	2890	1918	748	168

5years of endocrine prevention have a long-term protracted risk-reduction effect



Cuzick et al Lancet Oncol 2015; SABCS 2023



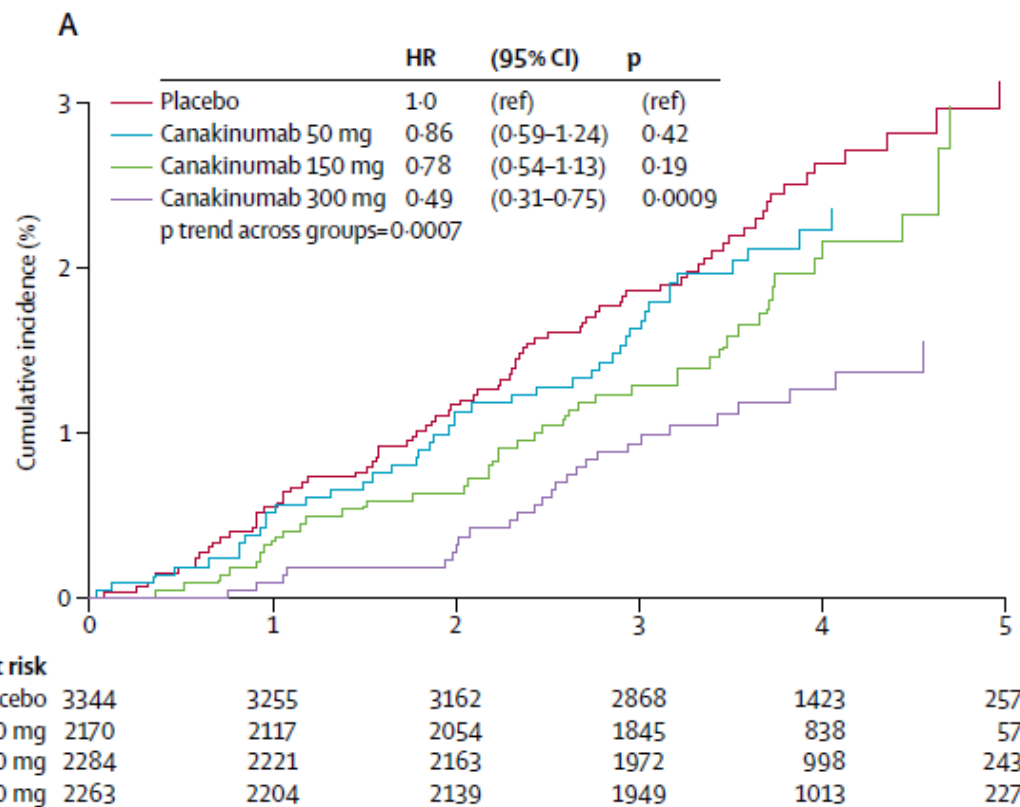
BUT A NUTRITIONAL INTERVENTION MAY HAVE MORE EFFECT ON BREAST CANCER MORTALITY THAN ENDOCRINE PREVENTION!

Trial	N	Follow-up ^a	Breast Cancer Incidence			Deaths From Breast Cancer		
			Tamoxifen	Placebo	RR (95% CI)	Tamoxifen	Placebo	
Royal Marsden ^b	2,494	13.2 years	82	104	0.78 (0.58 to 1.04)	12	9	Not reported
			Tamoxifen	Placebo	HR (95% CI)	Tamoxifen	Placebo	OR (95% CI)
NSABP P-1	13,388	74 months (mean)	145	250	0.57 (0.46 to 0.70)	12	11	Not reported
			Tamoxifen	Placebo	HR (95% CI)	Tamoxifen	Placebo	OR (95% CI)
IBIS-1	7,154	16.0 years (median)	251	350	0.71 (0.60 to 0.83)	31	26	1.19 (0.68 to 2.10)
			Anastrozole	Placebo	HR (95% CI)	Anastrozole	Placebo	
IBIS-II	3,864	131 months (median)	85	165	0.51 (0.39 to 0.66)	2	3	Not reported
			Exemestane	Placebo	HR (95% CI)	Exemestane	Placebo	HR (95% CI)
MAP.3	4,560	35 months (median)	11	32	0.35 (0.18 to 0.70)	1	0	Not reported
			Low-fat	Control	HR (95% CI)	Low-fat	Control	HR (95% CI)
WHI DM	48,835 ^a	19.6 years (median)	1,299 (0.44%)	2,075 (0.46%)	0.95 (0.89 to 1.02)	132 (0.037%)	251 (0.047%)	0.79 (0.64 to 0.97)
			CEE	Placebo	HR (95% CI)	CEE	Placebo	HR (95% CI)
WHI CEE-alone	10,739	20.3 years (median)	238 (0.30%)	296 (0.37%)	0.78 (0.65 to 0.93)	30 (0.031%)	46 (0.046%)	0.60 (0.37 to 0.97)

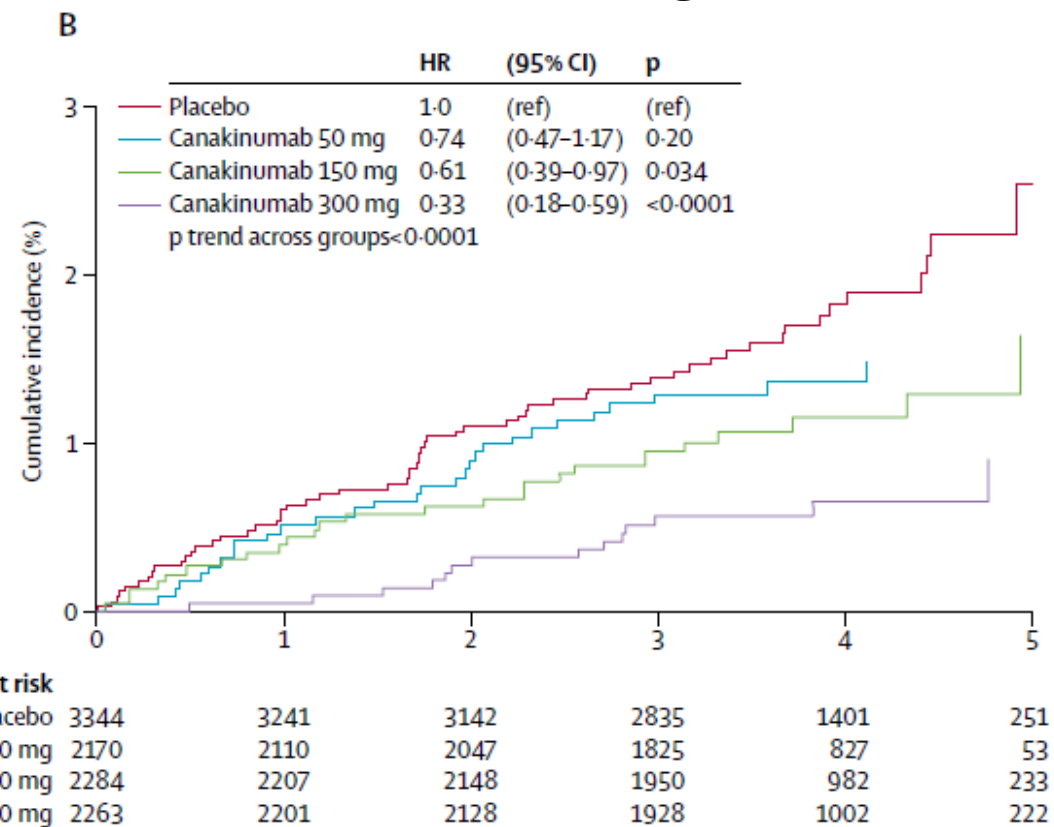


Canakinumab (anti IL1b) and lung cancer incidence among smokers (Cantos)

