

RPN 532 – Oncology for Scientist

An Introduction to Breast Cancer Translational Research

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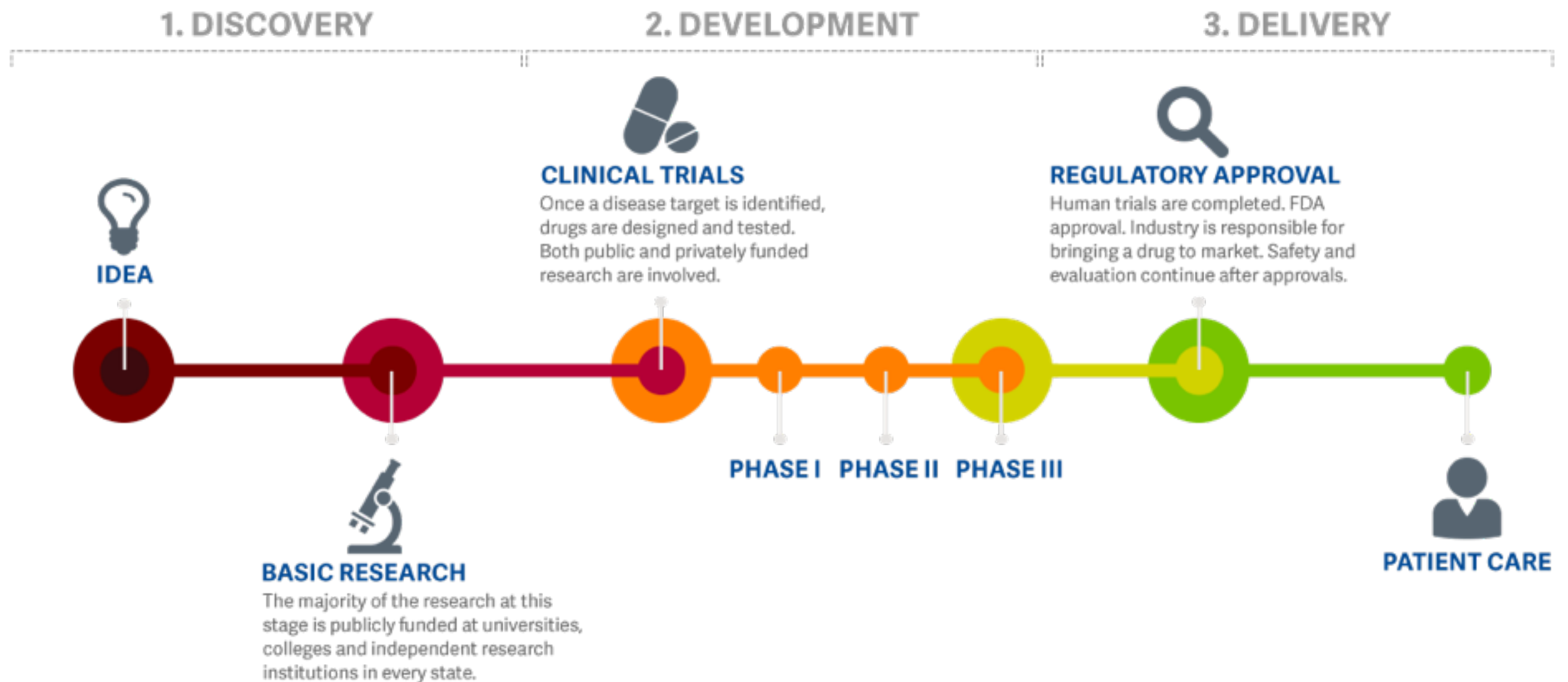
Roswell Park Cancer Institute

UNDERSTAND PREVENT
& CURE CANCER

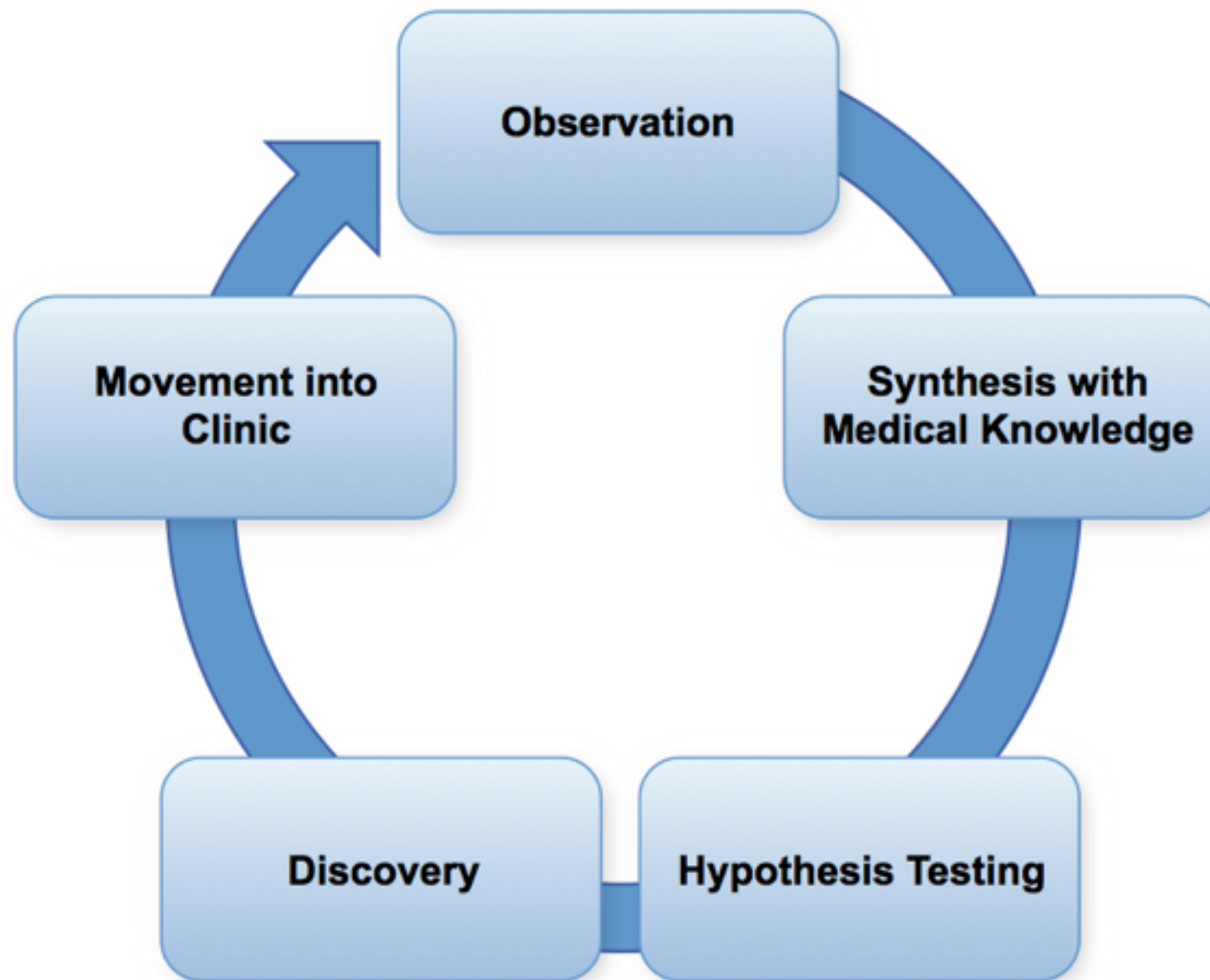


What is translational medicine?

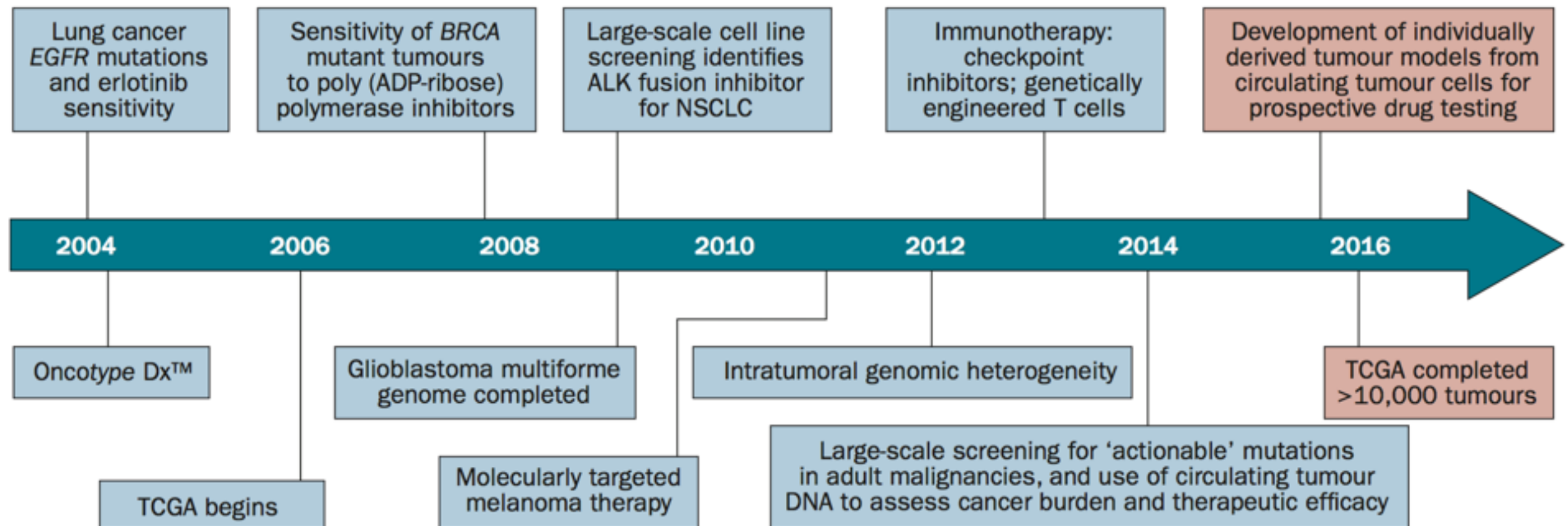
- **The application of a discovery to the practice of medicine - from “bench” to “bedside”**



