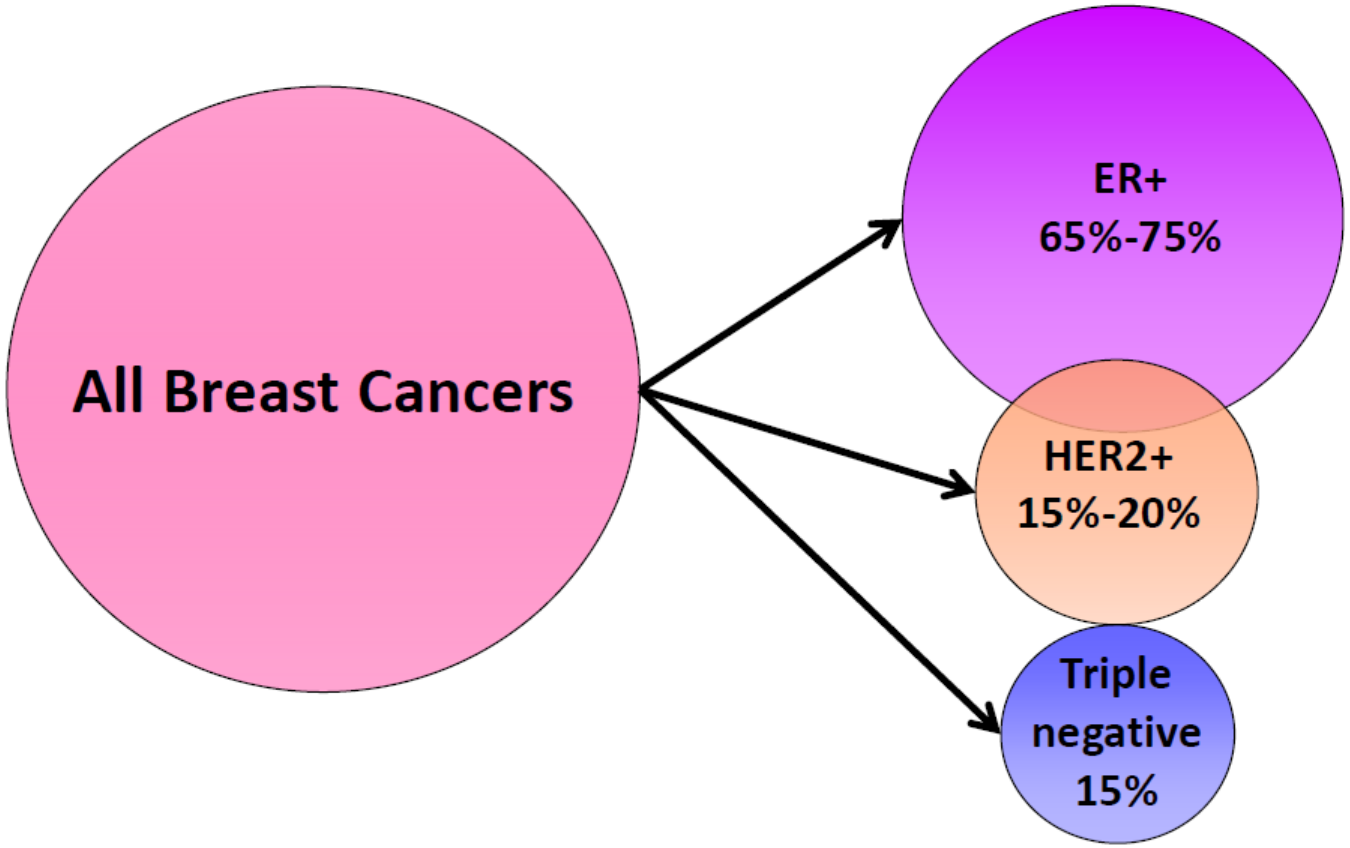
Invasive Breast Cancer Subsets Defined by IHC



Hormone receptor status

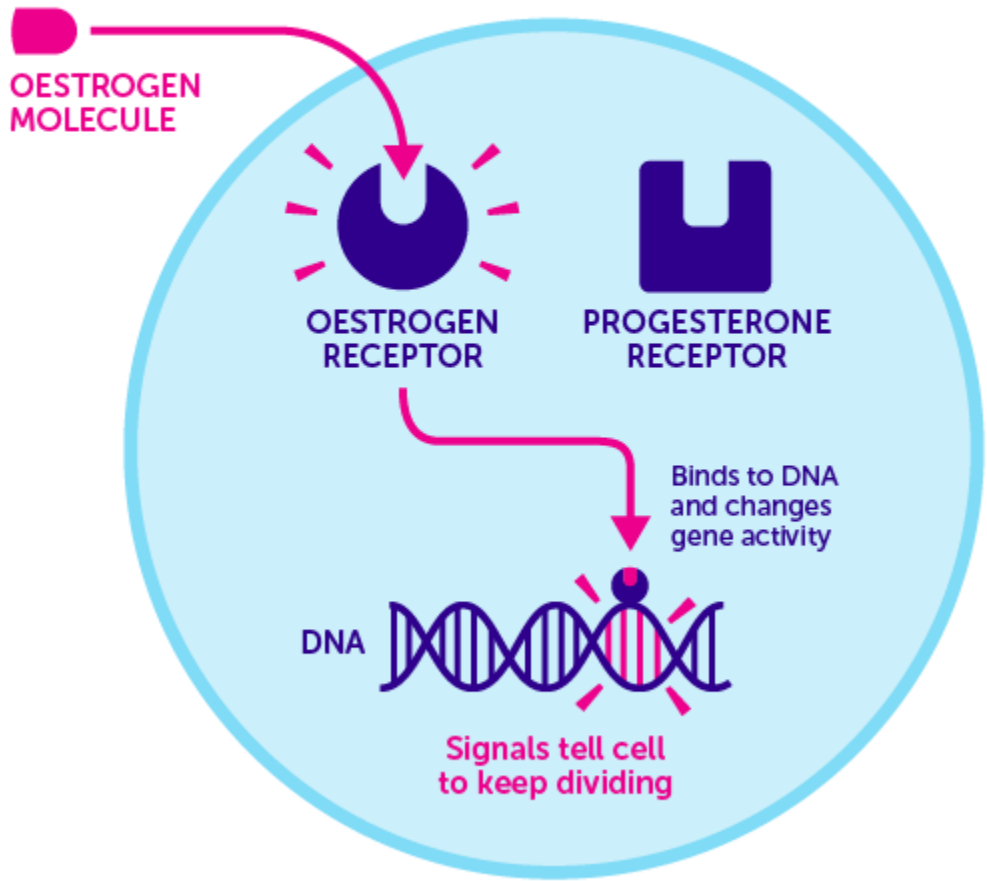
Some breast cancer cells need estrogen and/or progesterone (hormones produced in the body) to grow. These cancer cells have special proteins inside, called hormone receptors.

When hormones attach to hormone receptors, the cancer cells with these receptors grow.

A pathologist determines the hormone receptor status by testing the tumor tissue removed during a biopsy.

- **Hormone receptor-positive** tumors are estrogen receptor-positive (ER-positive) and progesterone receptor-positive (PR-positive). These tumors express (have a lot of) hormone receptors.
- **Hormone receptor-negative** tumors are estrogen receptor-negative (ER-negative) and progesterone receptor-negative (PR- negative). These tumors do not express (have few or no) hormone receptors.