Incidence all cancers



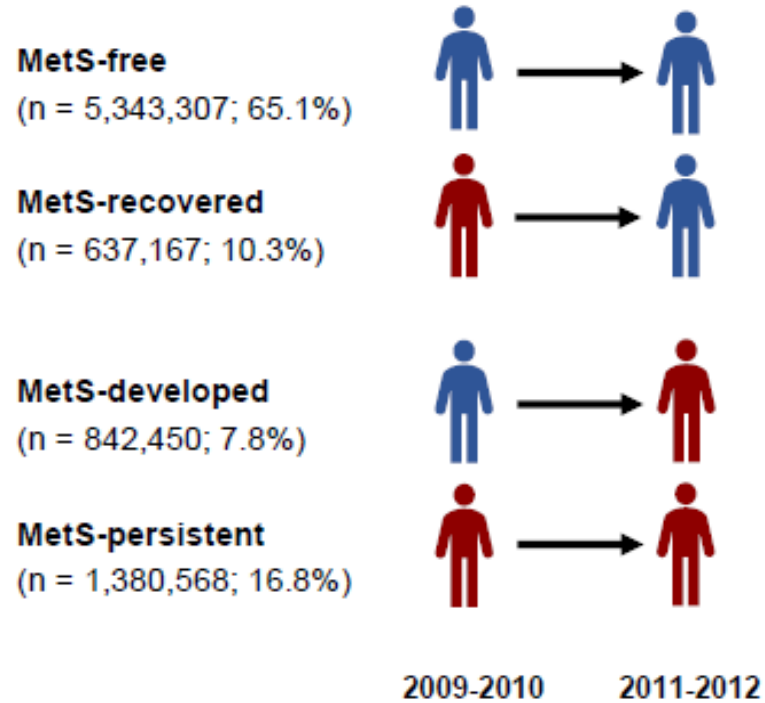
Incidence lung cancer



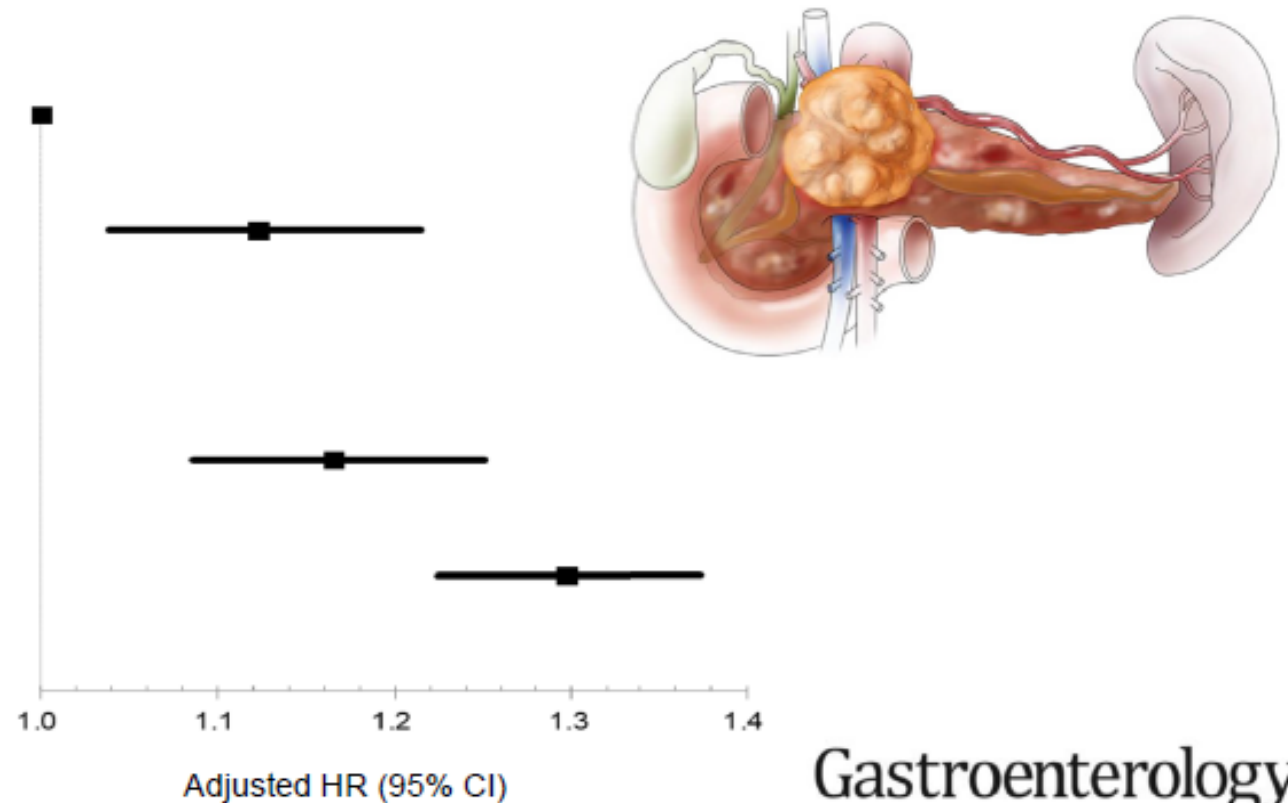
Tissue reprogramming and reversion: possible?

Dysmetabolism and pancreatic cancer

Changes in metabolic syndrome (MetS) status



Risk of pancreatic cancer during the study period



Gastroenterology

Plan

- Pourquoi combiner détection et interception
- Détecter précocement... le cancer ou la carcinogenèse?
- La détection par biopsie liquide est elle actionable?
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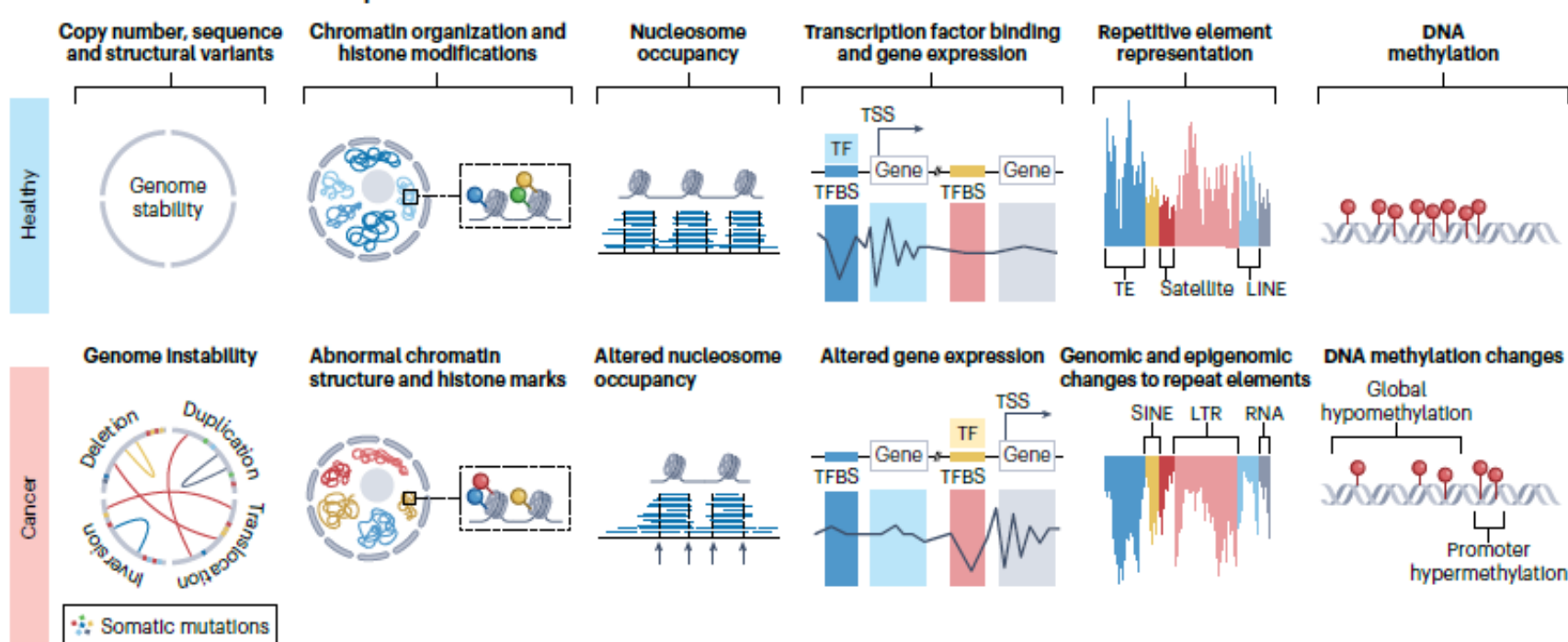
Biopsie liquide pour la détection précoce des cancers

Genomic and fragmentomic landscapes of cell-free DNA for early cancer detection

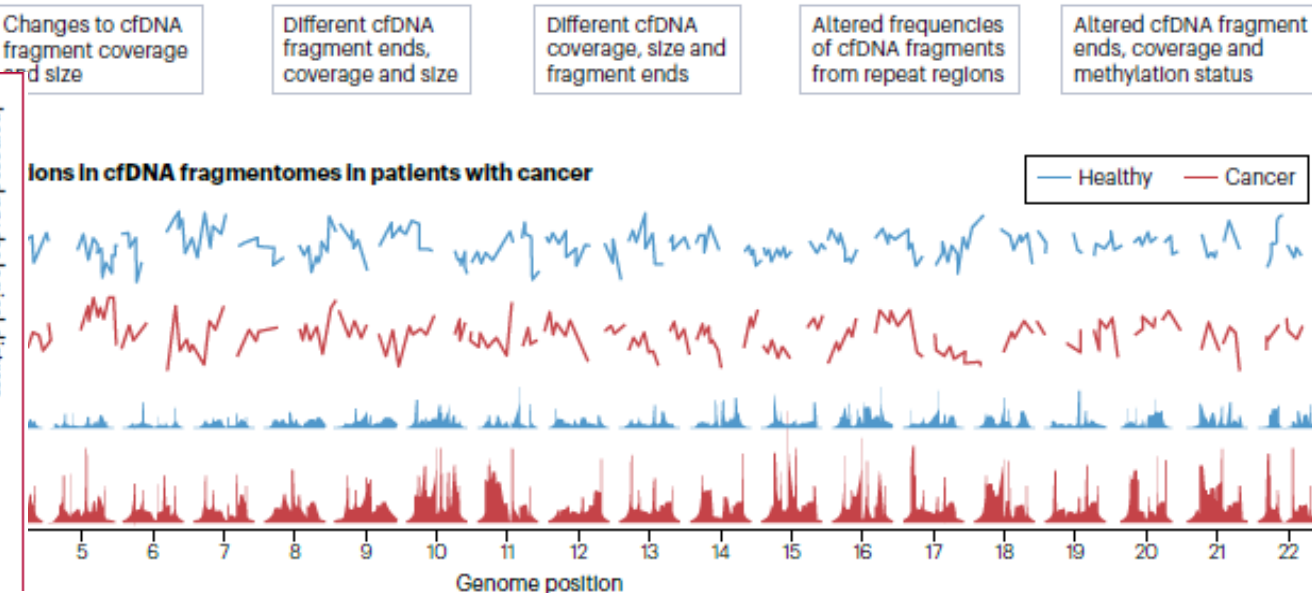
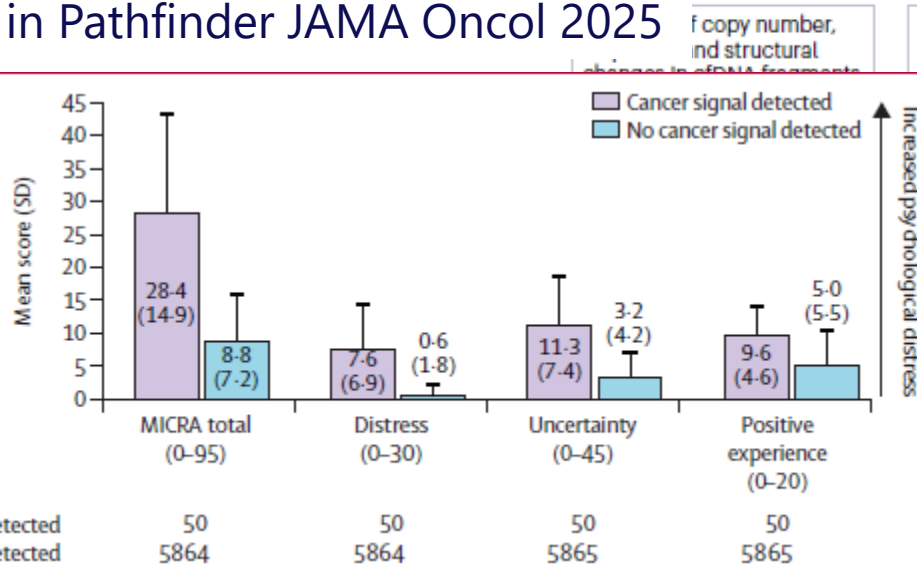
Daniel C. Bruhm¹, Nicholas A. Vulpesu¹, Zachariah H. Foda^{1,2}, Jillian Phallen¹, Robert B. Scharp^{1,3} & Victor E. Velculescu^{1,2}