Translational research cycle



Timeline of translational oncology in the last 10 years



Drugs developed on the basis of tumor biology

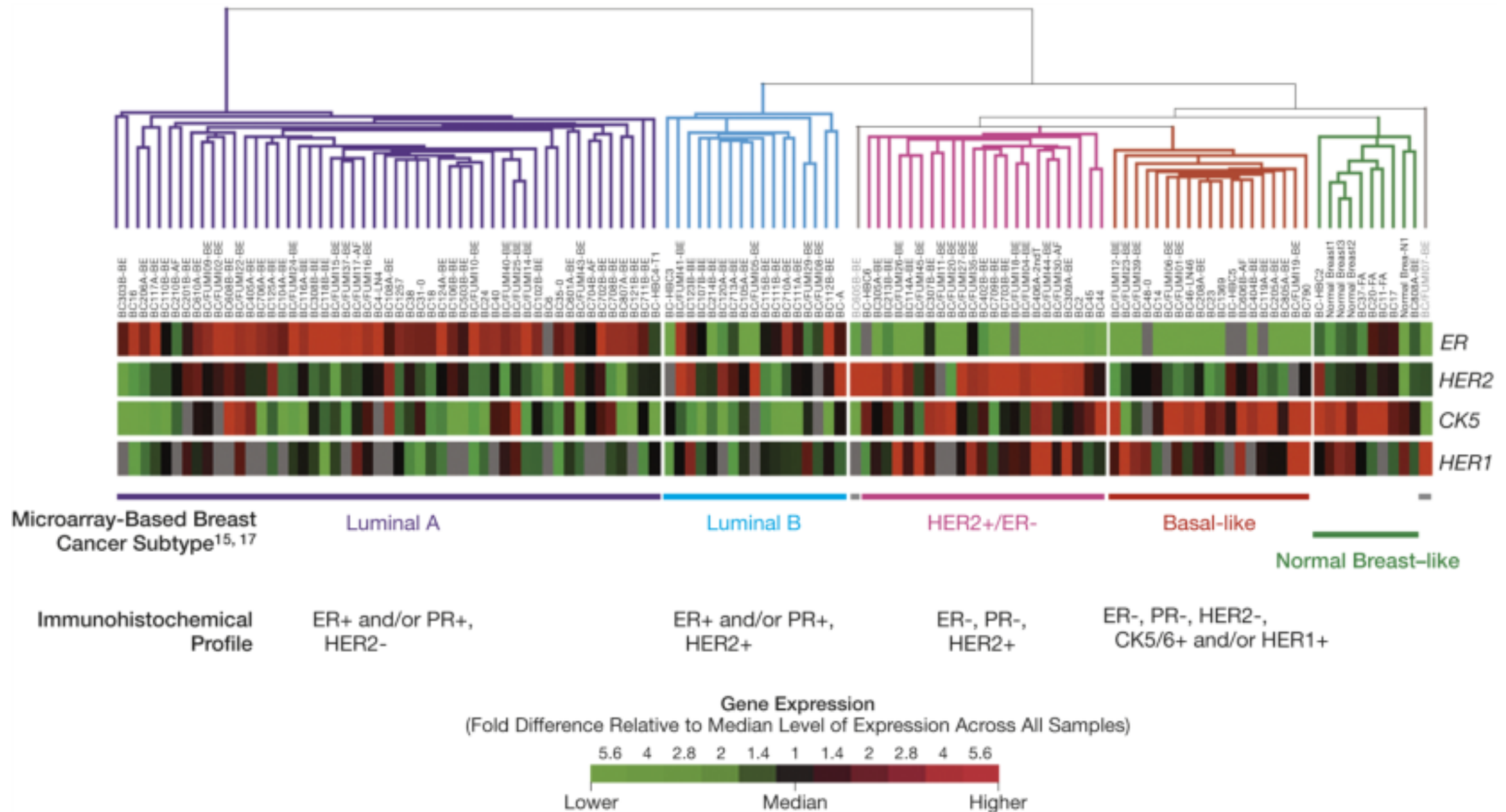
OCTOBER 2011 **CANCER DISCOVERY** | 383

Drug	Disease	Biology	Target	Mechanism of action
Tamoxifen (Nolvadex)	Breast	Estrogen dependence	Estrogen receptor	Selective estrogen receptor modulator
Fulvestrant (Faslodex)	Breast	Estrogen dependence	Estrogen receptor	Degradation of estrogen receptor
Anastrozole (Arimidex), letrozole (Femara), exemestane (Aromasin)	Breast	Estrogen dependence	Aromatase	Aromatase inhibitor
Trastuzumab (Herceptin)	Breast	HER2/neu expression drives cell growth and viability	HER2/neu extracellular domain	Binds HER2/neu, inhibits signaling, induces antibody-dependent cellular cytotoxicity
Abiraterone acetate (Zytiga)	Prostate	Androgen dependence	CYP17A1	Inhibits activity of CYP17, decreasing androgens to subcastration concentrations
Bicalutamide (Casodex), flutamide (Eulexin), nilutamide (Nilandron)	Prostate	Androgen dependence	Androgen receptor	Competitive inhibition of testosterone binding to androgen receptor
Leuprolide (Lupron)	Prostate	Androgen dependence	Gonadotropin-releasing hormone receptor agonist	Decreases circulating androgens
Imatinib (Gleevec)	Chronic myelogenous leukemia	Philadelphia chromosome	BCR-ABL tyrosine kinase abnormality produces oncogenic fusion protein BCR-ABL	TKI
Imatinib (Gleevec)	Gastrointestinal stromal tumors	cKIT drives proliferation and viability	cKIT tyrosine kinase	TKI
Dasatinib (Sprycel), nilotinib (Tasigna)	Chronic myelogenous leukemia	Mutations in BCR-ABL produce resistance to imatinib	BCR-ABL tyrosine kinase	TKI
Rituximab (Rituxan)	Lymphoma	CD20 is a commonly expressed surface antigen	CD20	Binds CD20 and activates antibody-dependent cellular cytotoxicity
Ipilimumab (Yervoy)	Melanoma	Immunogenicity of melanoma	CTLA4	Binds CTLA4, releasing inhibitory checkpoint
Drugs whose activity was revealed by later understanding of tumor biology				
Gefitinib (Iressa), erlotinib (Tarceva)	NSCLC	Activating mutations in EGFR increased dependence on target	EGFR	TKI
Bortezomib (Velcade)	Myeloma	Proteasomal inhibition in face of massive intracellular protein excess	Chymotrypsin-like β 5 subunit of the catalytic chamber of the 20S proteasome	Proteasome inhibitor

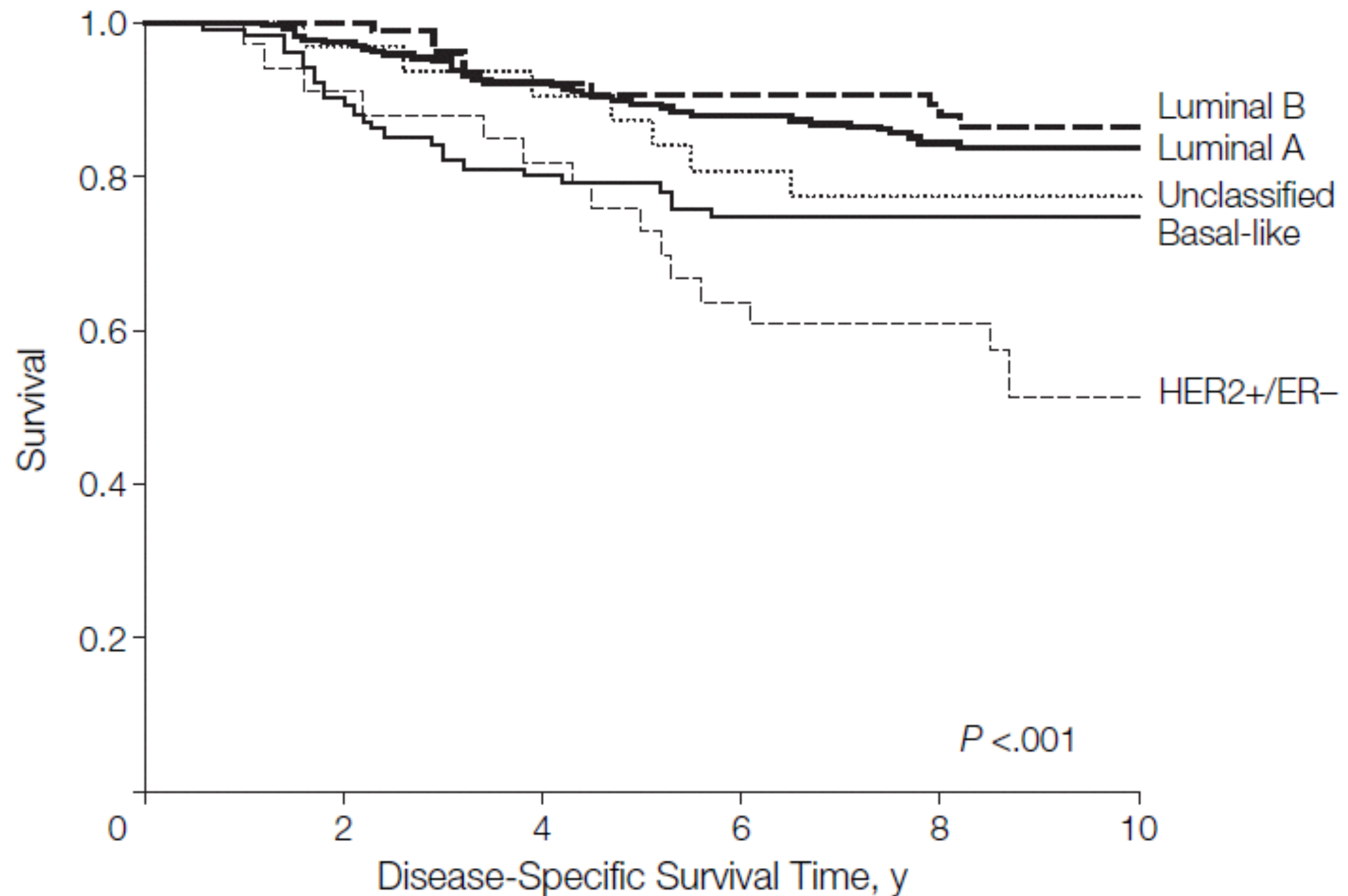
Breast cancer translational medicine

- **Multi-gene panels (e.g., OncoType Dx)**
- **CDK4/6 inhibitor – palbociclib**
- **Breast cancer immunotherapy**
- **Circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA)**
- **Balancing translational research between treatment and prevention**

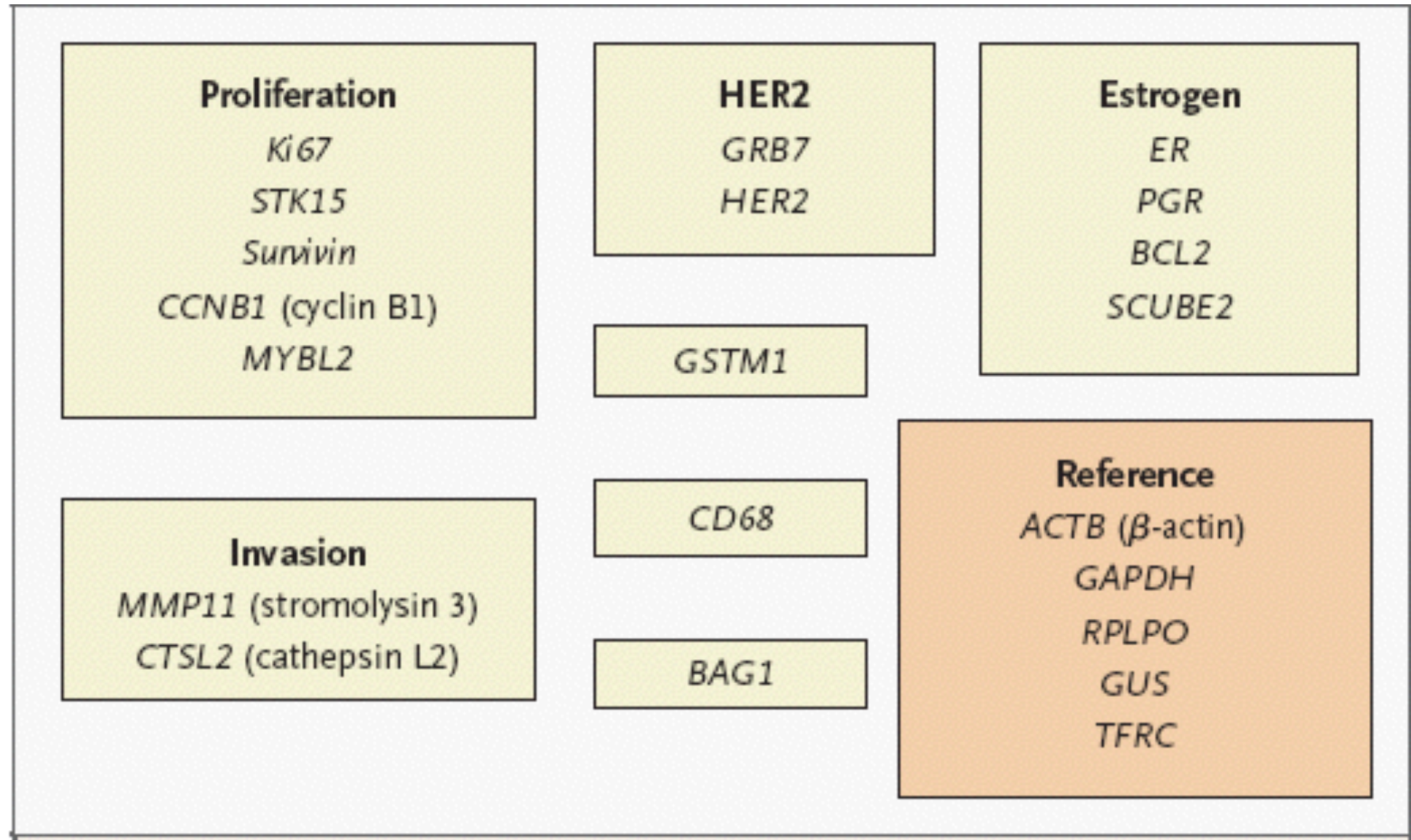
Breast Cancer Intrinsic Subtypes



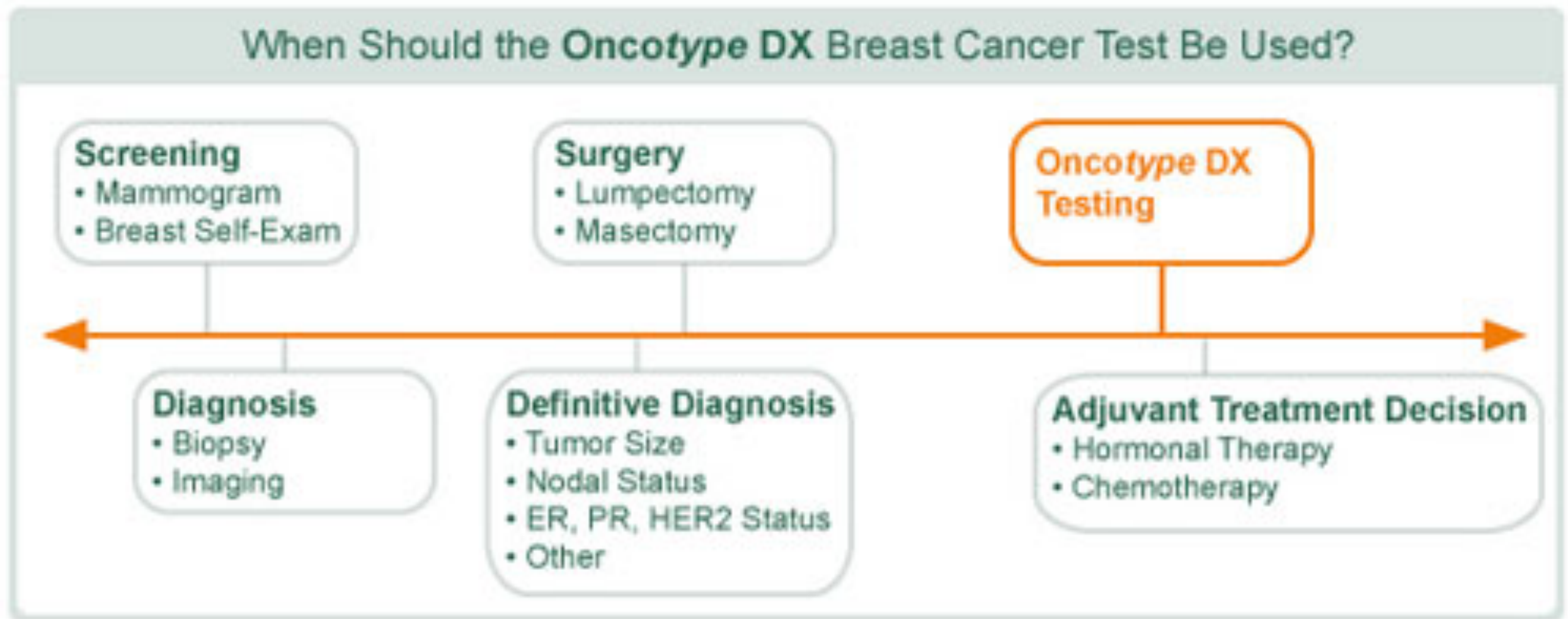
Intrinsic molecular subtypes



21-gene assay (Oncotype Dx)