OESTROGEN FUELS THE GROWTH AND DIVISION OF BREAST CANCER CELLS

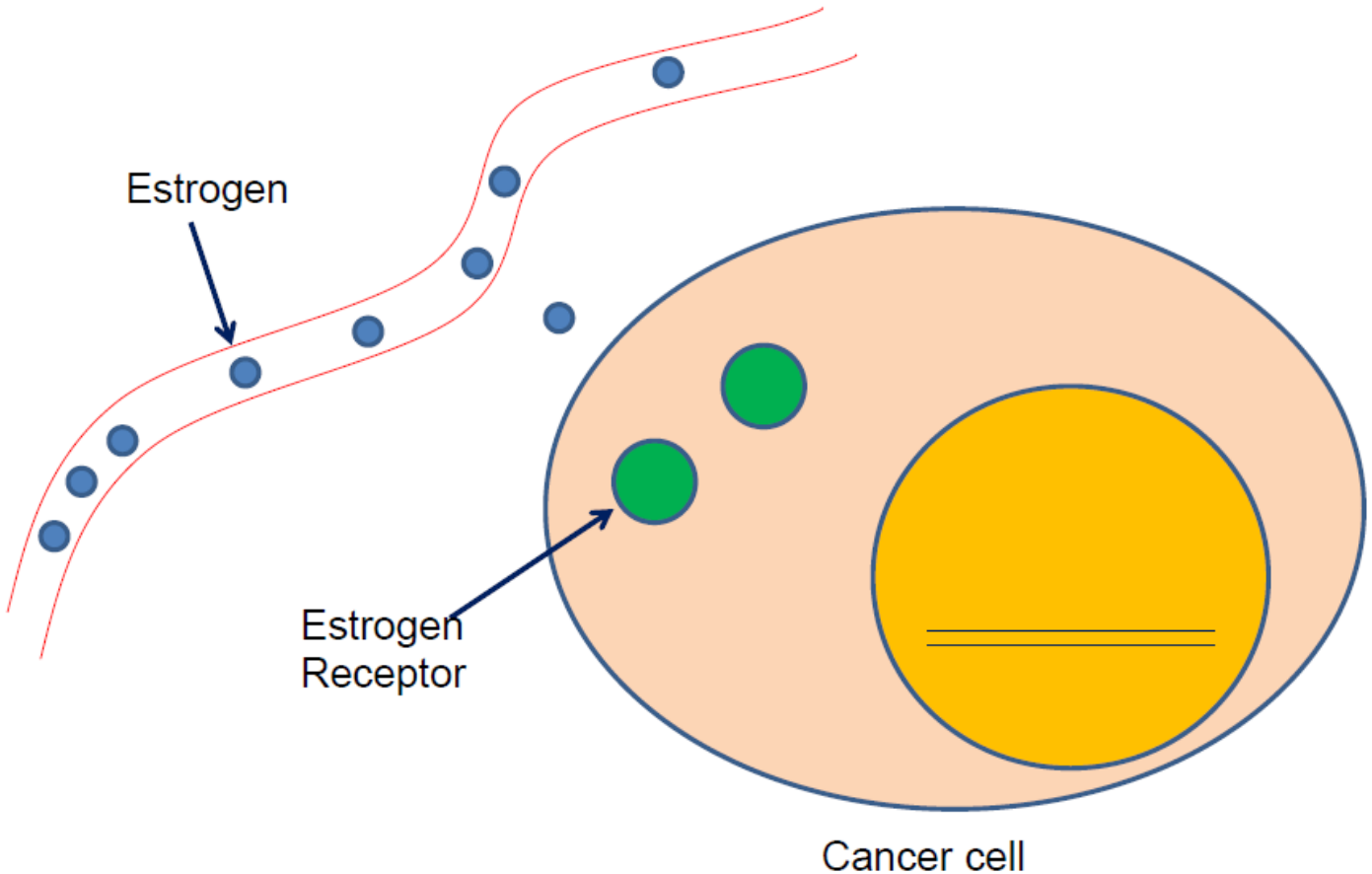


“Targeted” therapy

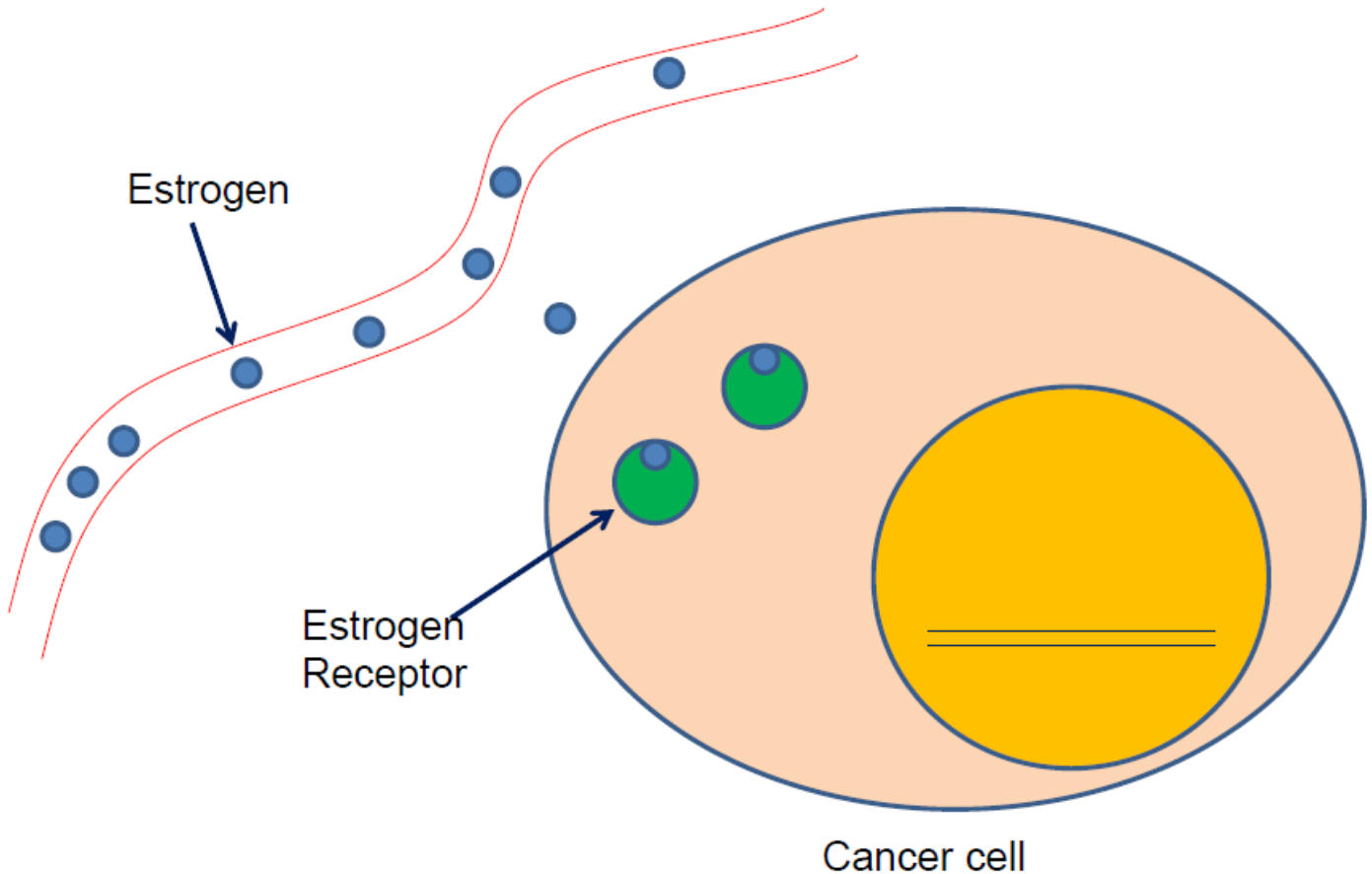
- Drug which inhibits a protein or molecule that is only expressed in cancer or which only the cancer is dependent