Nature Reviews Cancer | Volume 25 | May 2025 | 341-358

a Altered cfDNA characteristics in patients with cancer



Distress in Pathfinder JAMA Oncol 2025



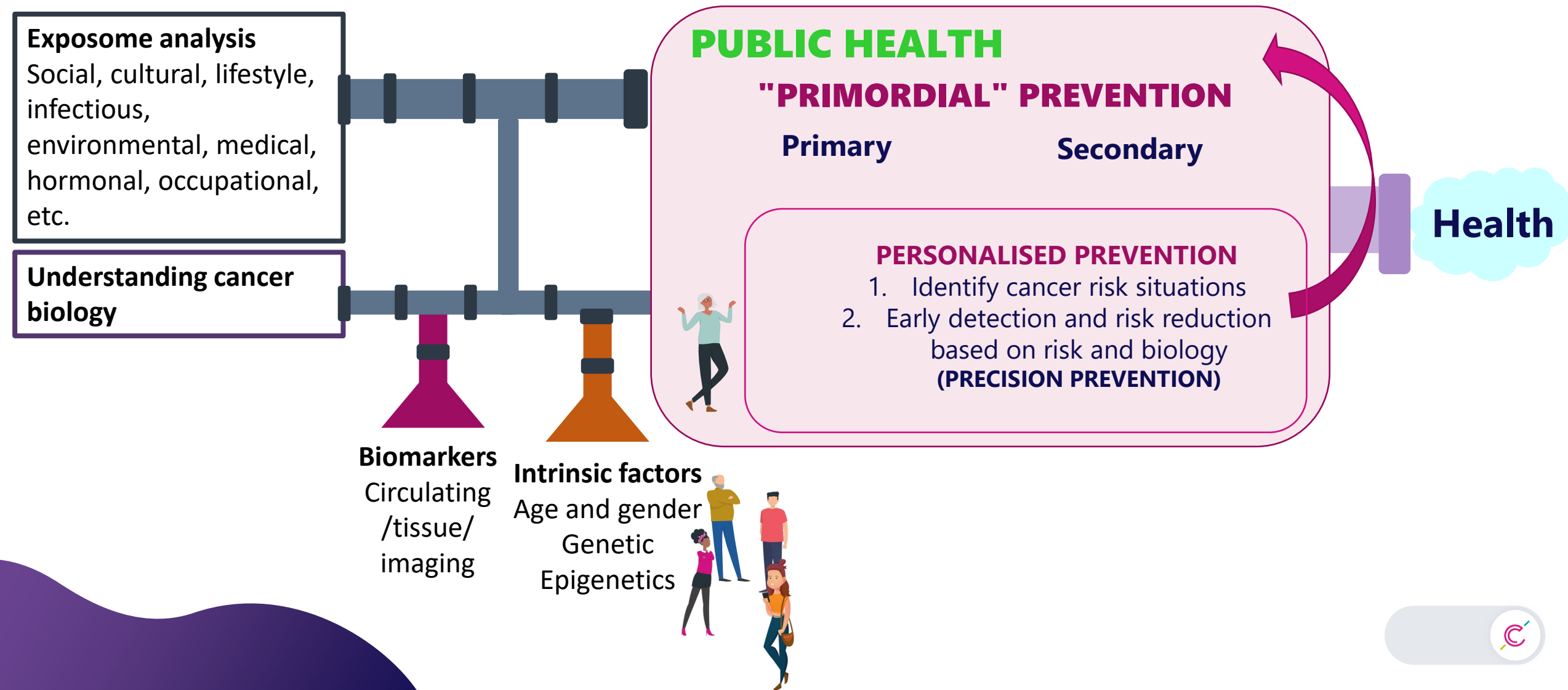
Biopsie liquide : « actionabilité »?

- En oncologie de précision: pas sur les techniques actuelles ADNc, oui avec d'autres biomarqueurs (cft présentations du jour)
- En chirurgie: intérêt du mini invasif, développement de la RI, mais surtout de l'imagerie de détection précoce associée!
- Intérêt de développer les réponses thérapeutiques associées à la détection précoce!!

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Precision cancer prevention must be built **at the public health level**



Precision prevention: germline genetics have opened the path

Focus on (some) high penetrance genetic conditions

Germline alterations - cancer	Early detection means (LoE)	Risk reduction measures (LoE)
BRCA1/2 – breast and ovarian	Breast MRI (+ mammography) (IIA)	Prophylactic mastectomy (IIA) and adnexectomy (IIA), endocrine therapies (IIIB), lifestyle interventions (IV)
Other BC genes – breast and ovarian	<i>Low level evidence, attitude derived from BRCA1/2 data</i>	
Lynch syndrome – broad spectrum	Colonoscopy/gastroscopy, pelvic ultrasound, etc. (II-III)	Prophylactic hysterectomy and adnexectomy (III), lifestyle (IV), aspirin (IIB)
Multiple genes - Pancreatic cancer	Pancreatic MRI / endoscopic ultrasound (III)	Lifestyle (IV)
TP53 – broad spectrum	Breast MRI (III), whole body MRI (IIB), other	Prophylactic mastectomy (IV) lifestyle (IV)

PRECISION PREVENTION IS ON THE WAY!

Effect of invitation to colonoscopy versus faecal immunochemical test screening on colorectal cancer mortality (COLONPREV): a pragmatic, randomised, controlled, non-inferiority trial

Antoni Castells*, Enrique Quintero*, Luis Bujanda, Susana Castán-Cameo, Joaquín Cubiella, José Díaz-Tasende, Ángel Lanas, Akiko Miquel Serra-Burriel, Eladio Frías-Arrocha, Cristina Hernández, Rodrigo Jover, Montserrat Andreu, Fernando Carballo, Juan Diego Mo Dolores Salas, Raquel Almazán, Inmaculada Alonso-Abreu, Jesús M Banales, Vicent Hernández, Isabel Portillo, Mercedes Vanadocha Mariola de la Vega, on behalf of the COLONPREV study investigators†

The Lancet 2025

JAMA Oncology | Original Investigation

Low-Dose Aspirin for Individualized Cancer Prevention in Older Adults A Secondary Analysis of the ASPREE Randomized Clinical Trial

Group	No. (%) of participants	Participants with incident cancer (n = 1009)		HR (95% CI)
		No. (%) of placebo events	No. (%) of aspirin events	
All participants	9350 (100)	513 (25.3)	496 (24.4)	0.96 (0.85-1.09)
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Test for heterogeneity: $P = .02$

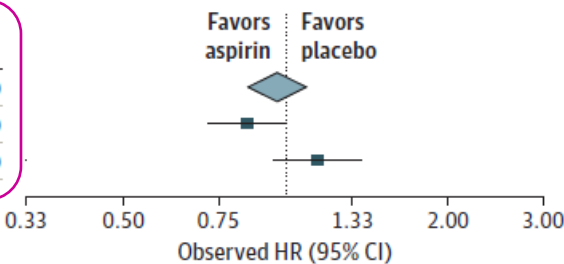
New Engl J Med 2025

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Assessment of a Polygenic Risk Score in Screening for Prostate Cancer

J.K. McHugh,^{1,2} E.K. Bancroft,^{1,2} E. Saunders,¹ M.N. Brook,¹ E. McGrowder,¹ S. Wakerell,¹ D. James,^{1,2} R. Rageevakumar,¹ B. Benton,^{1,2} N. Taylor,^{1,2} K. Myhill,^{1,2} M. Hogben,^{1,2} N. Kinsella,^{2,3} A.A. Sohaib,² D. Cahill,² S. Hazell,² S.J. Withey,² A. Osborne,^{1,2} S. Benafif,^{1,4} A.-B. Jones,^{1,2} D. Patel,⁵ J. Weller,² R. Nicholson,² F. Croft,² J. Sobczak,² C. McNally,² J. Easton,² Q. Karlsson,¹ T. Dadaev,¹ S. Saya,^{1,6} S. Merson,¹ S. Hussain,¹ A. Thwaites,¹ S. Hussain,¹ I. Rafi,⁷ M. Ferris,⁸ S. Pashayan,⁹ Z. Kote-Jarai,¹ and R.A. Eeles,^{1,2} for the Screening Committee and Collaborators*



Modelling is key!!