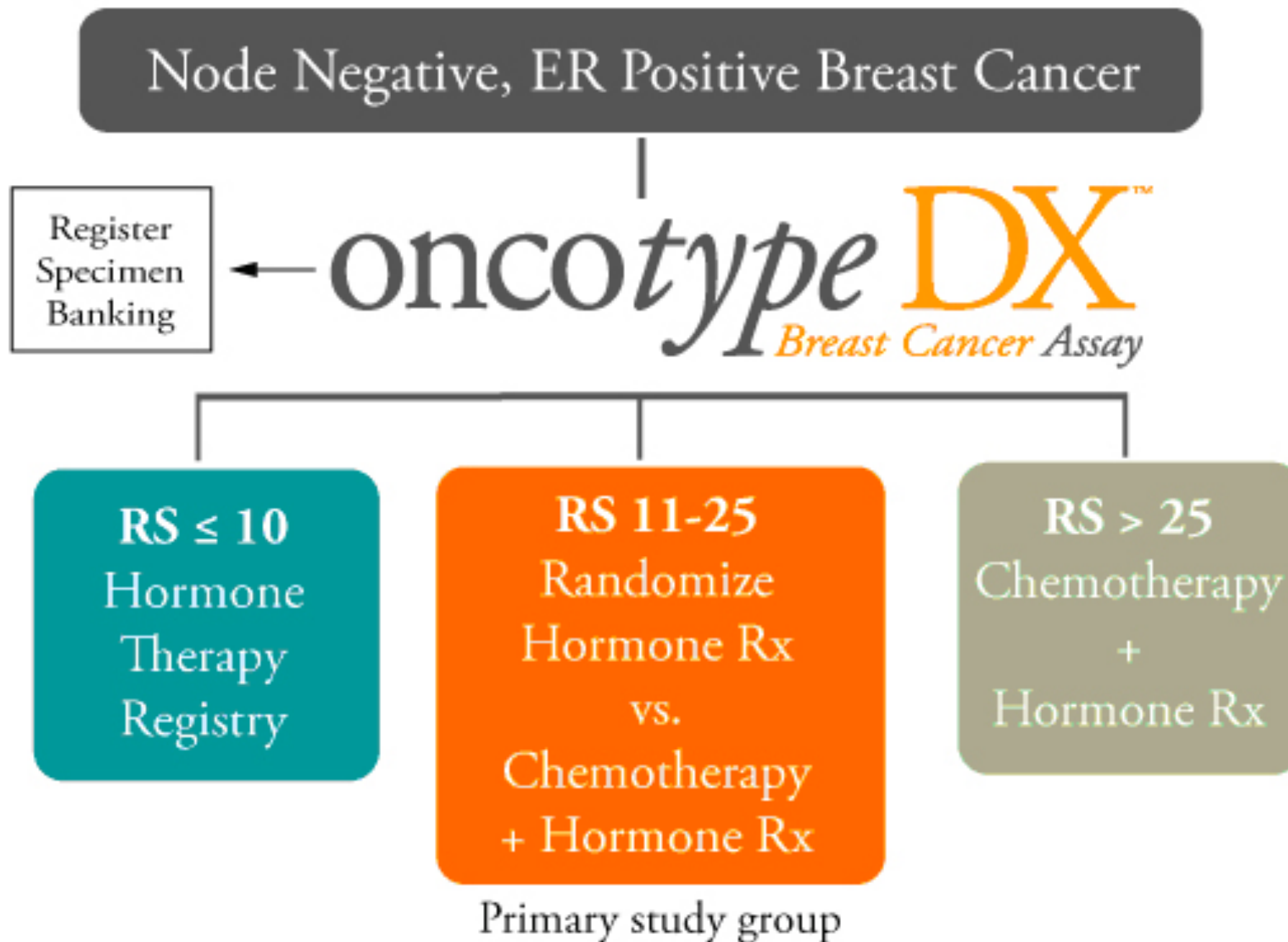


21-gene assay (Oncotype Dx)