- Offer the promise of reduced side effects compared to less targeted drugs

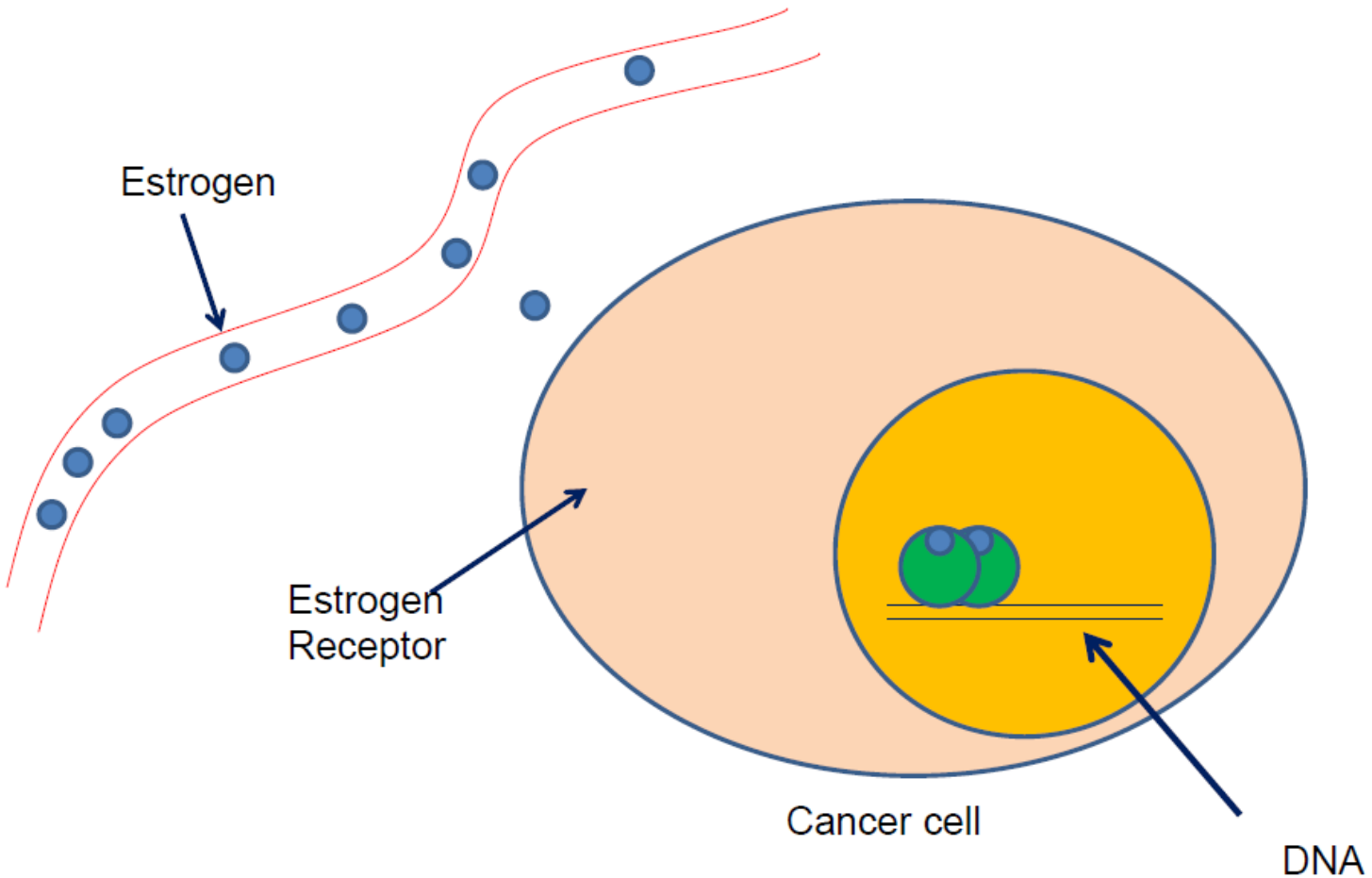
Estrogen Receptor Function: The Basics



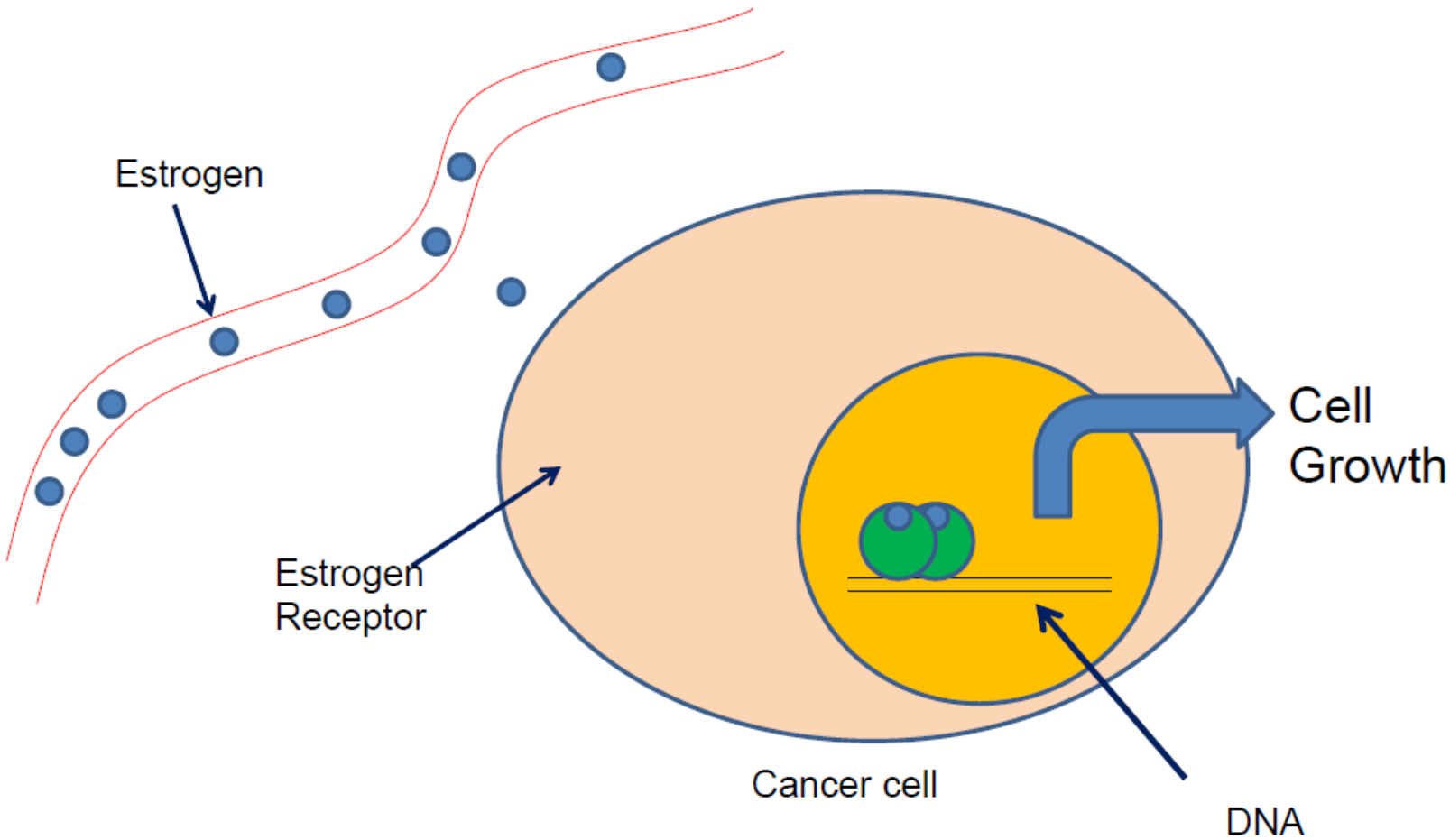
Estrogen Receptor Function: The Basics



Estrogen Receptor Function: The Basics



Estrogen Receptor Function: The Basics



How do hormone therapies work?

Hormone therapies slow or stop the growth of hormone receptor-positive tumors by preventing the cancer cells from getting the hormones they need to grow.

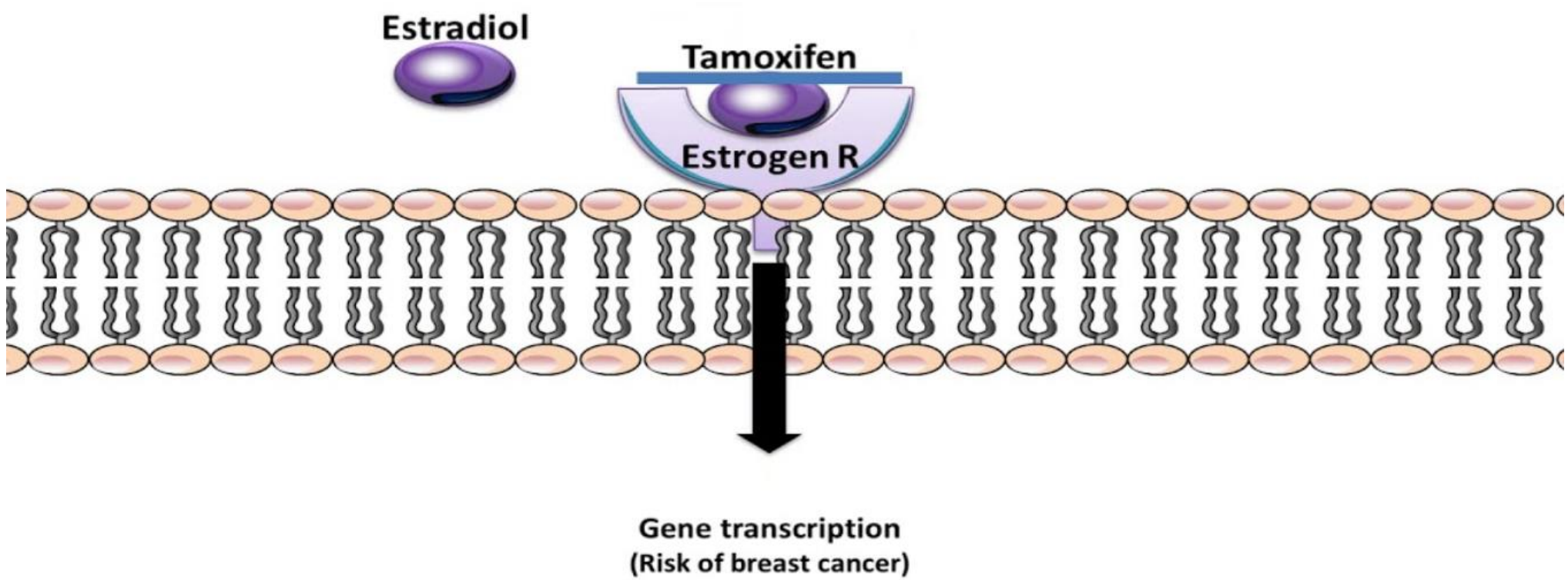
They do this in a few ways:

- Some hormone therapies, like tamoxifen, attach to the receptor in the cancer cell and block estrogen from attaching to the receptor.
- Some hormone therapies, like aromatase inhibitors and ovarian suppression, lower the level of estrogen in the body so the cancer cells can't get the estrogen they need to grow.

Hormonal therapy

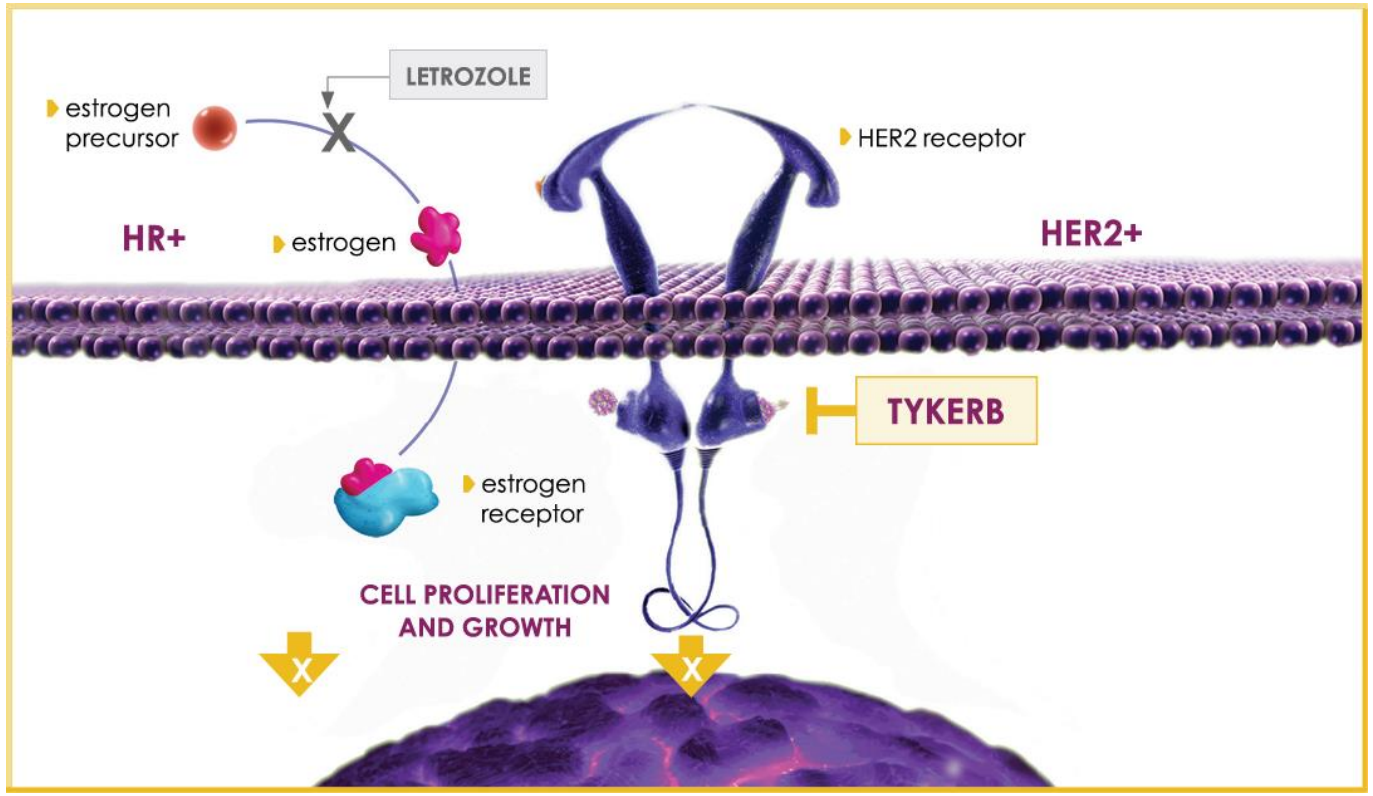
- The original targeted therapy

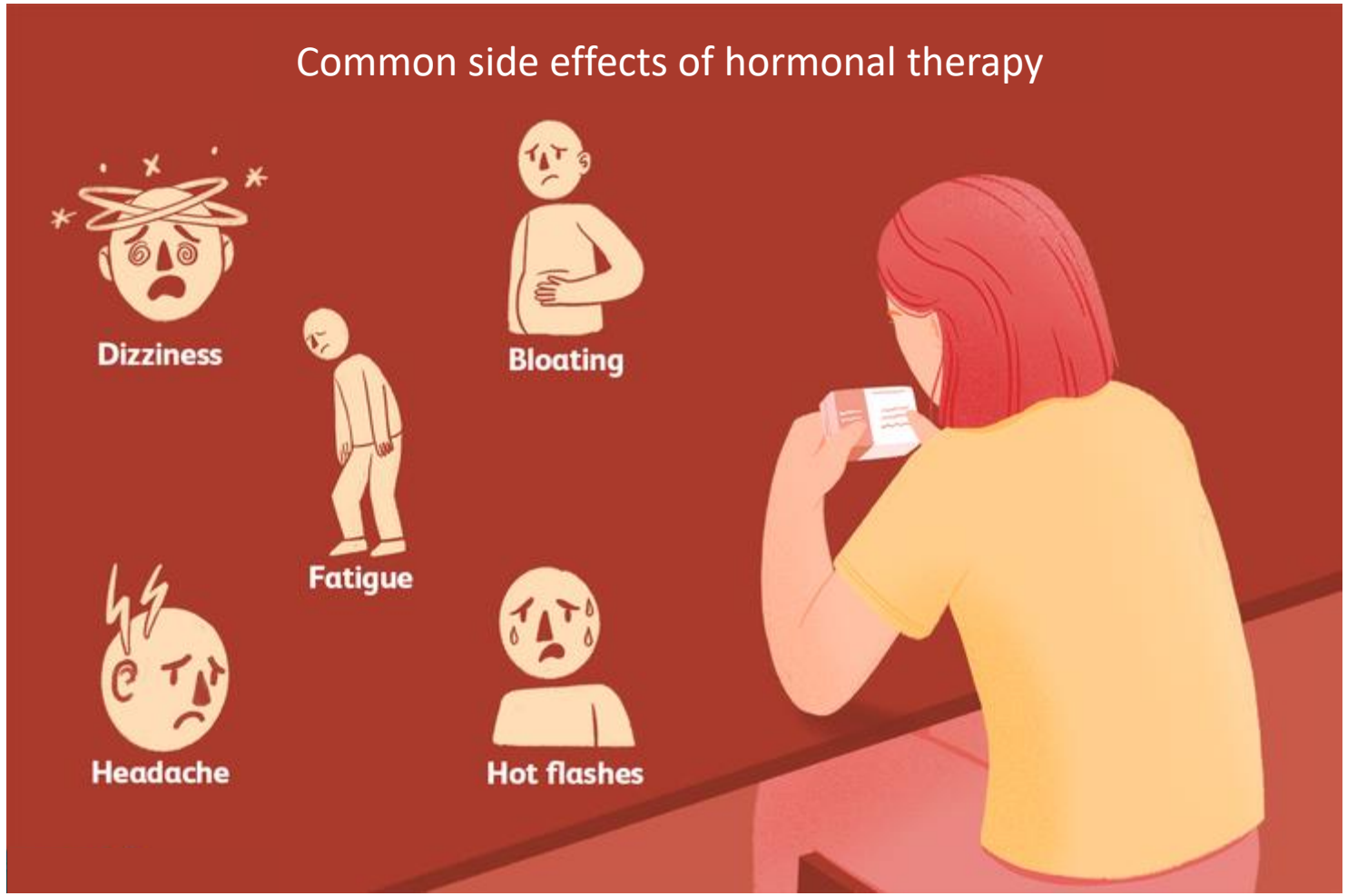
- Several types:
  - Tamoxifen
    - Blocks estrogen from binding to ER
  - Aromatase inhibitors (anastrozole, letrozole, exemestane)
    - Blocks production of estrogen
  - Fulvestrant (Faslodex)
    - Blocks estrogen from binding to ER and helps degrade ER