Subgroups varying in risk and density highlight the potential for stratified breast cancer screening

Eugenio Gil Quessep^{a,*}, Danielle van der Waal^{b, ID}, Jim Peters^{c, ID}, Suzette Delaloge^d, Carla van Gils^e, Harry J. de Koning^{a, ID}, Mireille Broeders^{b, c, ID}, Nicolien van Ravesteyn^{a, ID}

European Journal of Cancer 217 (2025) 115220

Benefits and harms of
mammographic screening by
risk and density (NL)

The one size fits all model
could be improved
importantly!

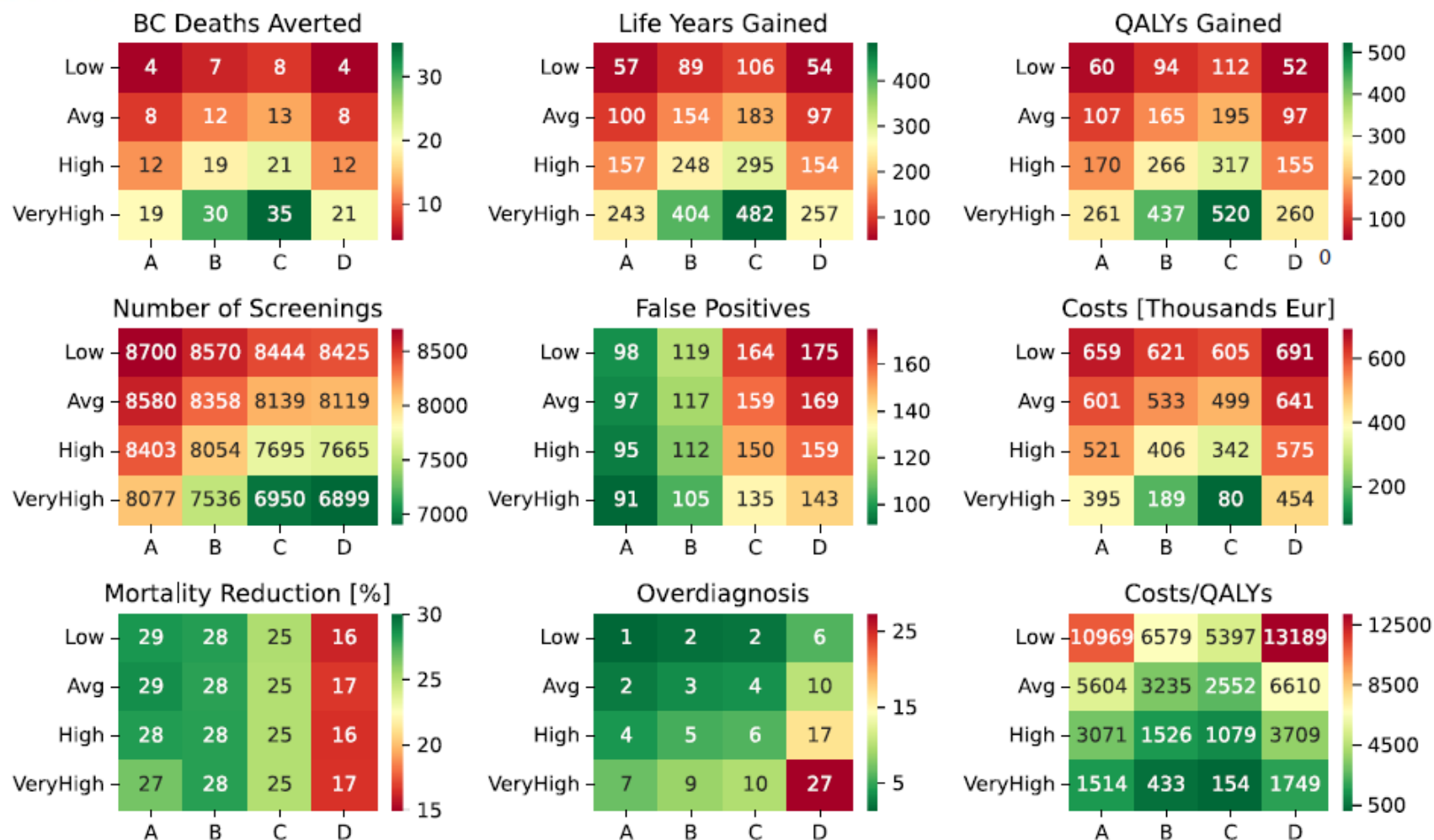
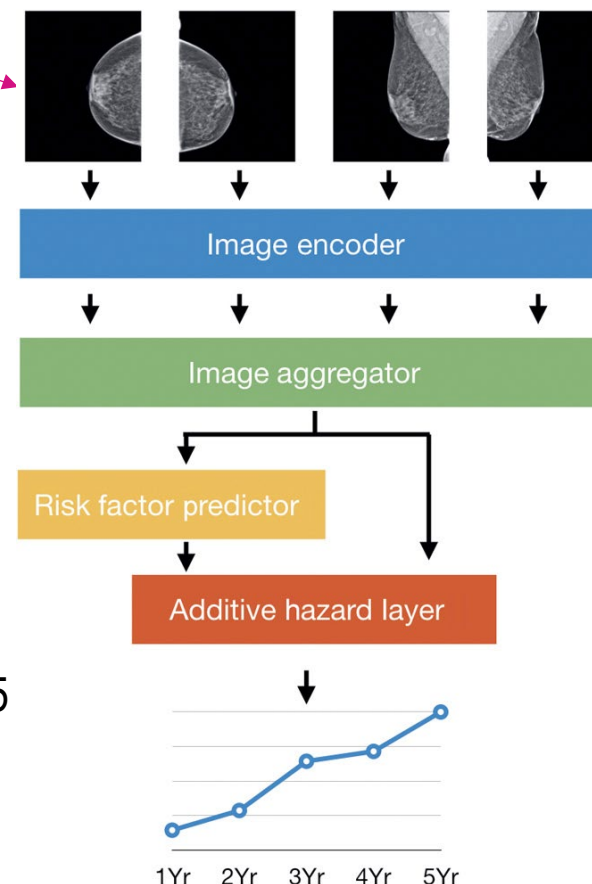
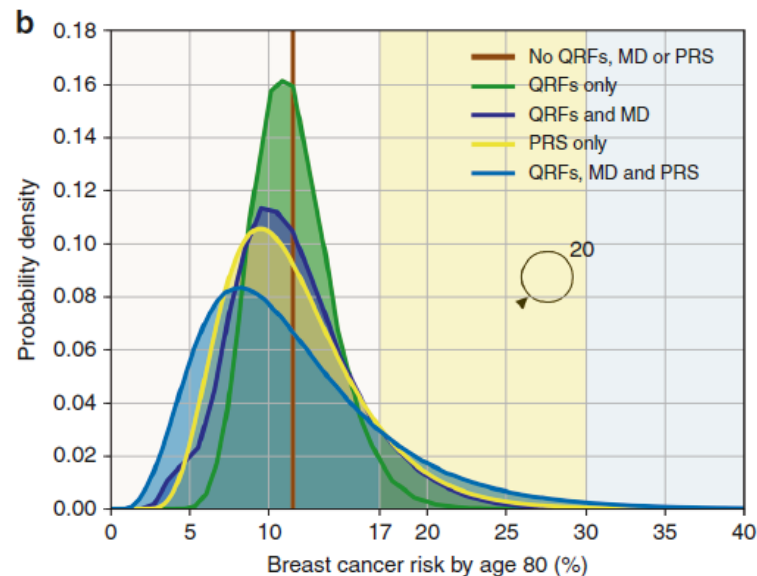
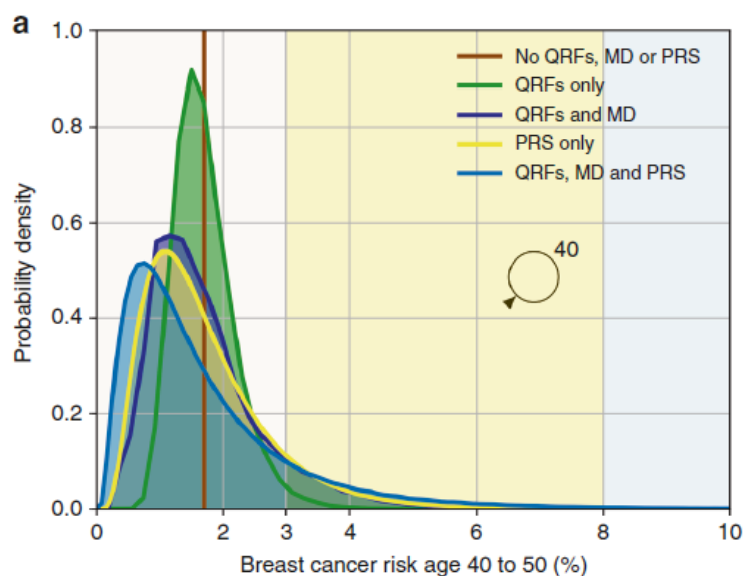


Fig. 1. Heatmaps of outcomes per 1000 women from a one-size-fits-all screening strategy. Results from nine health and economic outcomes when performing mammography every 2 years from age 50–74y for each subgroup of risk level and breast density. BC: breast cancer; QALYs: quality-adjusted-life-years.