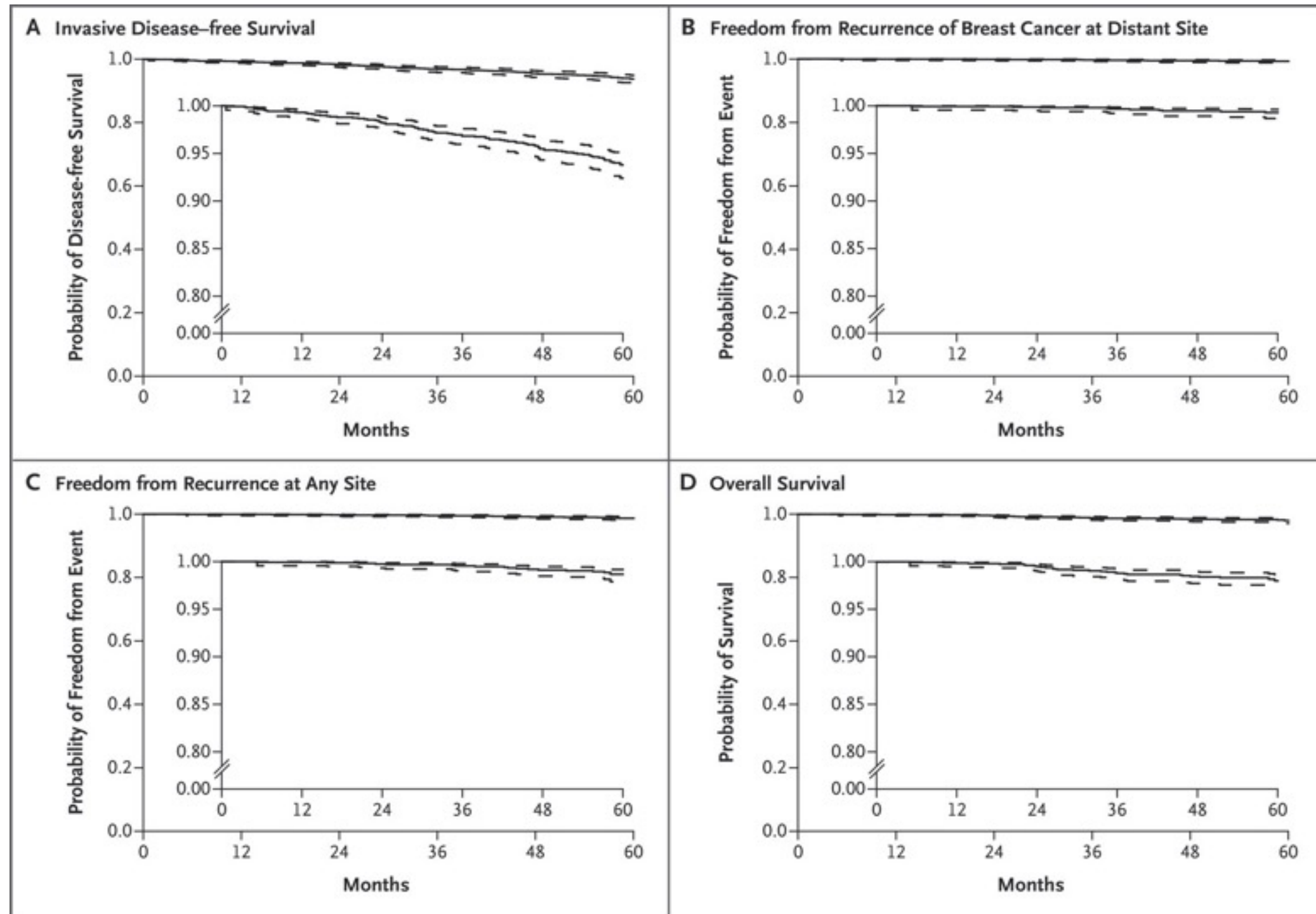


Ongoing trial - TAILORx

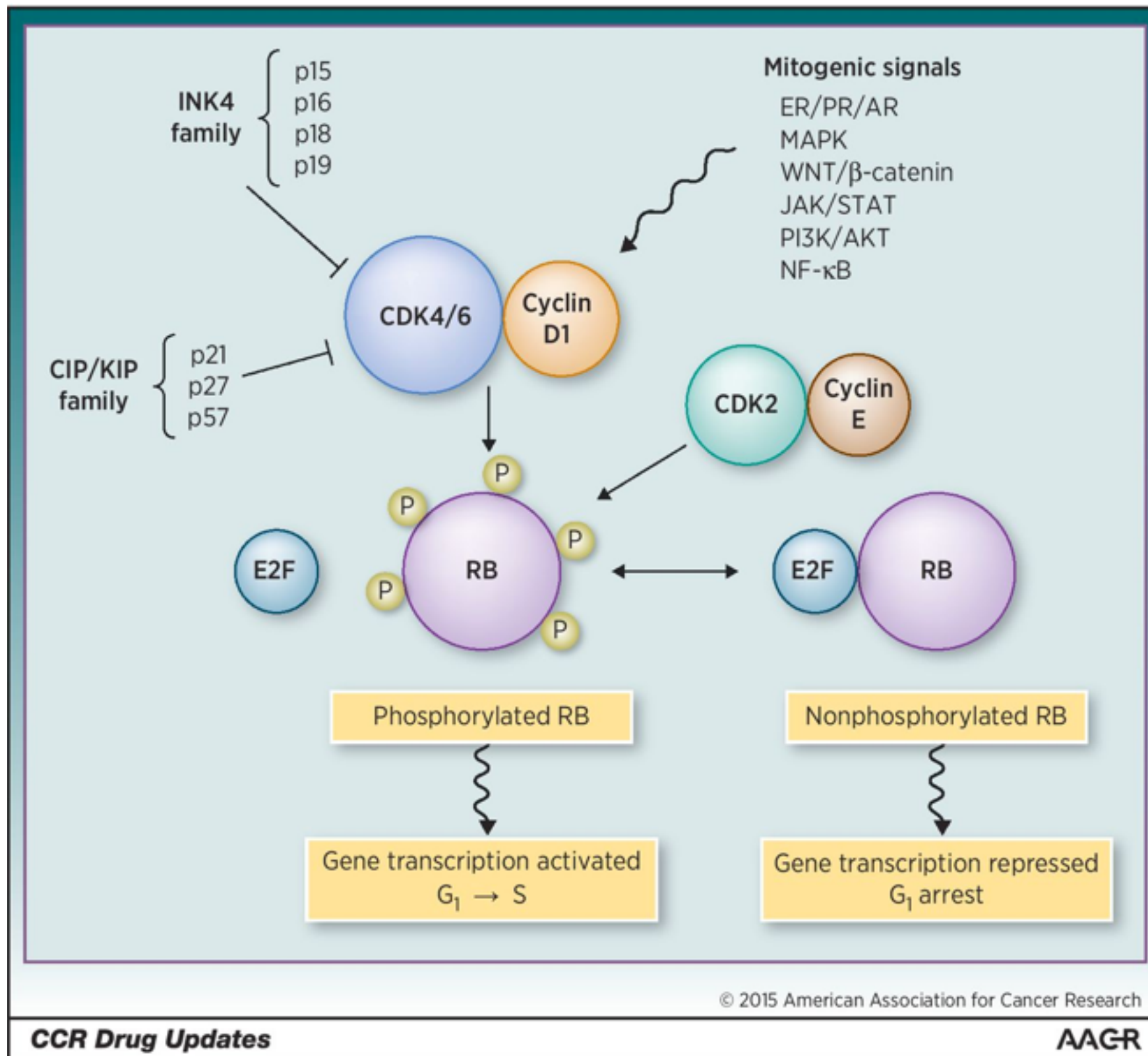
Schema: TAILORx



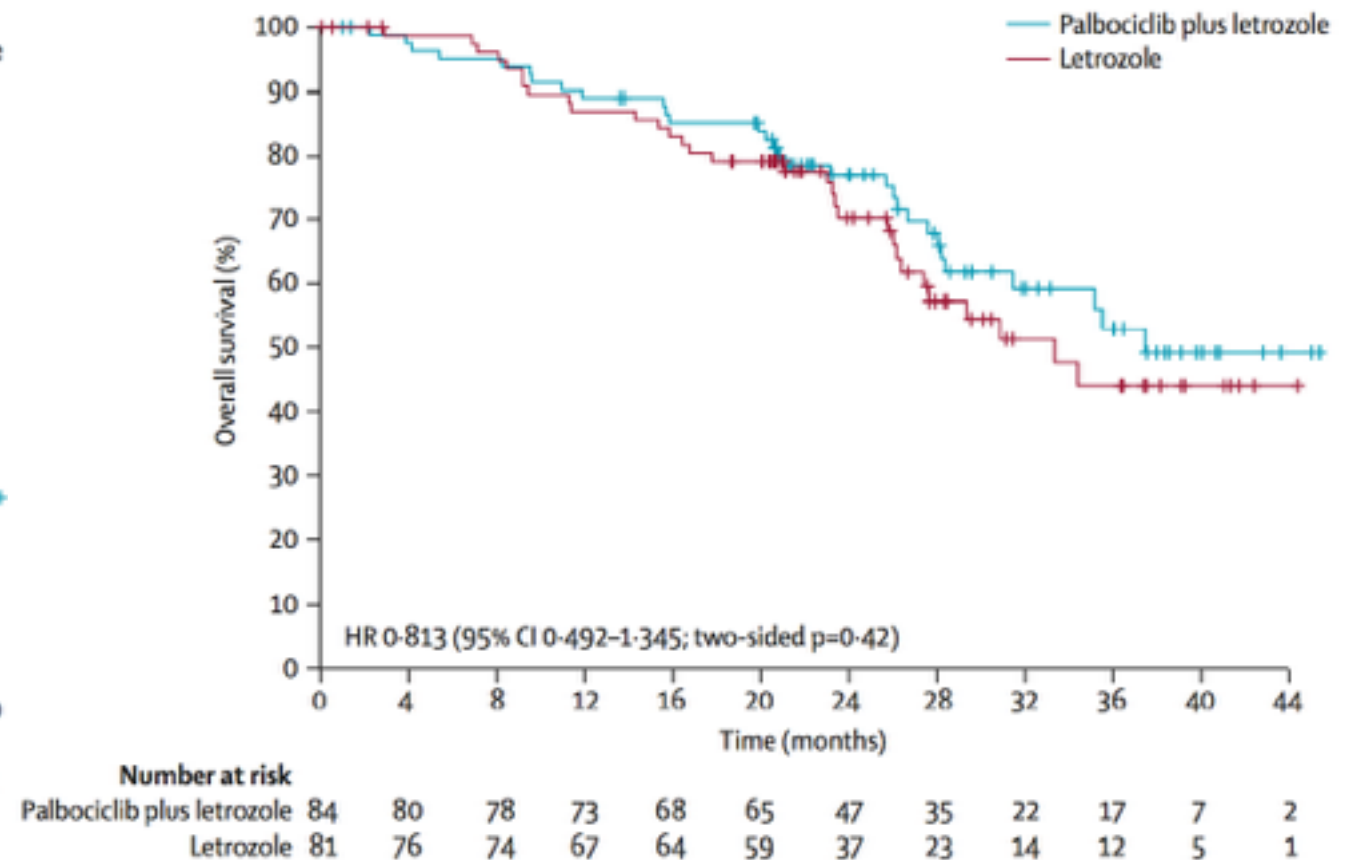
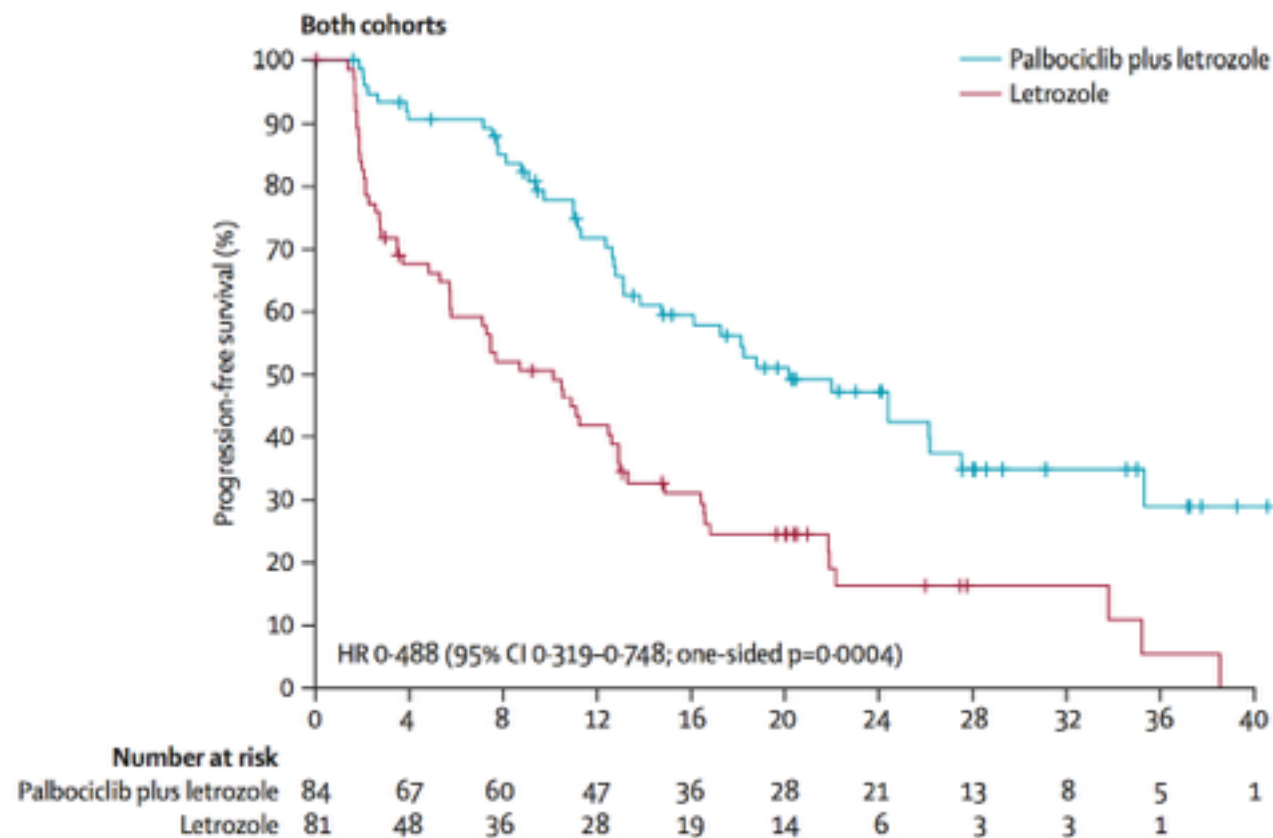
Kaplan–Meier Estimates in the Analyses of Invasive Disease–free Survival, Freedom from Recurrence of Breast Cancer at a Distant Site, Freedom from Recurrence at Any Site, and Overall Survival.