Prevents breast cancer

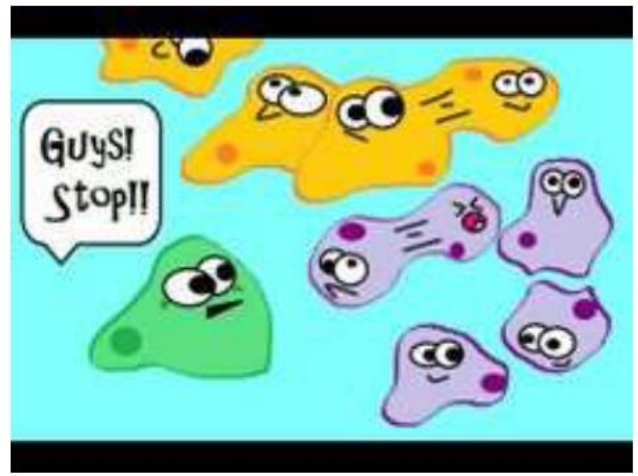
Letrozole blocks production of estrogen



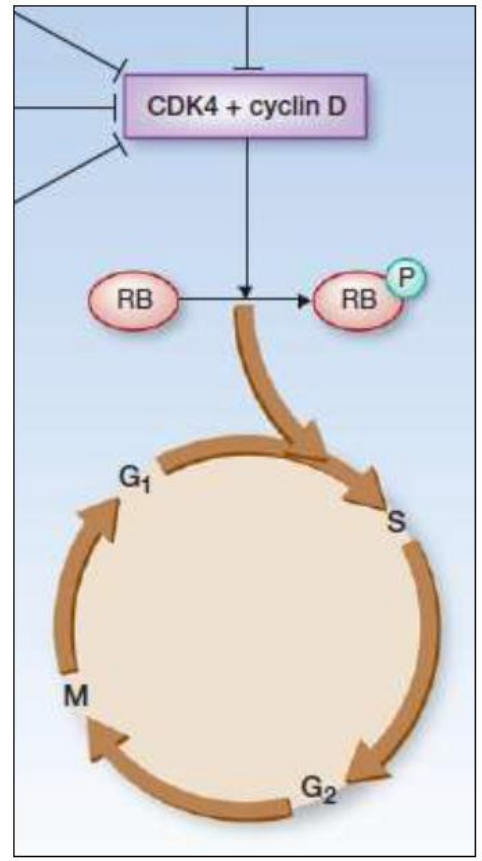

Common side effects of hormonal therapy
Dizziness
Bloating
Fatigue
Headache
Hot flashes

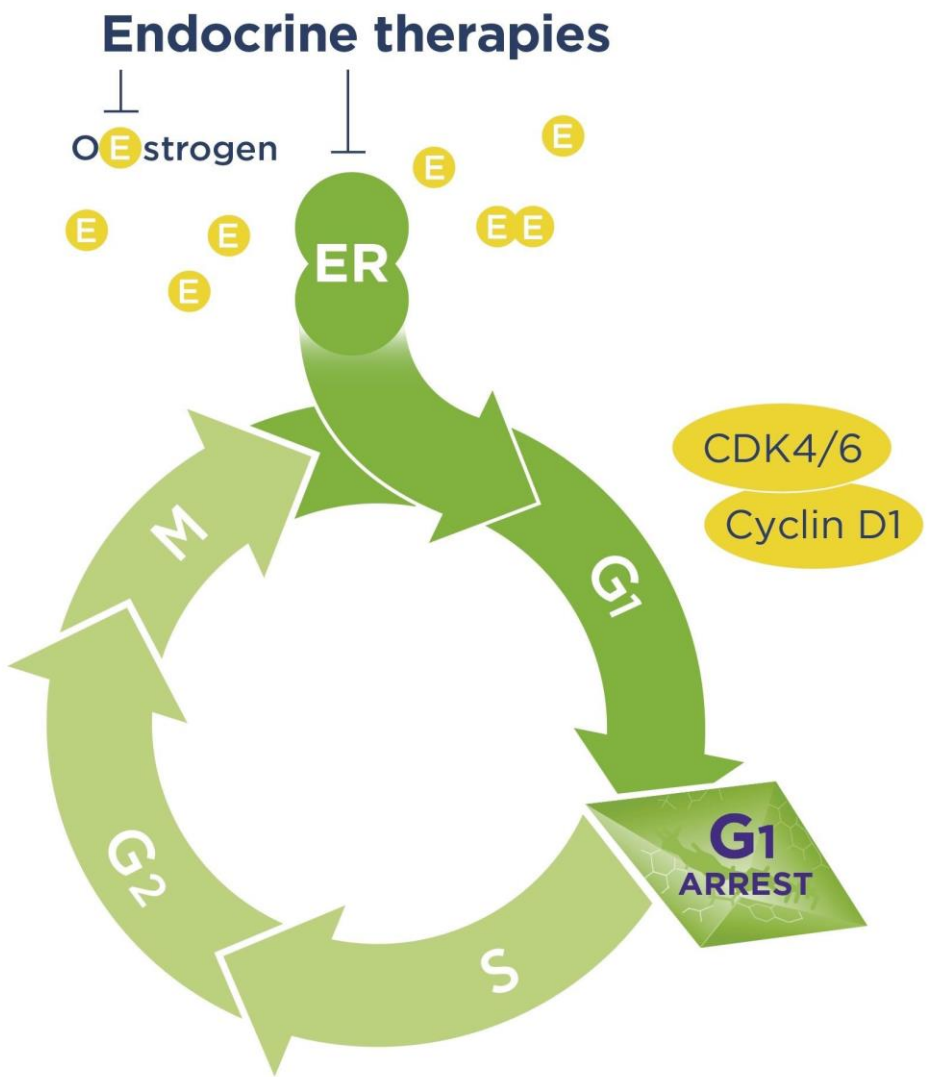
Blocking cancer cell growth: Cyclin Dependent Kinase (CDK 4/6) inhibition