Predicting cancer risk: clinical data- or image/IA-based?

BREAST CANCER

Personal genetics (SNP scores) + exposures + timely biomarkers



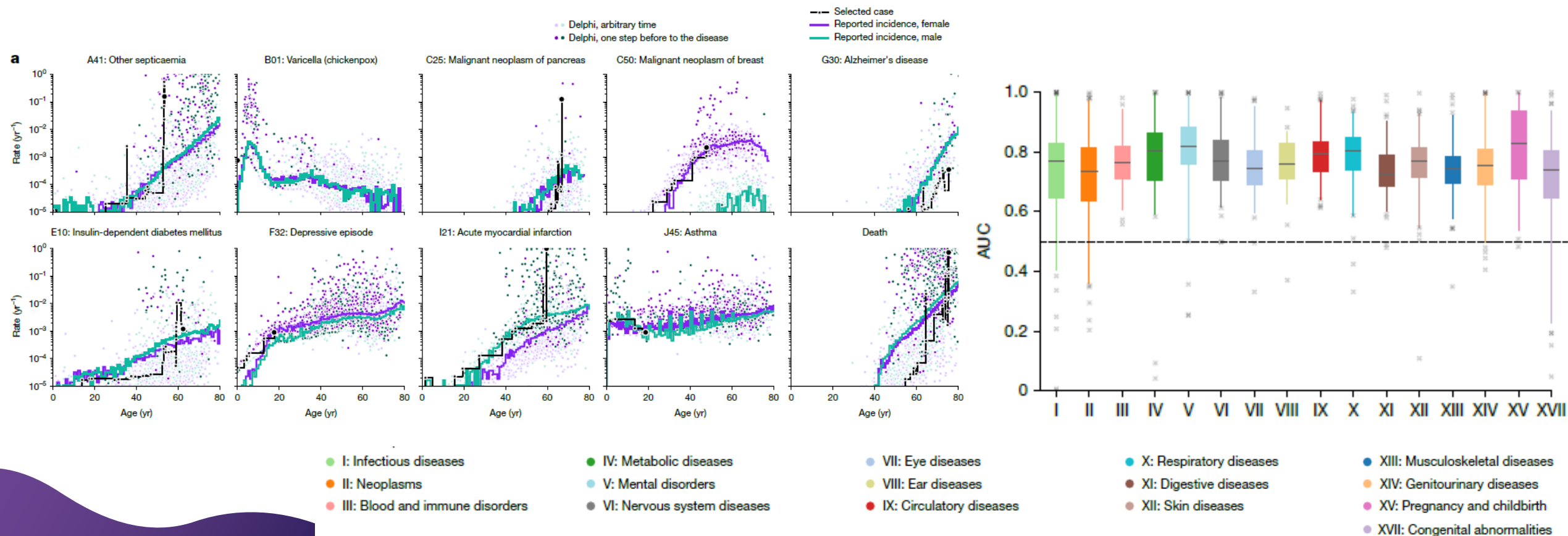
Clairity™ FDA release June 2025

Lee genet Med 2019
Lehmann J Natl Cancer Inst 2022

Predicting cancer risk: disease-specific versus pan-health?

Learning the natural history of human disease with generative transformers

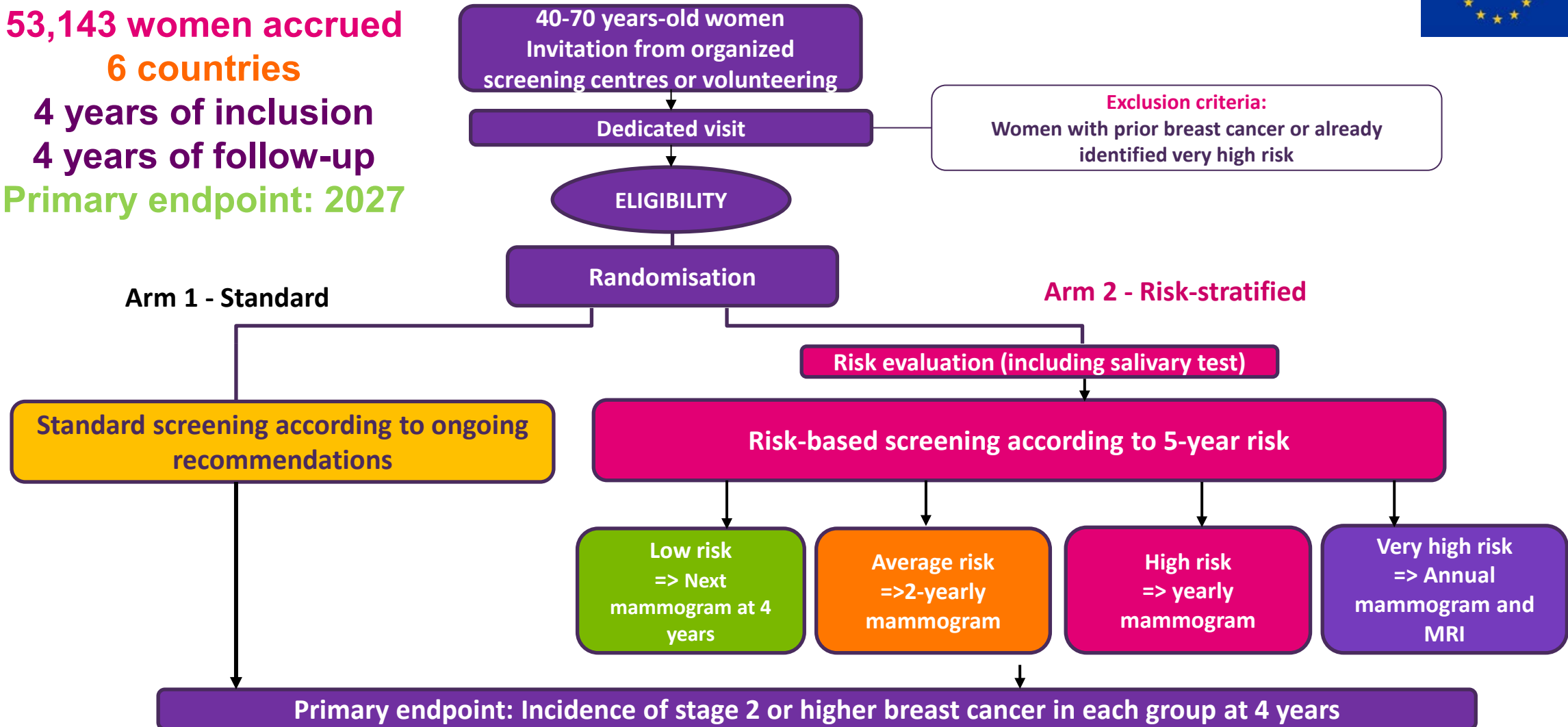
<https://doi.org/10.1038/s41586-025-09529-3>