CDK4/6 inhibitor - palbociclib

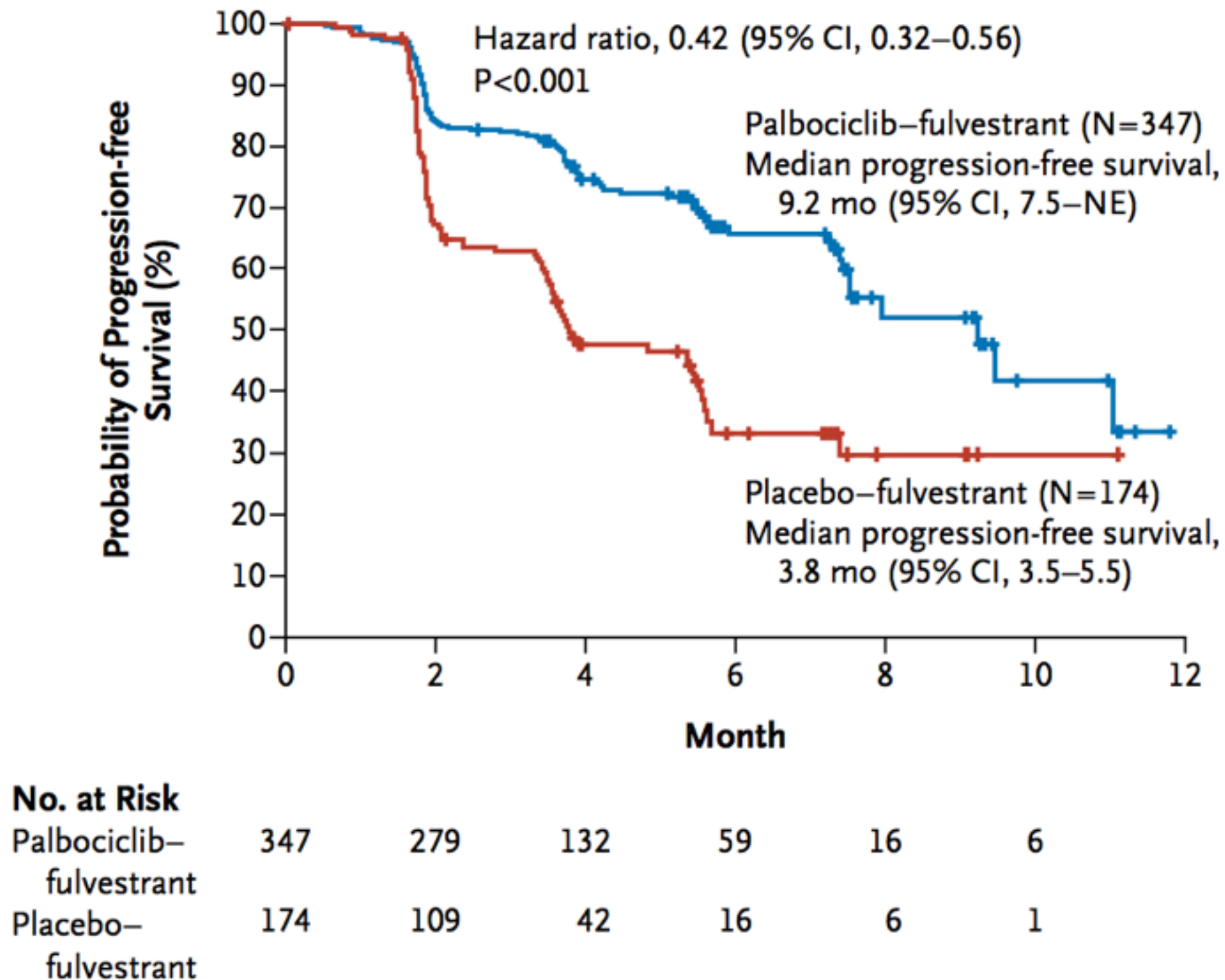


CDK4/6 inhibitor - palbociclib

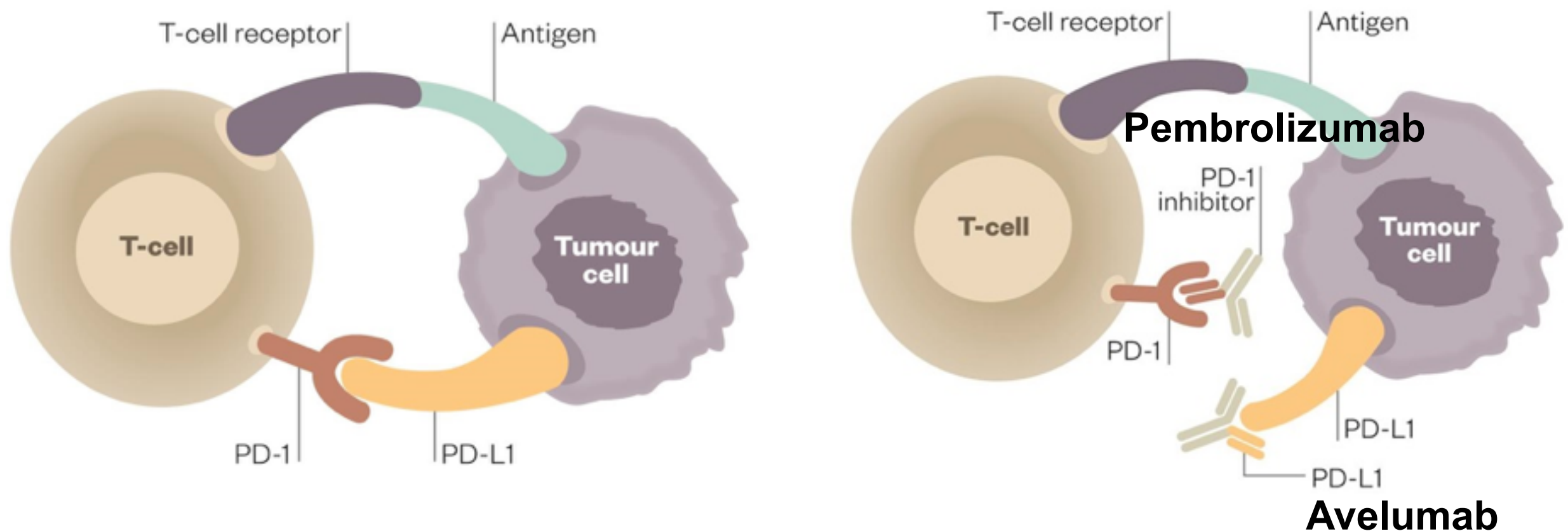


Lancet Oncol 2015; 16: 25-35

CDK4/6 inhibitor - palbociclib



Breast cancer immunotherapy



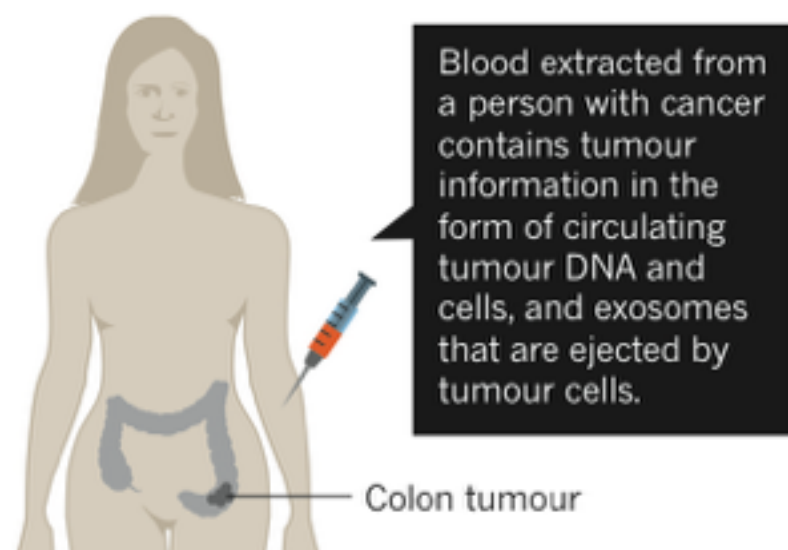
<http://www.pharmaceutical-journal.com/news-and-analysis/feature/immune-checkpoint-inhibitors-bring-new-hope-to-cancer-patients/20067127.article>

Breast cancer immunotherapy

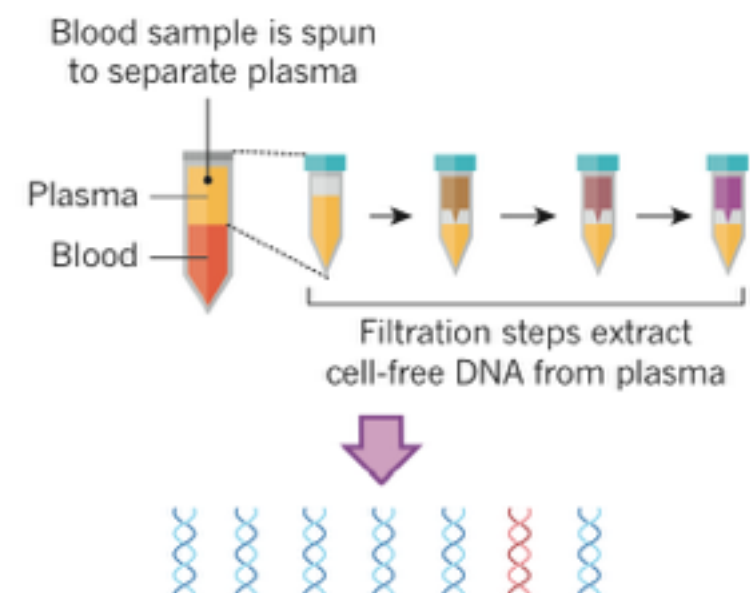
- Dirix LY, Takacs I, Nikolinakos P, et al: Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: A phase Ib JAVELIN solid tumor trial. 2015 San Antonio Breast Cancer Symposium. Abstract S1-04. Presented December 9, 2015.
 - **overall response rate: 4.8% (8/168)**
 - **5/8 had triple-negative cancer, and 4 had PD-L1 positive immune cells**
- Rugo HS, Delord J-P, Im S-A, et al: Preliminary efficacy and safety of pembrolizumab (MK-3475) in patients with PD-L1–positive estrogen receptor–positive/HER2-negative advanced breast cancer enrolled in KEYNOTE-028. 2015 San Antonio Breast Cancer Symposium. Abstract S5-07. Presented December 11, 2015.
 - **ER-positive HER2 negative PD-L1 expressing**
 - **Of 25 evaluable patients, response rate 12%, plus 8% stable disease**

SCALPEL-FREE BIOPSIES

Three different non-invasive techniques allow scientists to monitor tumours by performing 'liquid biopsies' on vials of blood.



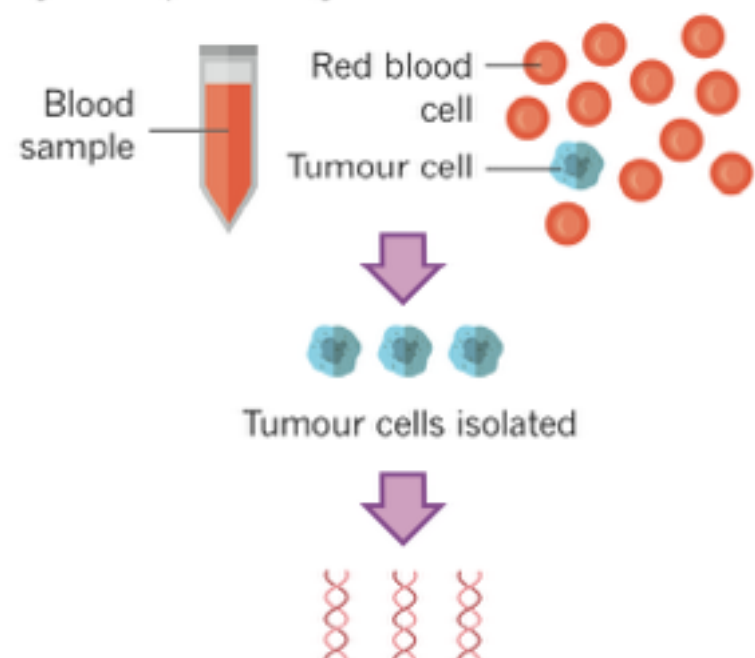
Circulating tumour DNA



DNA fragments from malignant cells (red) are separated from normal DNA (blue) and analysed by next-generation sequencing or digital polymerization chain reaction (dPCR).

Circulating tumour cells

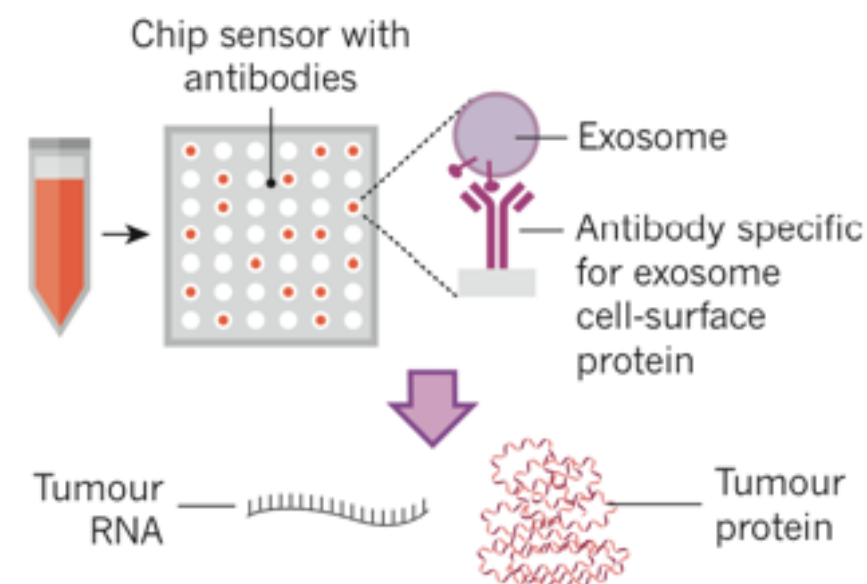
Circulating tumour cells are isolated from blood by cell-separation systems.



Cells are broken up to obtain tumour DNA that can be analysed by whole-genome sequencing.

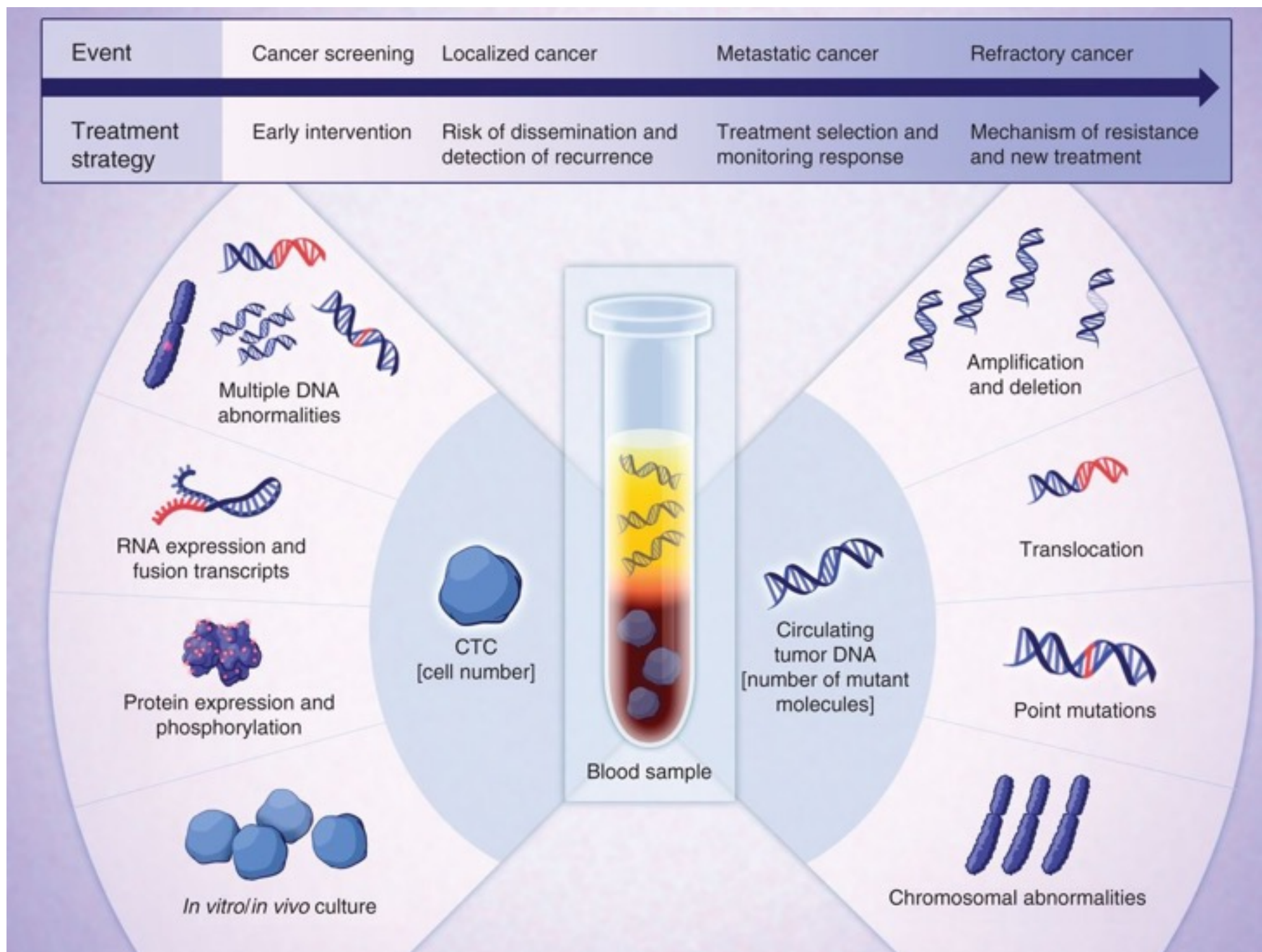
Exosomes

Tumour exosomes are extracted from blood samples using different assays.