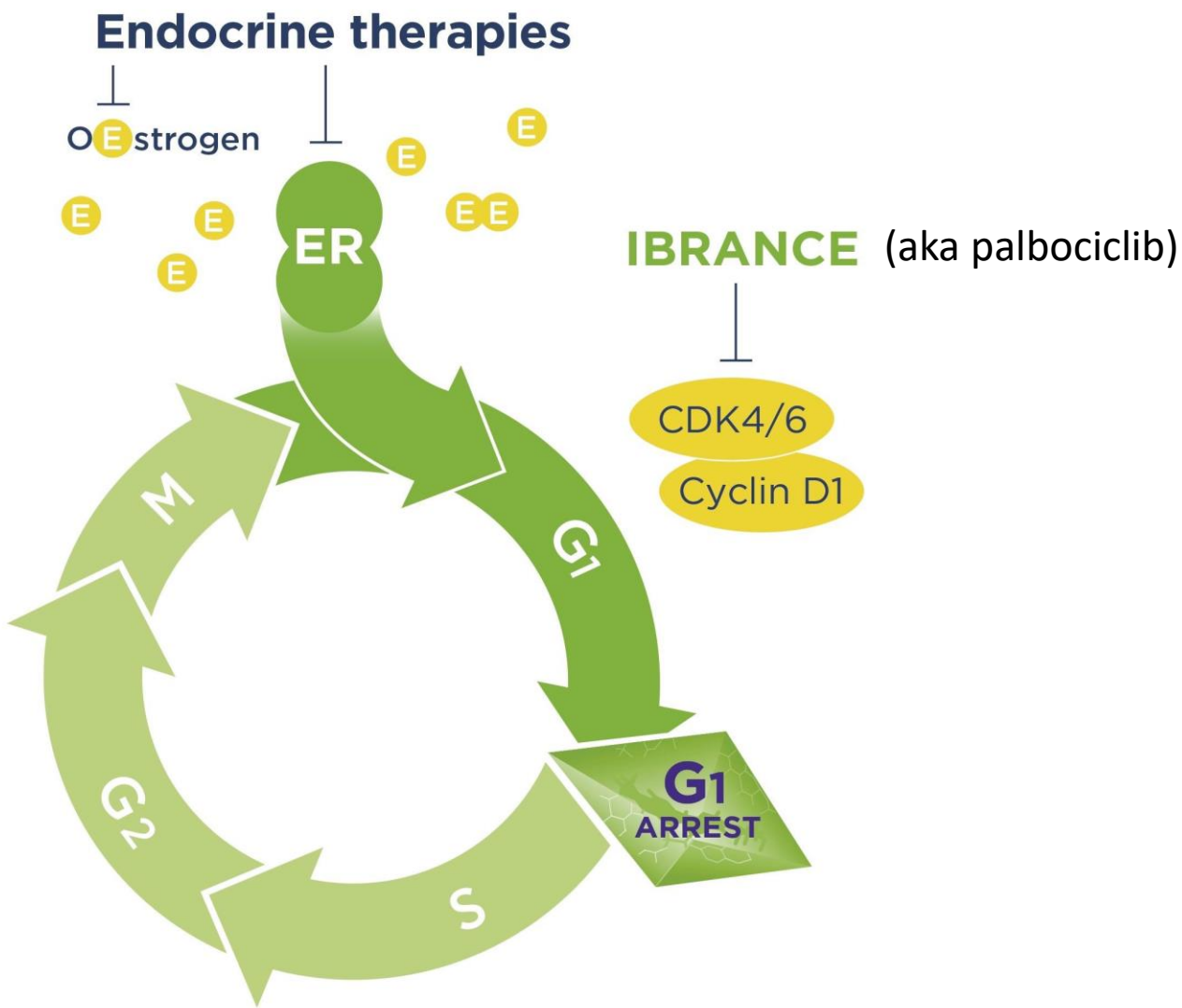
- A classic feature of breast cancer is uncontrolled growth



- In ER+ breast cancer, out-of-control growth may be due to a failure in the braking system: overactive CDK4/6




Endocrine therapies
Oestrogen
E
ER
CDK4/6
Cyclin D1
G1
S
G2
M
G1
ARREST

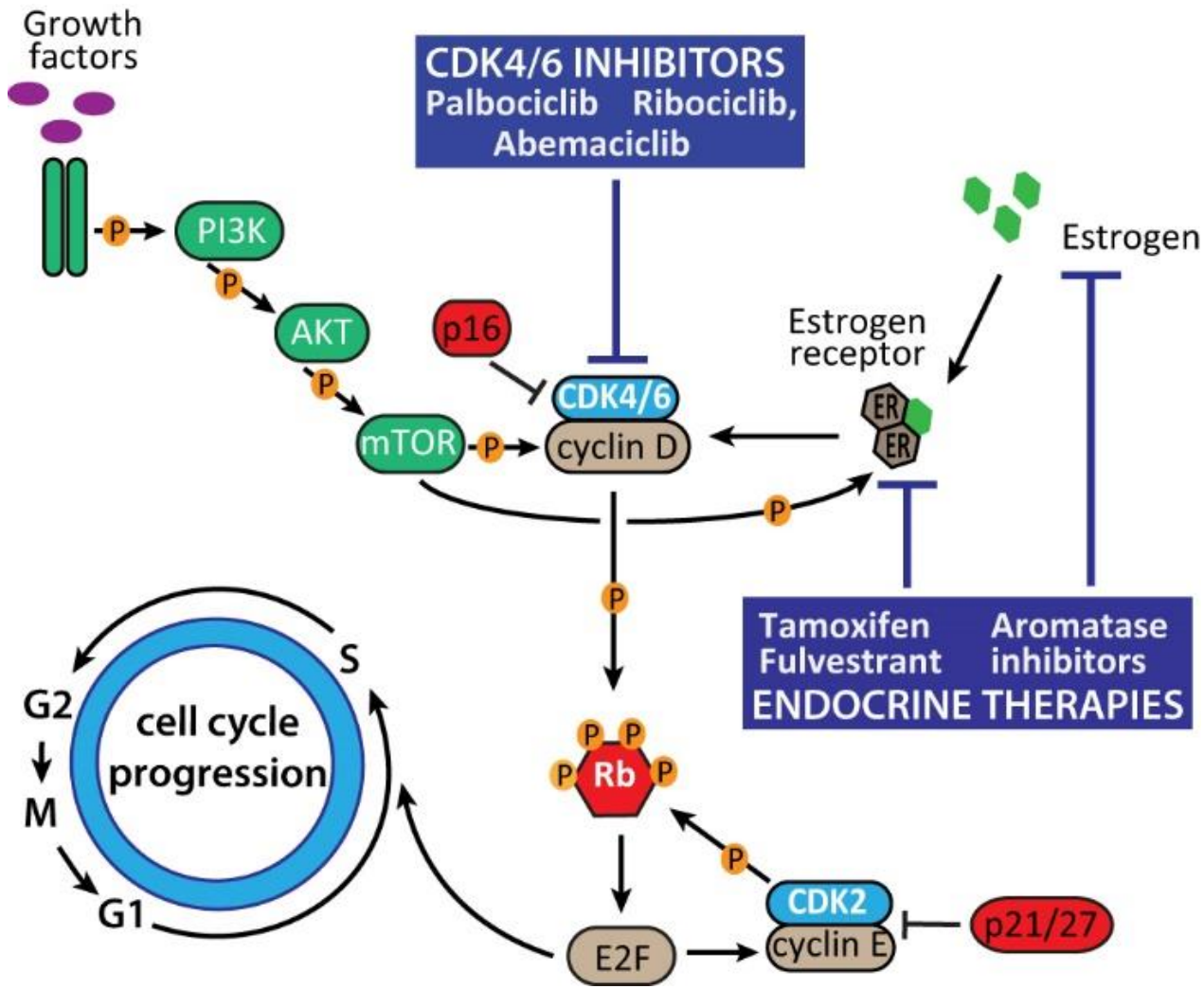

Endocrine therapies
Oestrogen
ER
IBRANCE
(aka palbociclib)
CDK4/6
Cyclin D1
M
G1
G2
S
G1
ARREST

CDK4/6 kinase inhibitors are used in combination with endocrine therapy, and they significantly increase the progression-free survival of patients with advanced estrogen receptor-positive (ER+) breast cancer in the first-line treatment setting.

Palbociclib (Ibrance)