Demonstrating the value of risk-based BC screening

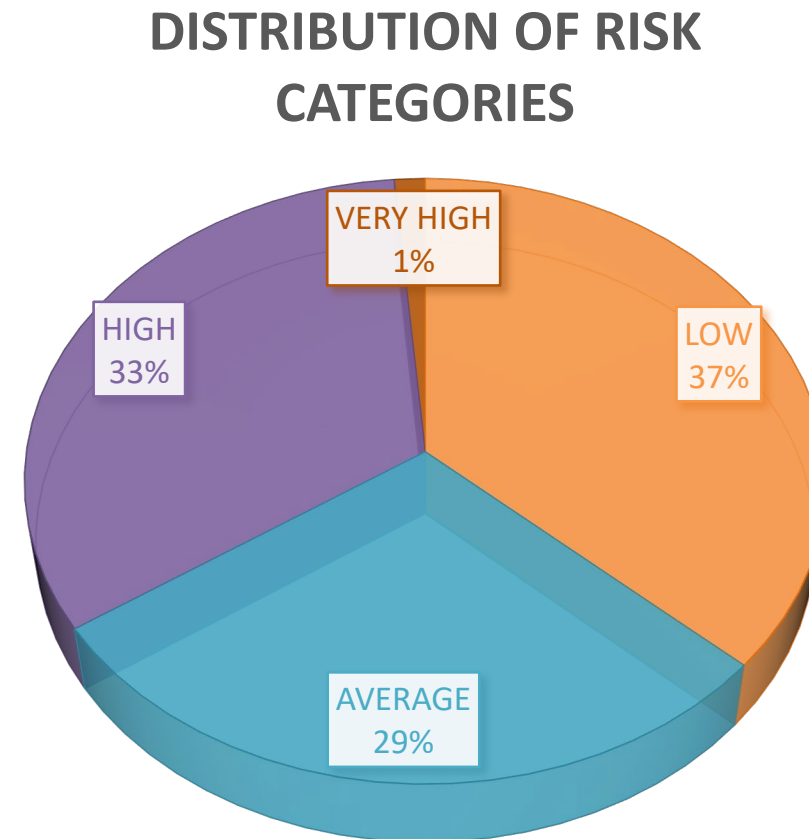
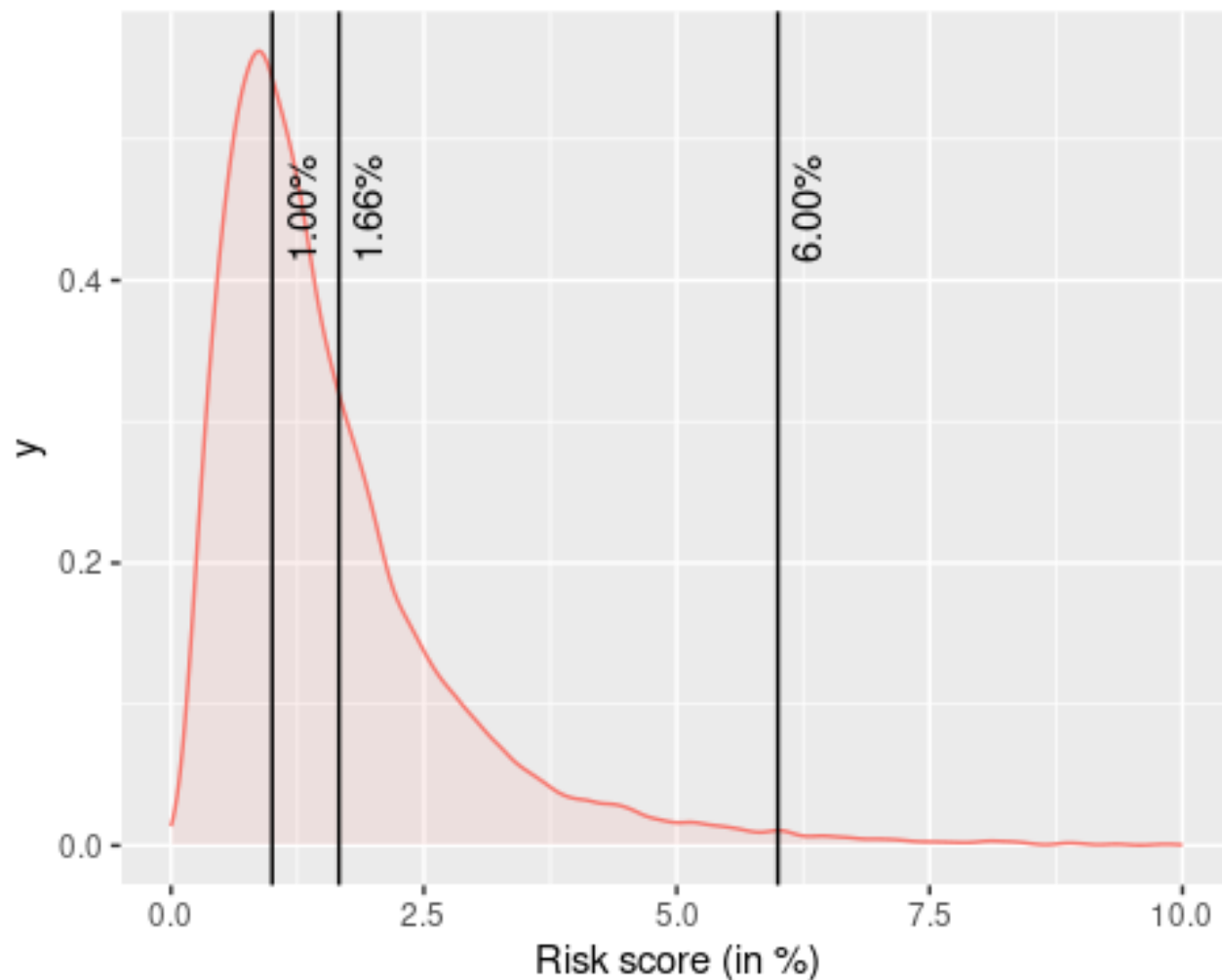


53,143 women accrued
6 countries
4 years of inclusion
4 years of follow-up
Primary endpoint: 2027





Distribution of complete risk score & risk categories (all)





- Ipina et al, Early detection conf 2025

[illegible]

Construire les parcours de prevention - INTERCEPTION pilot program

INTERCEPTION is a unique and innovative pilot program for personalized prevention in people at high risk of cancer.

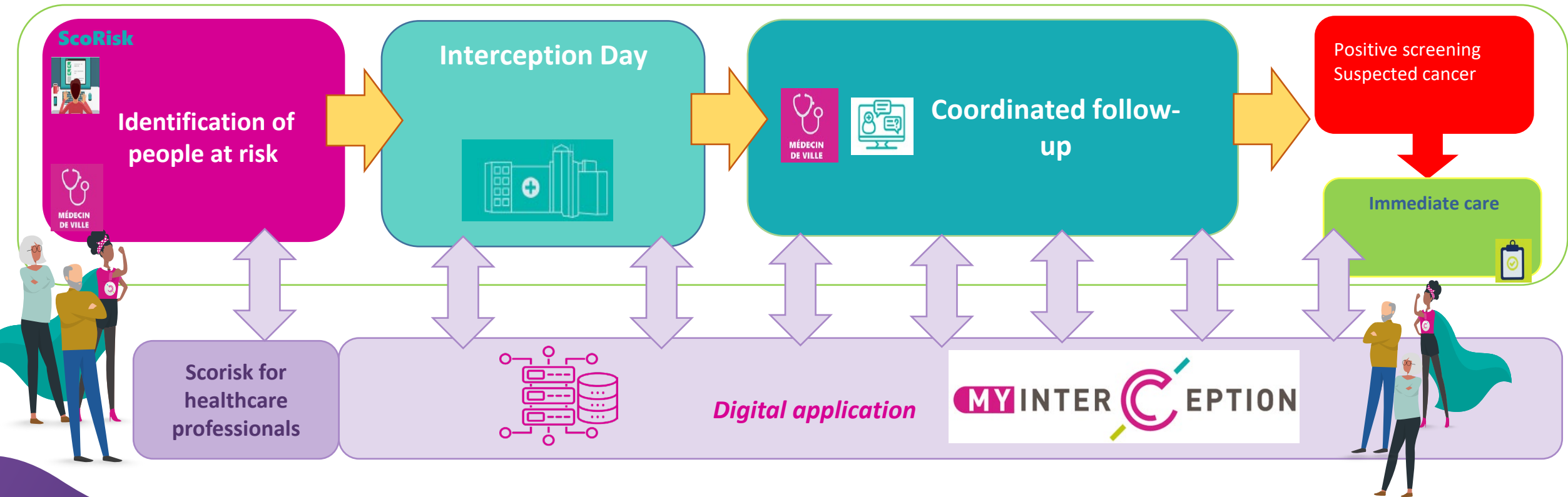
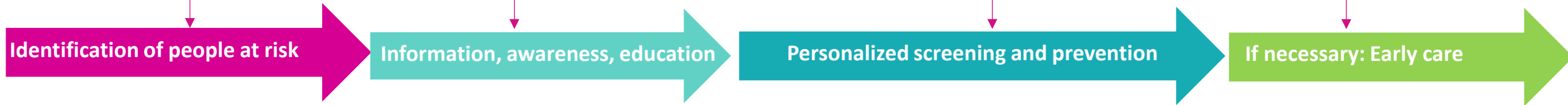
- It enables and structures a new, largely digitalized healthcare pathway dedicated to
- It is based on a replicable mixed digital and physical city-hospital infrastructure.
- It aims to scientifically demonstrate the benefits of this new healthcare pathway for individuals and society
- and to develop high-level research in prevention to improve the health of those concerned.

INTERCEPTION provides a new, systematic, organized, and innovative way to

- Identify people at risk
- Inform them and help them make preventive choices
- Set up a personalized prevention and early detection monitoring program
- Provide high-quality and rapid care in cases of suspected cancer or cancer.

A mixed physical and digital community-hospital personalized prevention program for patients at high risk of cancer, rolled out nationwide