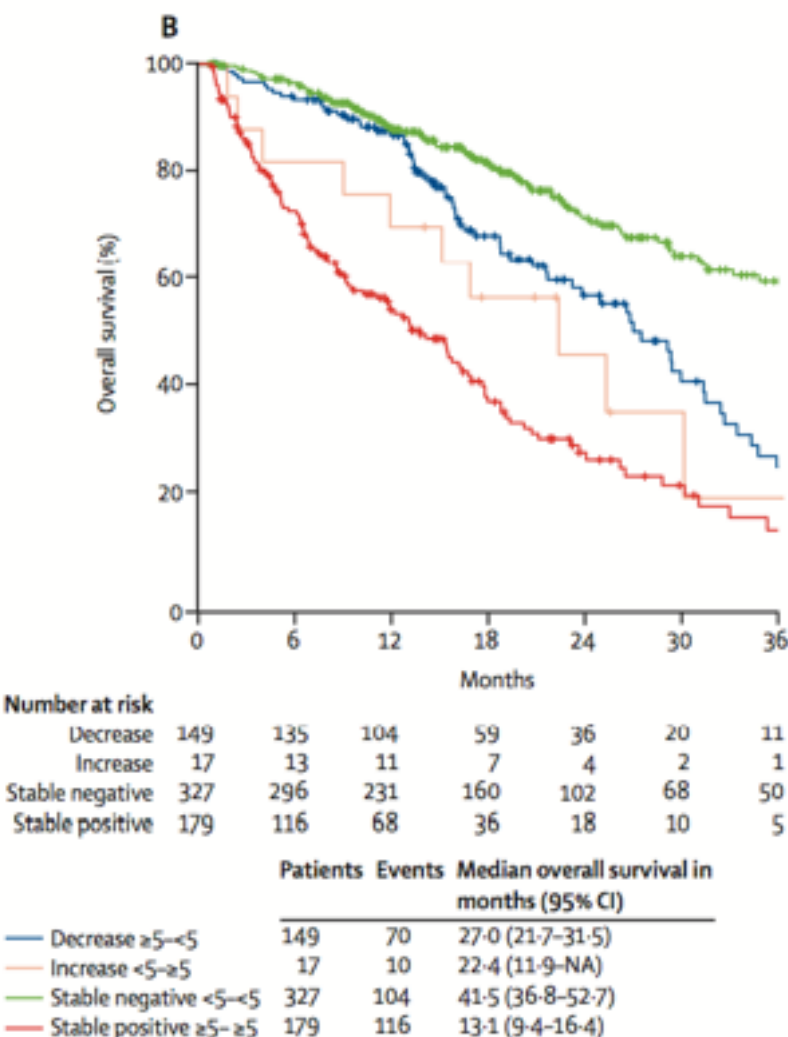
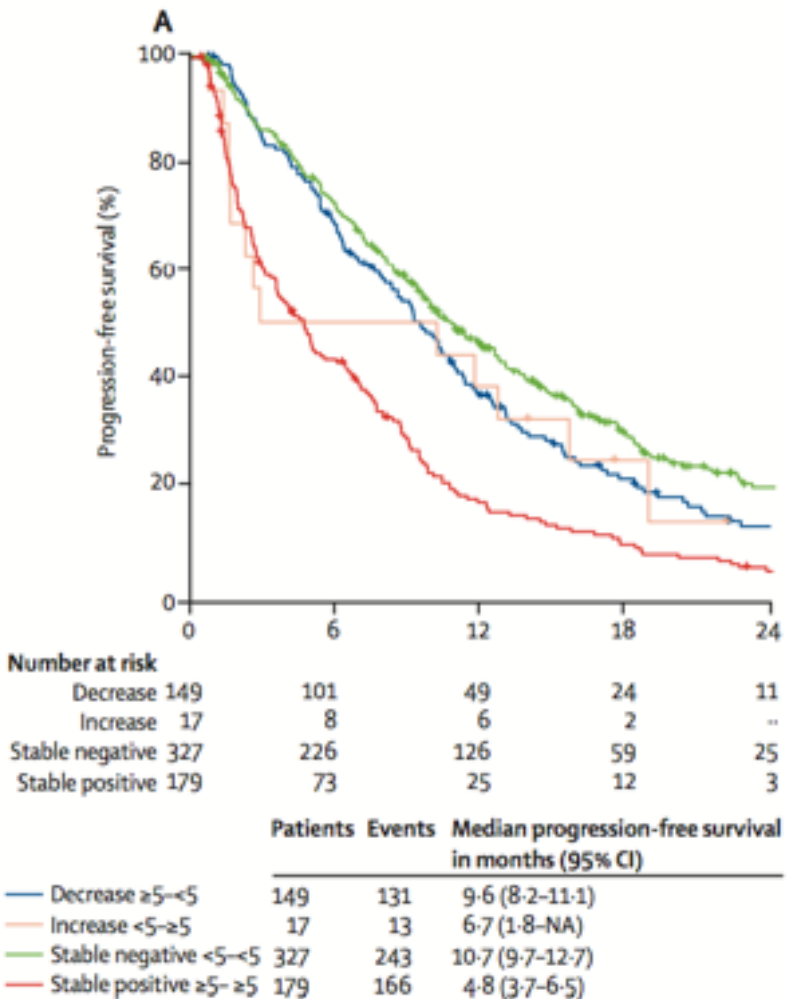
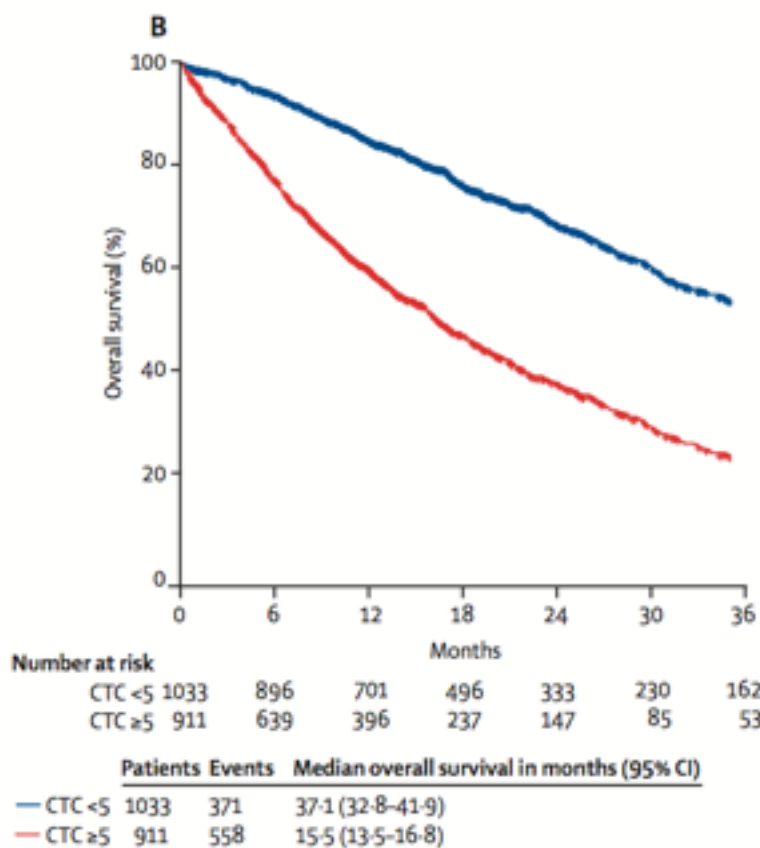
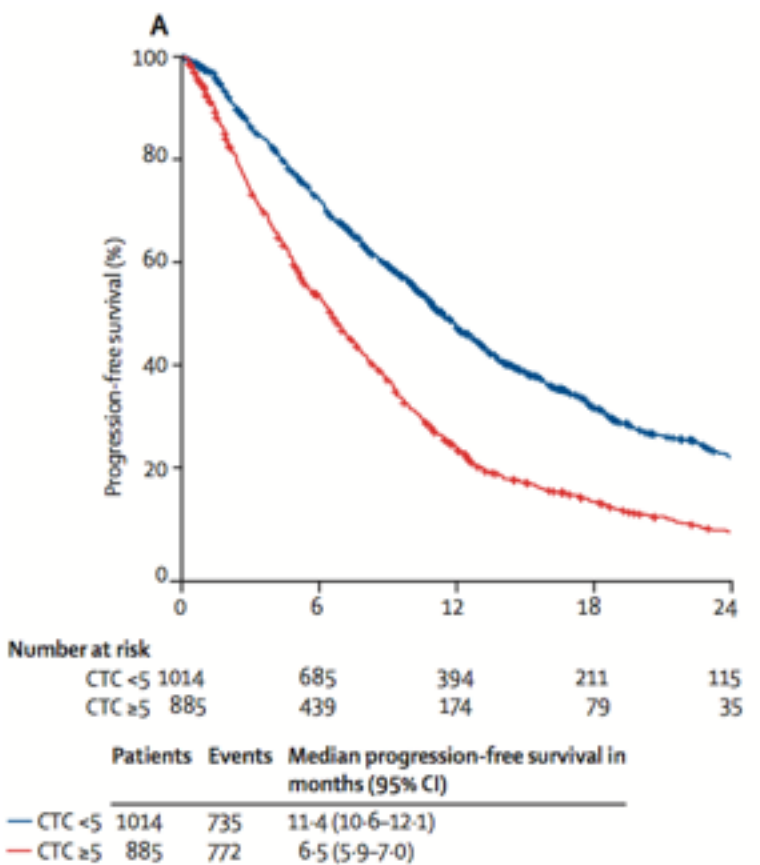
The material inside the captured exosomes — RNA and/or proteins — is then analysed.

Clinical applications of CTC and ctDNA analyses in cancer care.