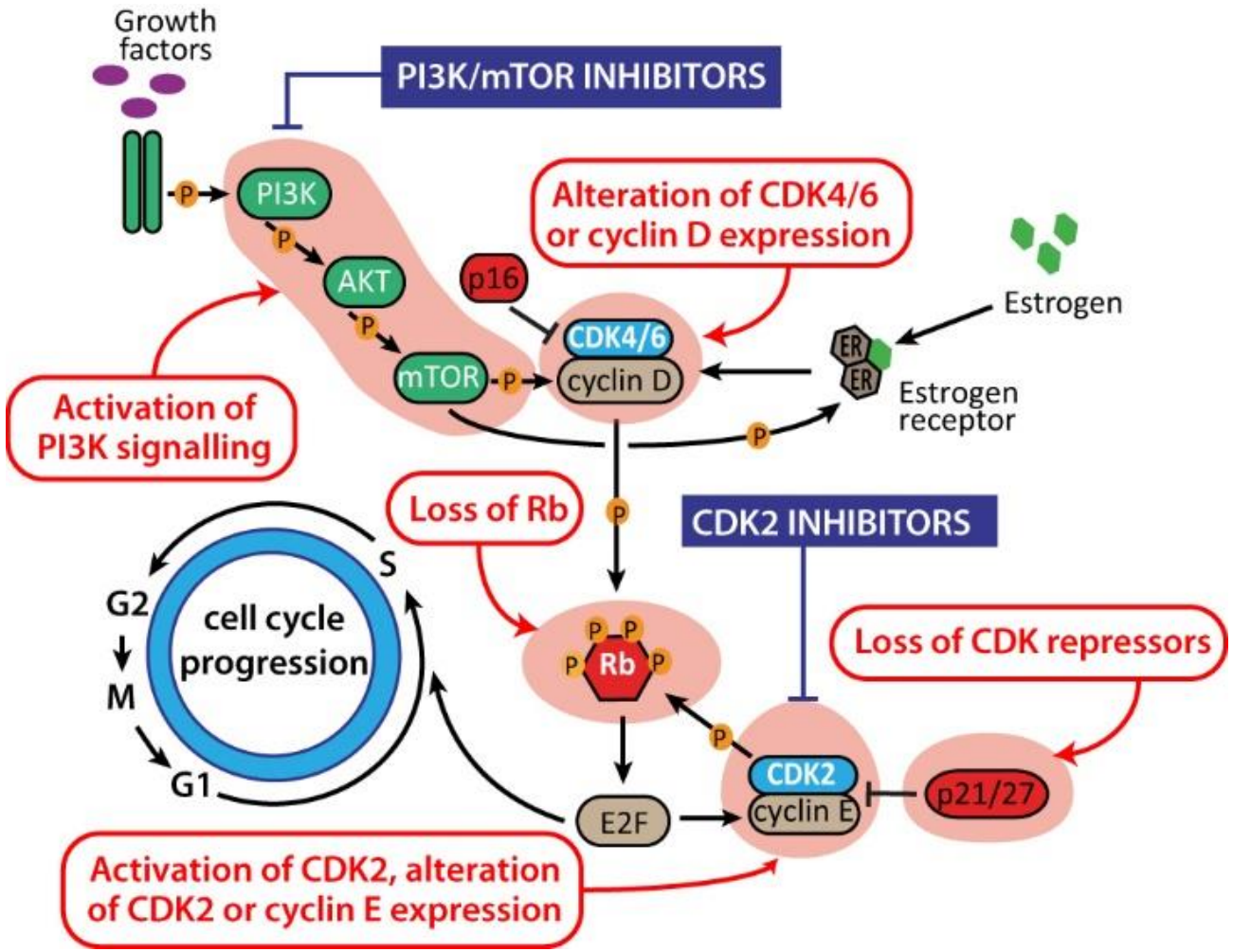
- Palbociclib: oral inhibitor of CDK 4/6
- Taken daily, 3 weeks on, 1 week off
- Most common toxicities: low white blood cell count (but no infections), fatigue, mild hair thinning

Regulation of cell cycle in ER+ breast cancer. Key pathways in promoting entry into the cell cycle in ER+ breast cancer and the nodes to which current therapies are targeted.

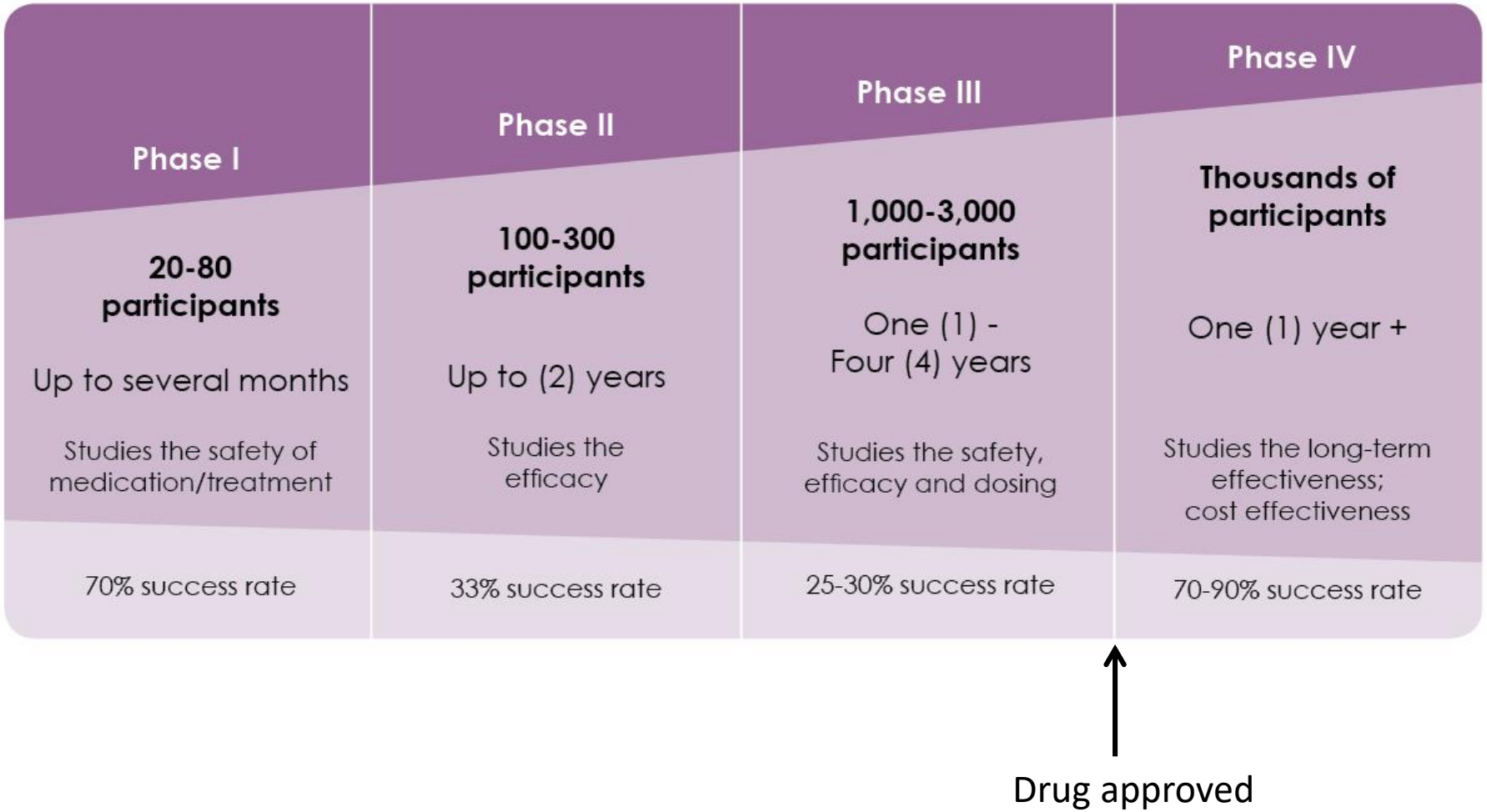


As the new standard of care in some countries, there is the clinical emergence of patients with breast cancer that is both CDK4/6 inhibitor and endocrine therapy resistant.

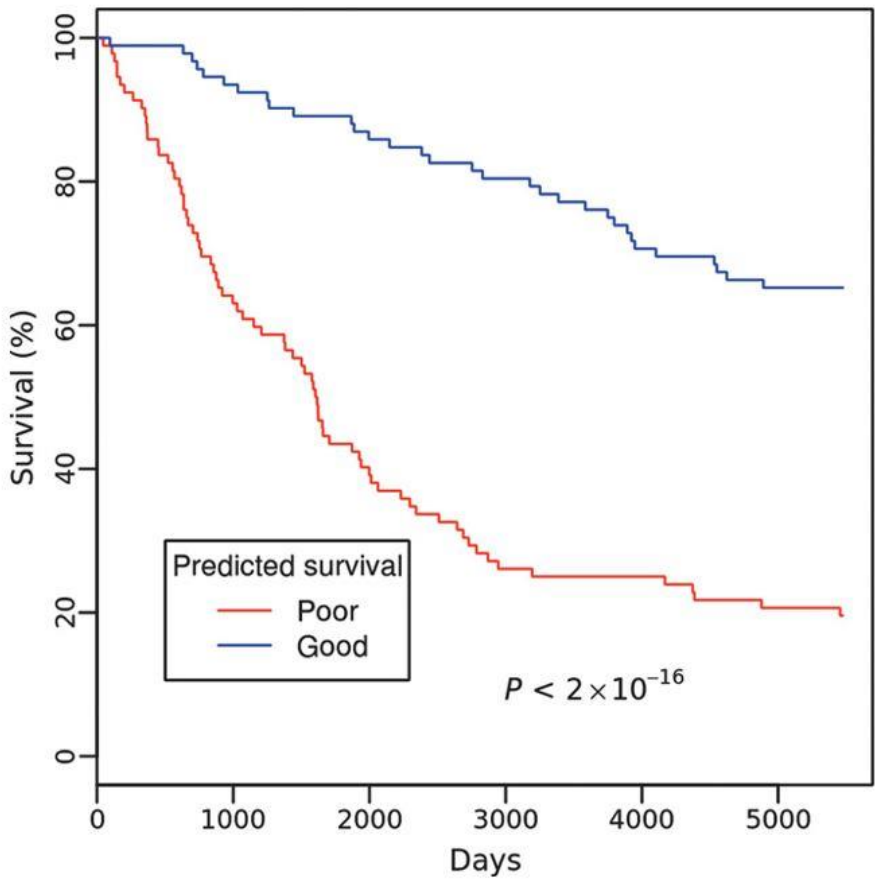
Mechanisms for development of resistance to CDK4/6 inhibitors are highlighted