4 pillars

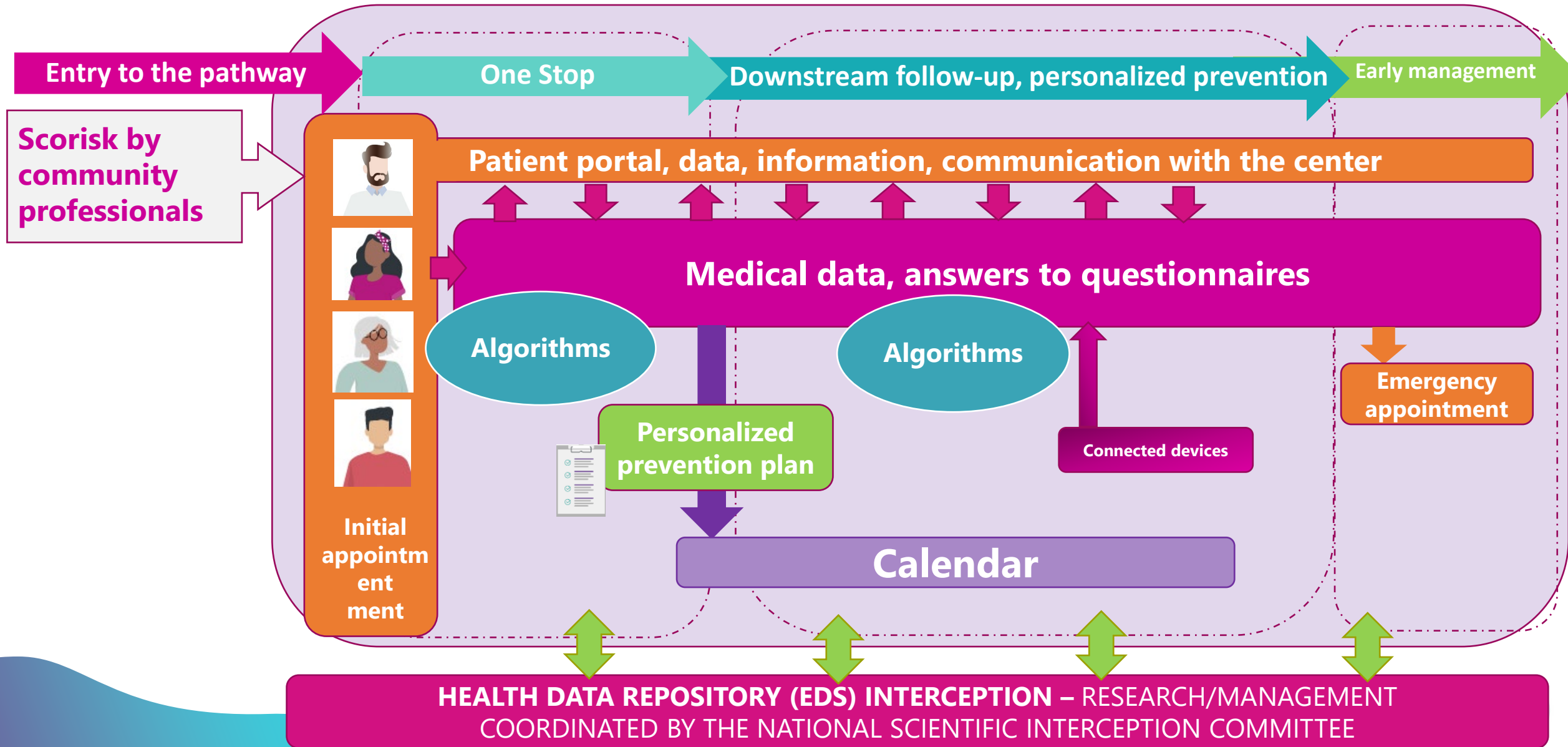


Interception pathways

interception@gustaveroussy.fr

Pathway: risk situation	Who
High breast cancer risk – non genetic 	Women at high risk of breast cancer > 2.5% at age 5 (family history, atypical lesions, composite score, etc.)
High risk of pancreatic adenocarcinoma 	erPeople <u>over</u> 45 with two first-degree relatives with pancreatic cancer, or TIPMP, or chronic pancreatitis, or germline mutations: <i>CDKN2A</i> , Peutz Jeghers, <i>BRCA2</i> , <i>BRCA1</i> , <i>PALB2</i> , <i>ATM</i> , or Lynch with one family history
High risk of lung cancer 	People $\geq$ 50 years <u>old</u> , smoking > 20 pack-years and quit < 10 years ago
High risk of hepatocellular carcinoma (2025)	People with liver fibrosis from any cause, including MASH
High risk of (non genetic) colon cancer	Family history without predisposition, high-risk polyps, other
BRCA syndrome and co	Women with germline mutations in the <i>BRCA1</i> , <i>BRCA2</i> , <i>PALB2</i> genes
Lynch syndrome	Carriers of germline mutations in the <i>MLH1</i> , <i>MSH2</i> , <i>MLH6</i> , or <i>PMS2</i> genes
BRCA for men	Men who carry germline mutations in the <i>BRCA1</i> , <i>BRCA2</i> genes
Carriers of TP53 mutations (2025)	People with a germline mutation in the <i>TP53</i> gene
ENT oral lesions at risk	Leukoplakia-type oral lesions, erythroplakia, actinic cheilitis
Childhood exposures	Adults exposed to chemotherapy and/or radiation therapy before age 18
CHIP carriers	Carriers of clonal hematopoiesis