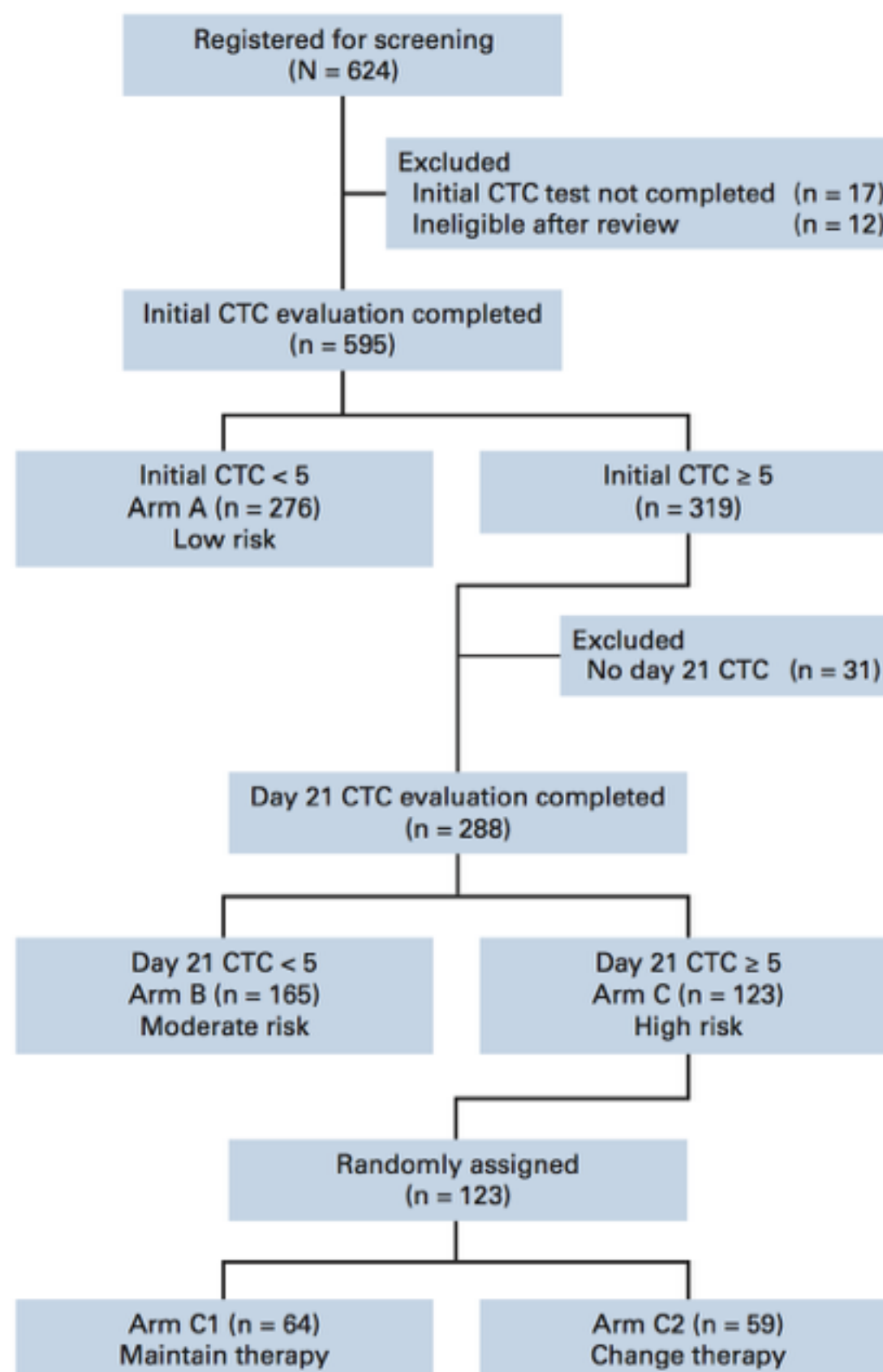


Daniel A. Haber, and Victor E. Velculescu *Cancer Discovery* 2014;4:650-661

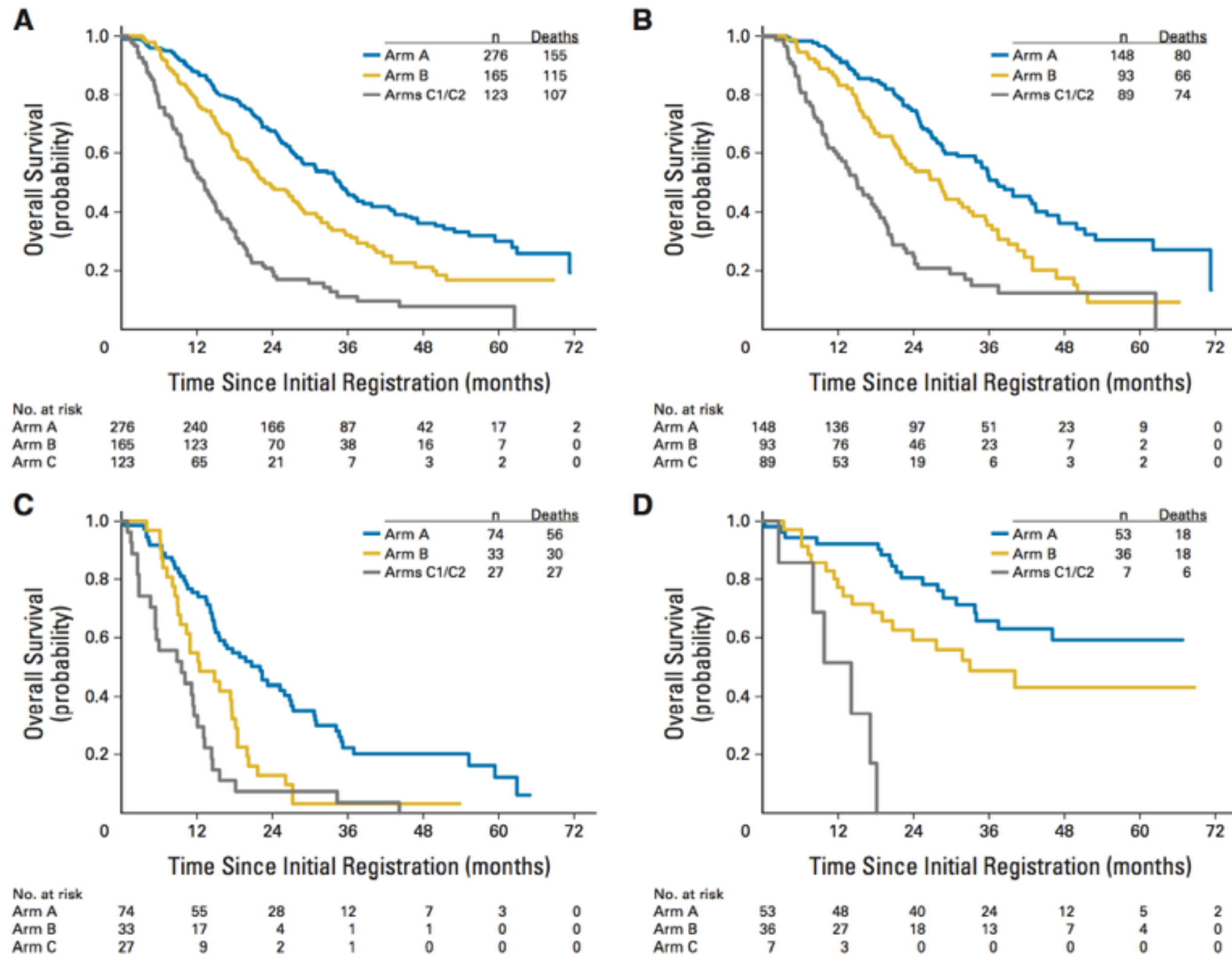
A pooled-analysis of CTC in breast cancer



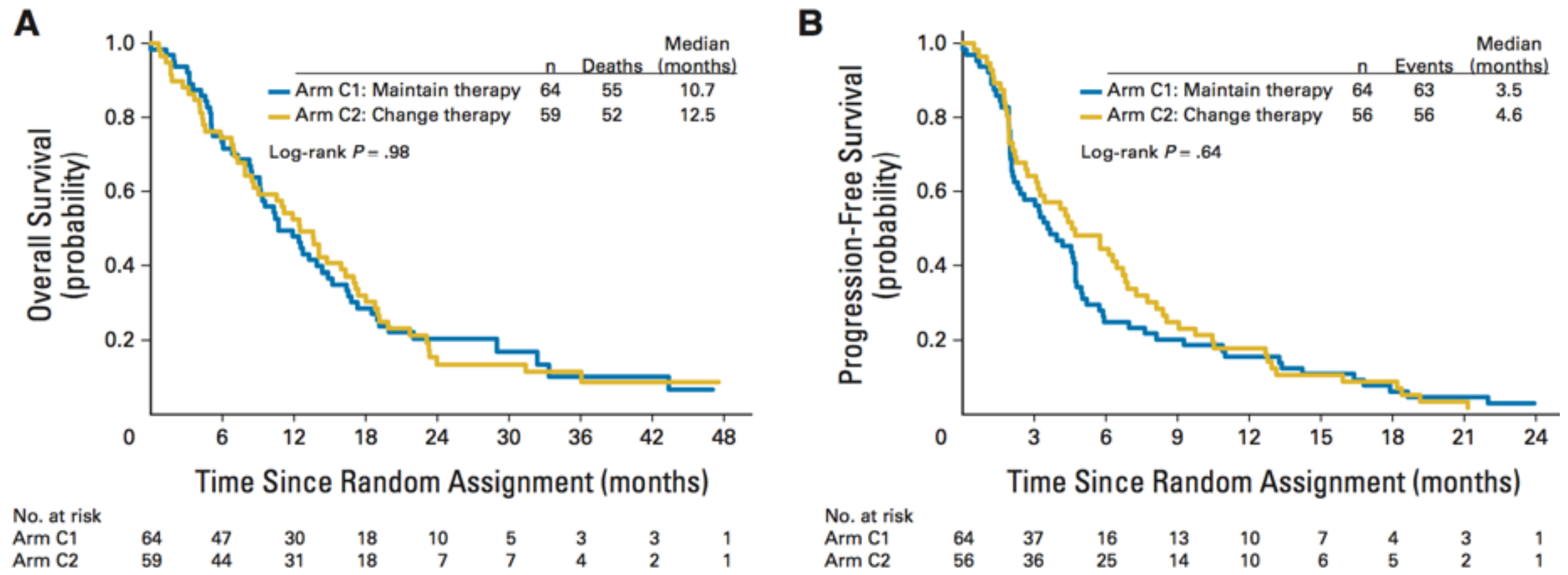
Circulating Tumor Cells and Response to Chemotherapy in Metastatic Breast Cancer: SWOG S0500



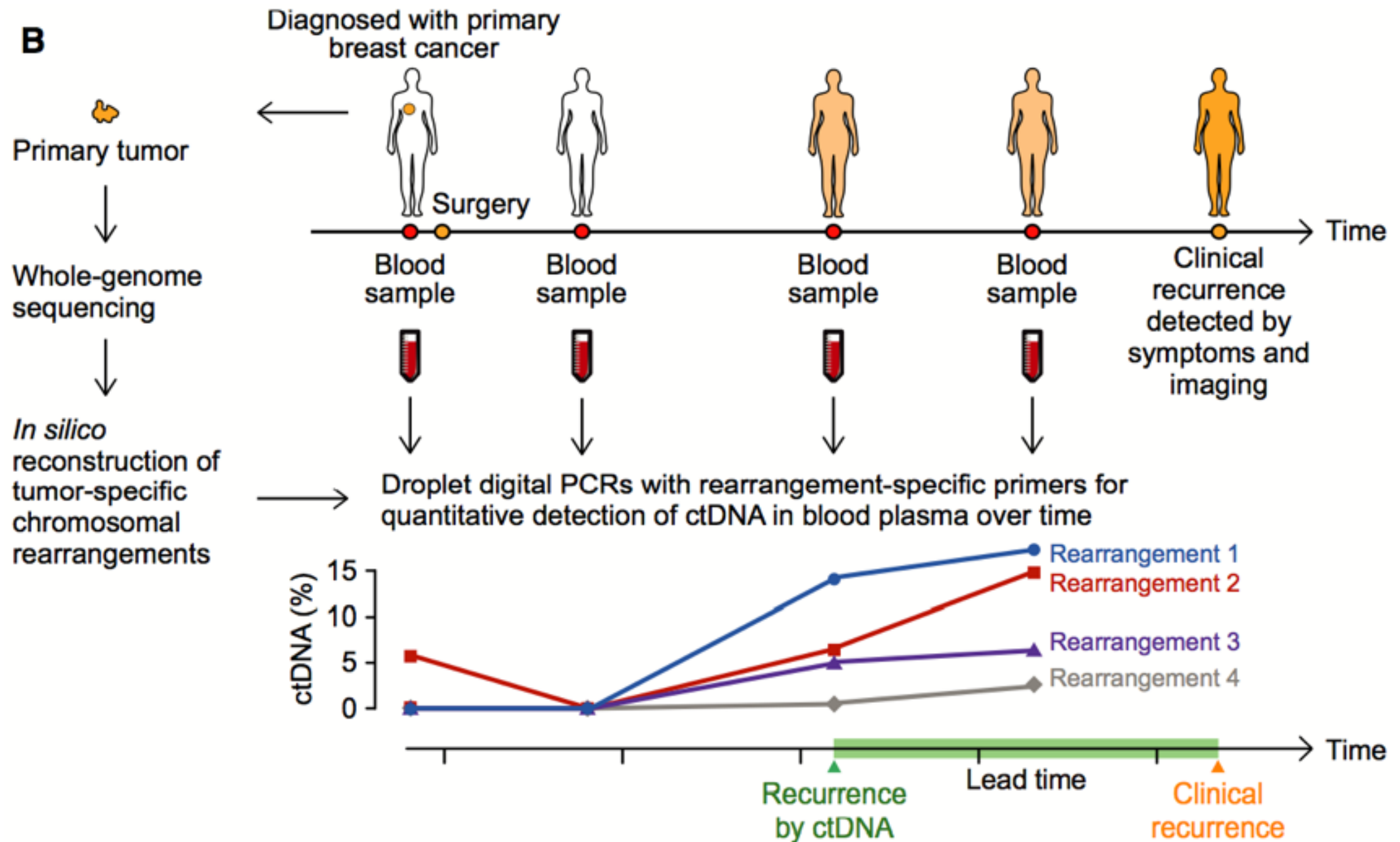
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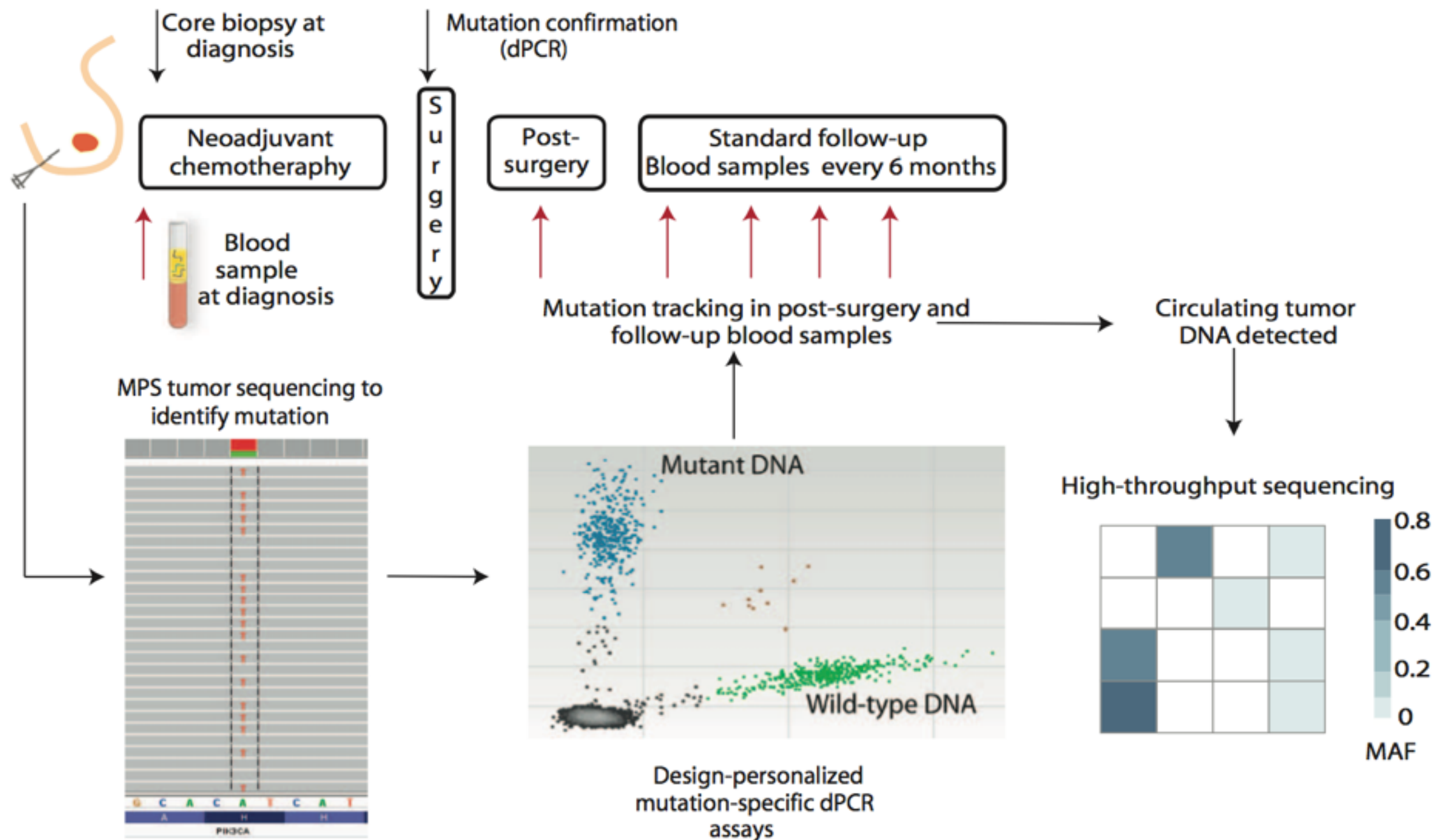
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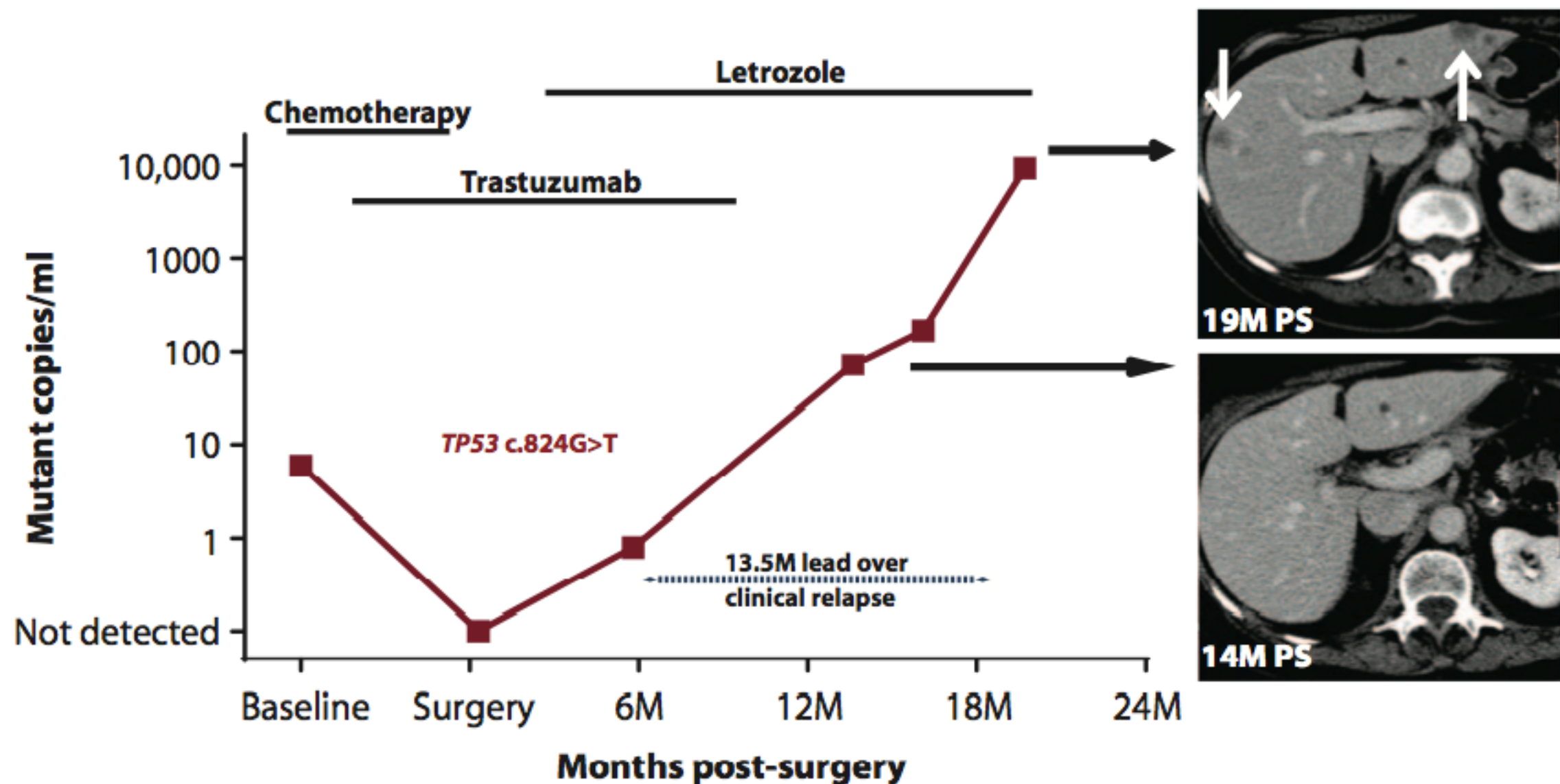
Serial monitoring of circulating tumor DNA in patients with primary breast cancer for detection of occult metastatic disease



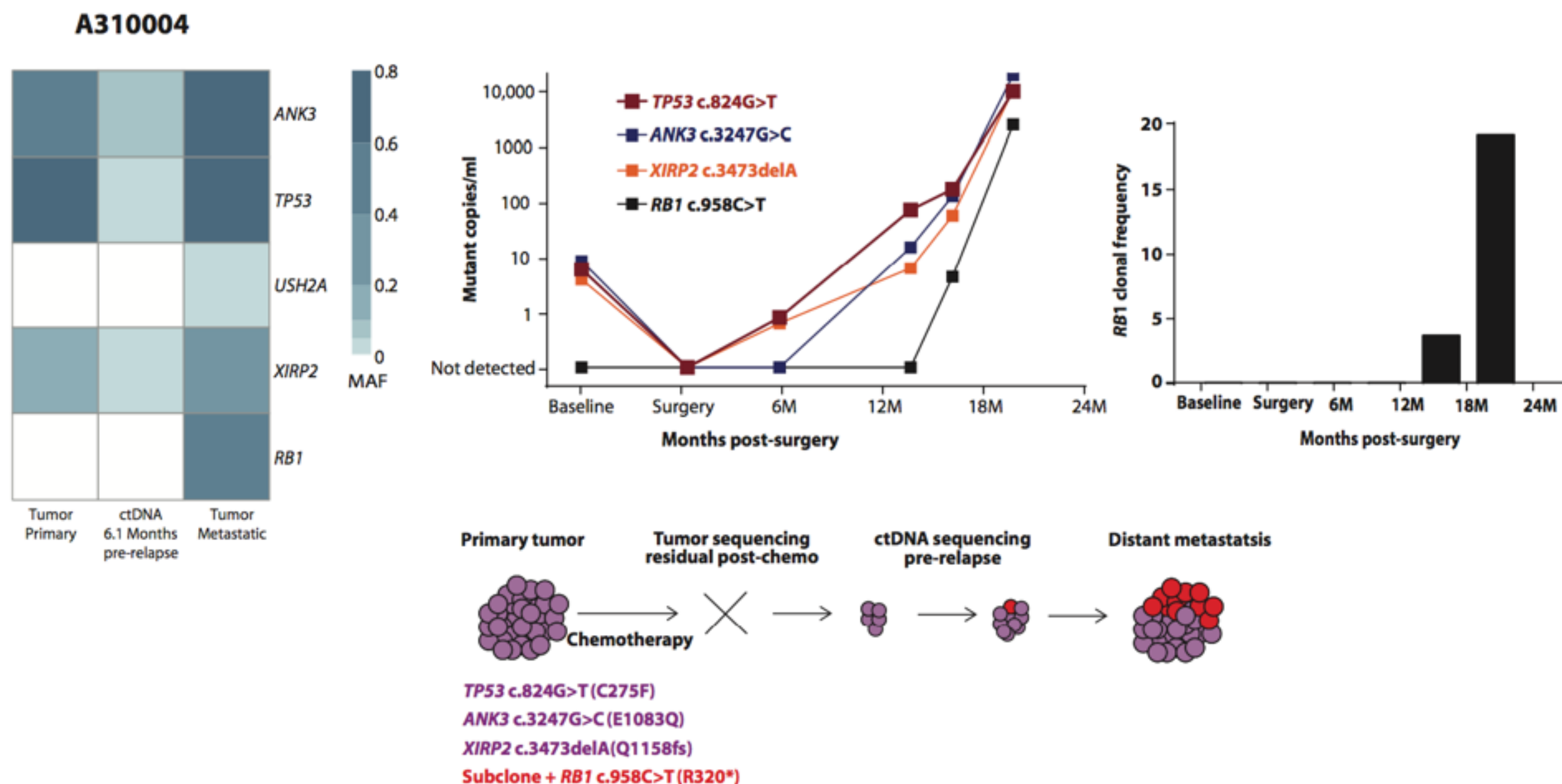
Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer



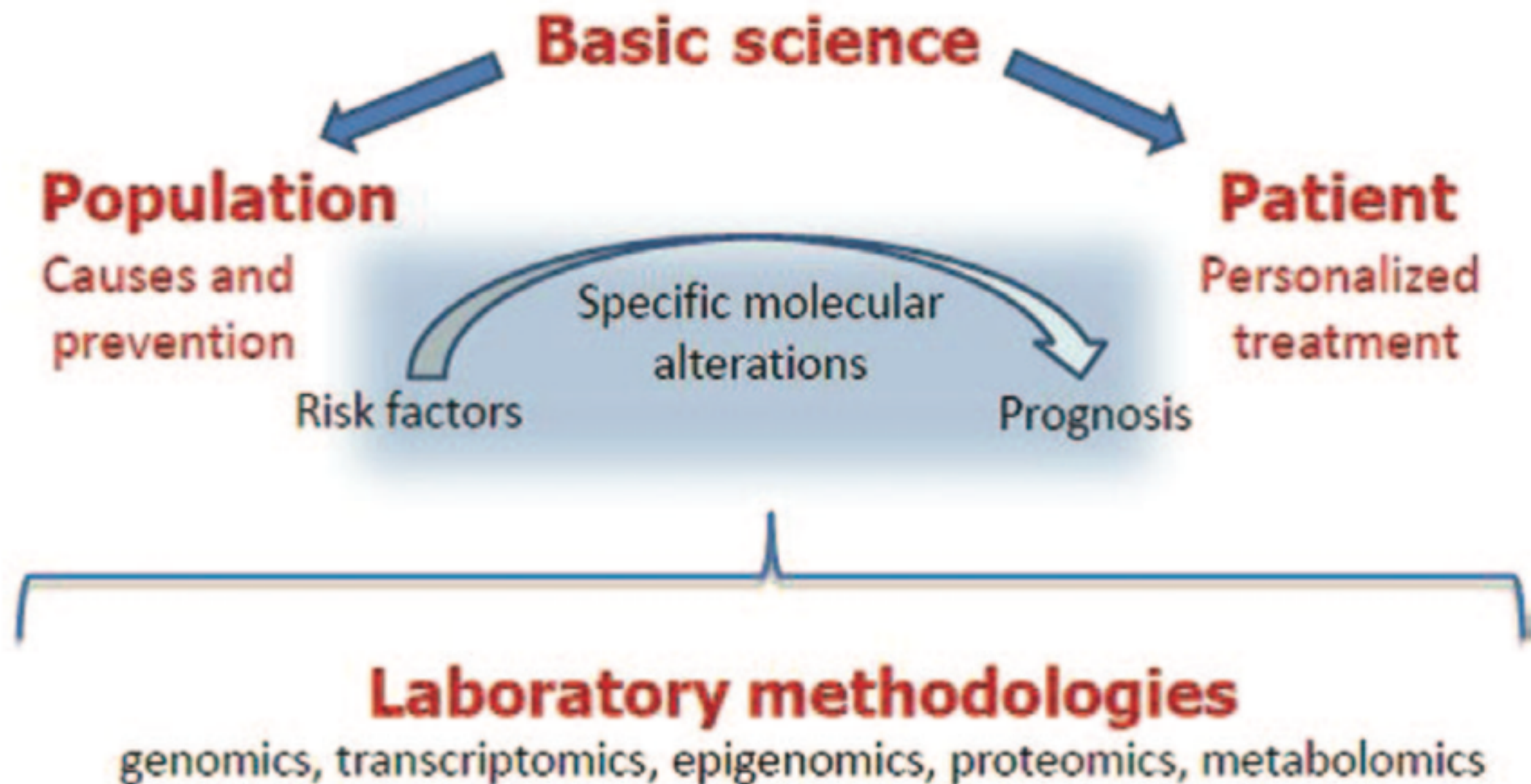
Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer



Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer



Two-way translational cancer research



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