A multifunctional digital platform/application supports all activities



Personalized prevention program: Clinical impact after 1 year

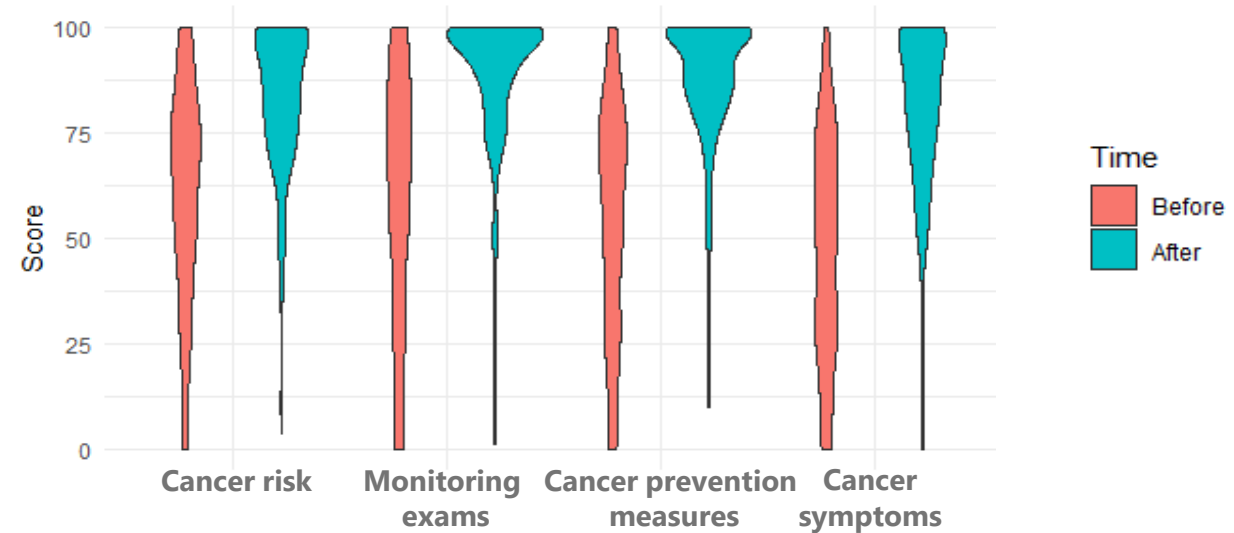


Improvement ≥ 1 point
WCRF 41%

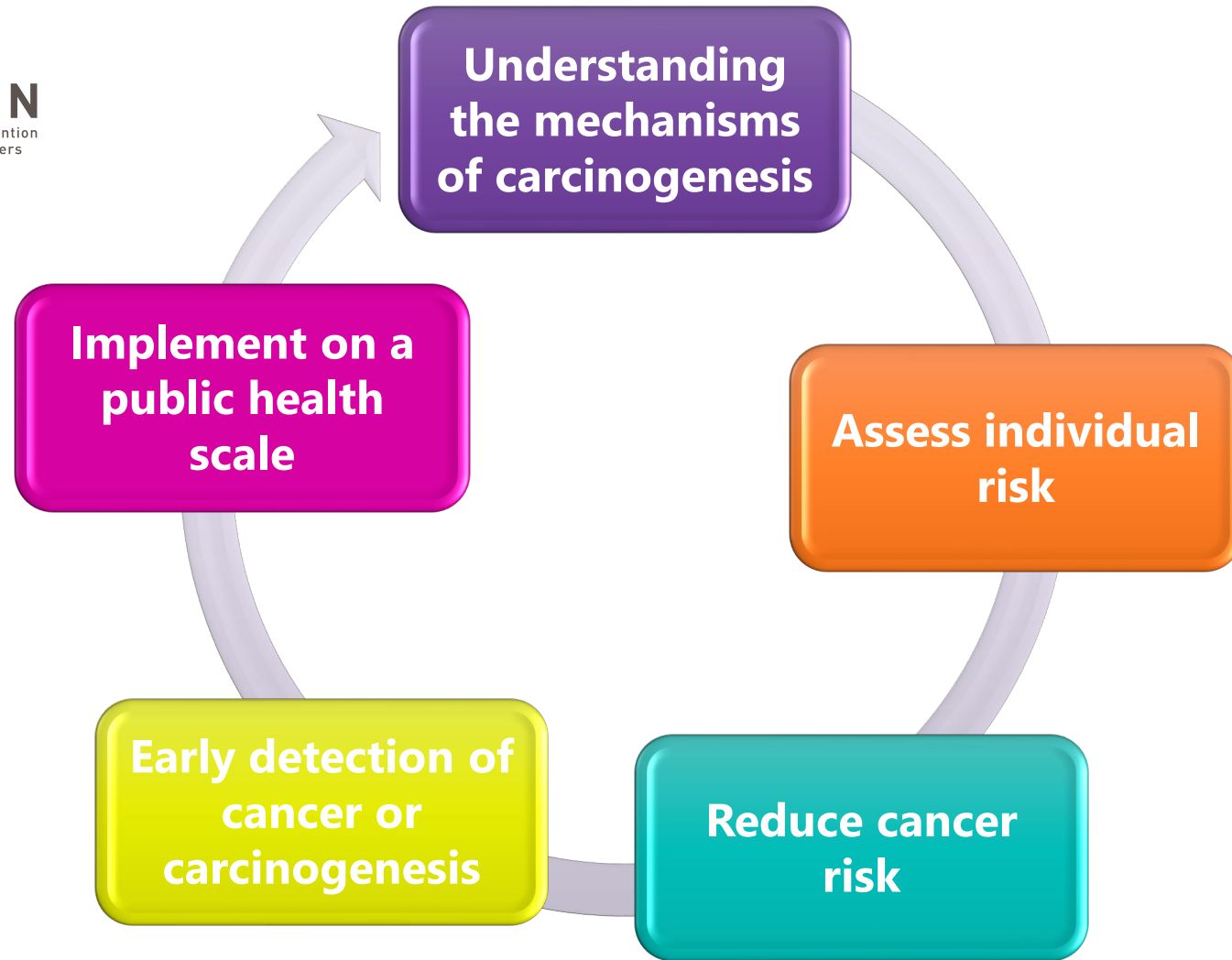


High adherence to
specialized screening
85-100%

Major increase in awareness

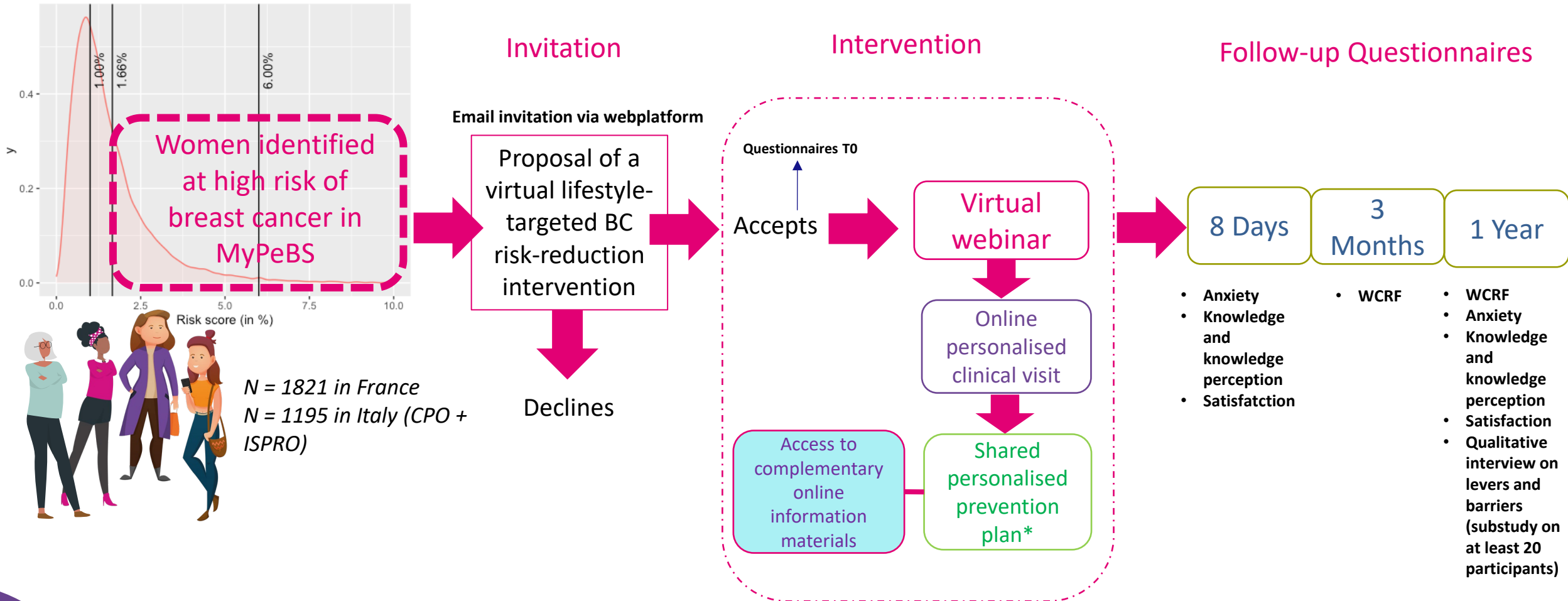


CROSSTALK AND CROSS FEEDING for precision prevention research



Fragmentation is a major issue!

Reunify screening and prevention MyPREV (JA-PREVENT NCD)

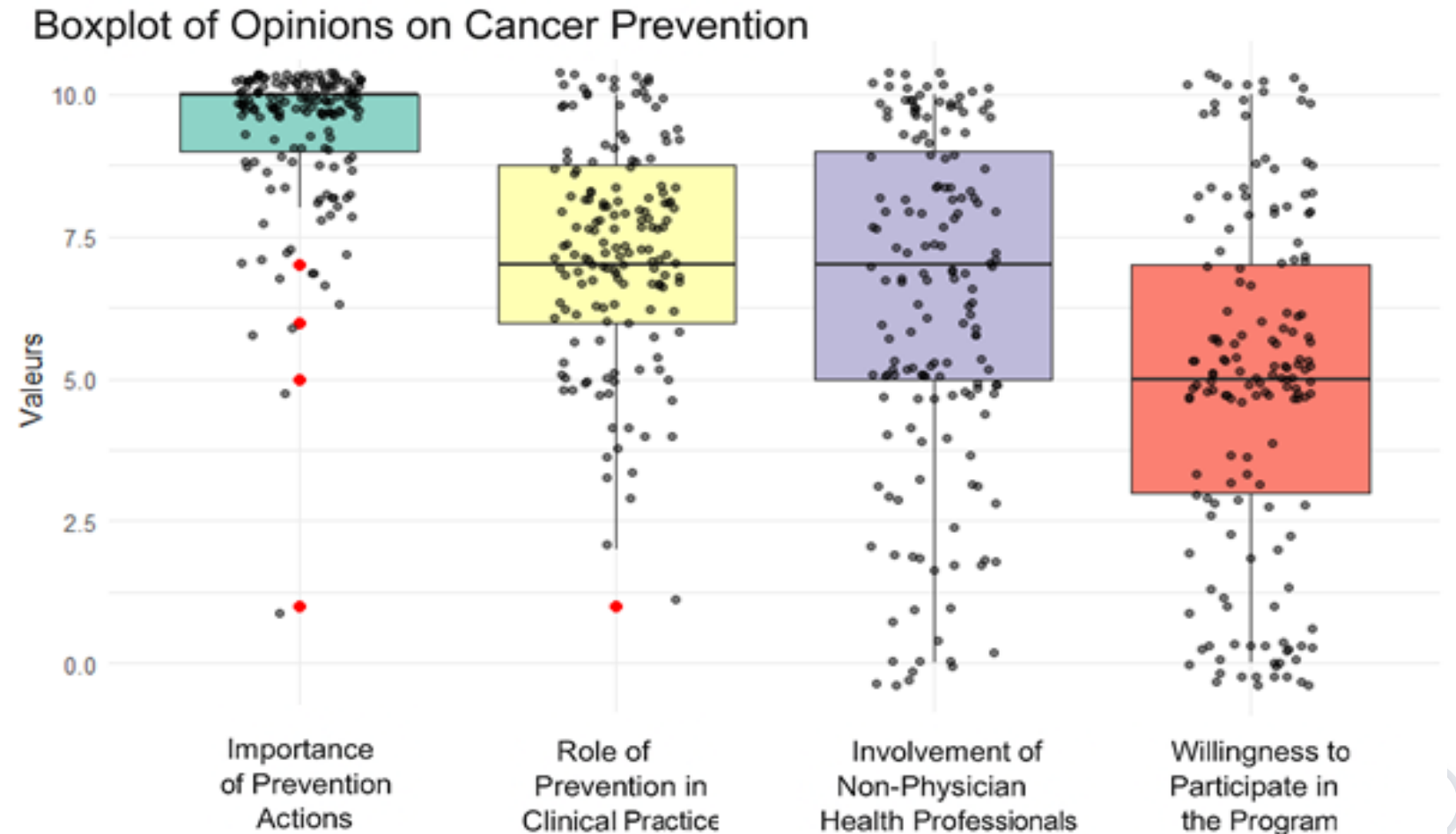


*Personalised (stratified and predefined) measures regarding weight, nutrition, physical activity, hormone exposures, other exogenous exposures to be discussed and decided in a shared decision process

Who is in charge of cancer prevention?

Perceptions and practices of general and personalized prevention (PP) of cancer in primary care and their determinants – a mixed method study

Primary care physicians with > 20 years practice had a decreased perception of the importance of cancer prevention (OR 0.3, 95% CI 0.13-0.7, $p=0.008$).



Plan

- Pourquoi combiner détection et interception
- La carcinogenèse en cours est elle une bonne cible?
- La détection par biopsie liquide est elle actionable
- La prévention de précision aujourd'hui
- Conclusions & perspectives

Conclusions and perspectives

- Primary and secondary prevention are key for the future of oncology
- Personalised (including precision) prevention has a great potential but :
 1. Requires large scale prospective demonstration before implementation
 2. Must be developed at the public health level
- Prevention research and prevention clinics are multidisciplinary!
- A close collaboration between research areas has the potential to accelerate developments in the field and tackle the major challenges



MERCI



INTERCEPTION
GUSTAVE ROUSSY
Le programme de prévention
personnalisée des cancers



DÉPISTAGE
DESCANCERS
Centre de coordination
Île-de-France



CANCEPT
Cancer Primary Prevention Transdisciplinary
Nutrition and Environment Research Network



CPTS de la Bièvre
Cachan | Chevilly-Larue | Fresnes | L'Hay-les-Roses | Rungis



PREVALUNG-EU



FONDATION PHILANTHROPIA

LOMBARD ODIER



université PARIS-SACLAY



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