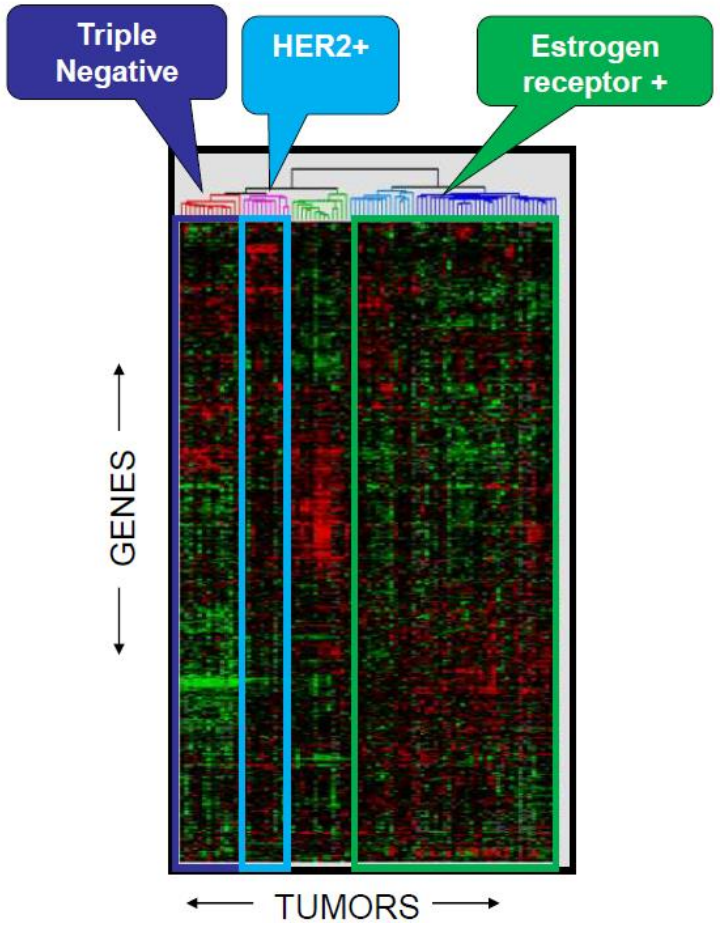
Clinical Trials for drugs



Efficacy in Phases II-III



Breast cancer is family of different cancers



Accurate grouping of breast cancers into clinically relevant subtypes is of particular importance for therapeutic decision making and thus urgently called for.

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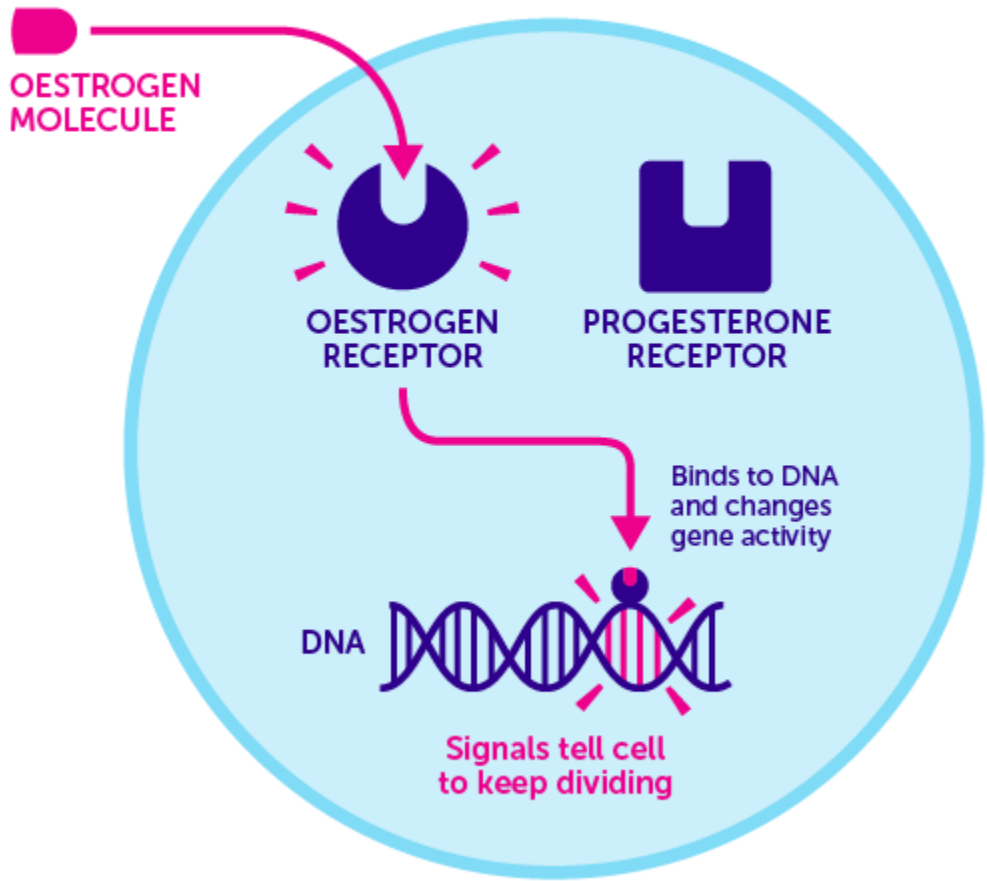


HER2 status

HER2 (human epidermal growth factor receptor 2) is a protein that appears on the surface of some breast cancer cells. It may also be called HER2/neu or ErbB2.

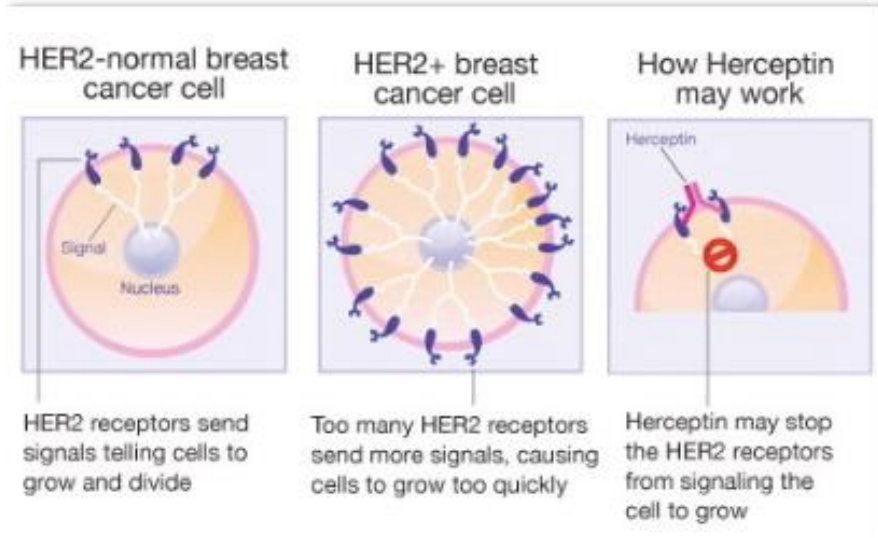
The HER2 protein is an important part of the pathway for cell growth and survival.

- **HER2-positive** breast cancers have a lot of HER2 protein. You also may hear the term HER2 over-expression.
- **HER2-negative** breast cancers have little or no HER2 protein.

About 10-20 percent of newly diagnosed breast cancers are HER2-positive [20,41].

HER2 status is part of breast cancer staging and helps guide your treatment.

Herceptin (aka trastuzumab)

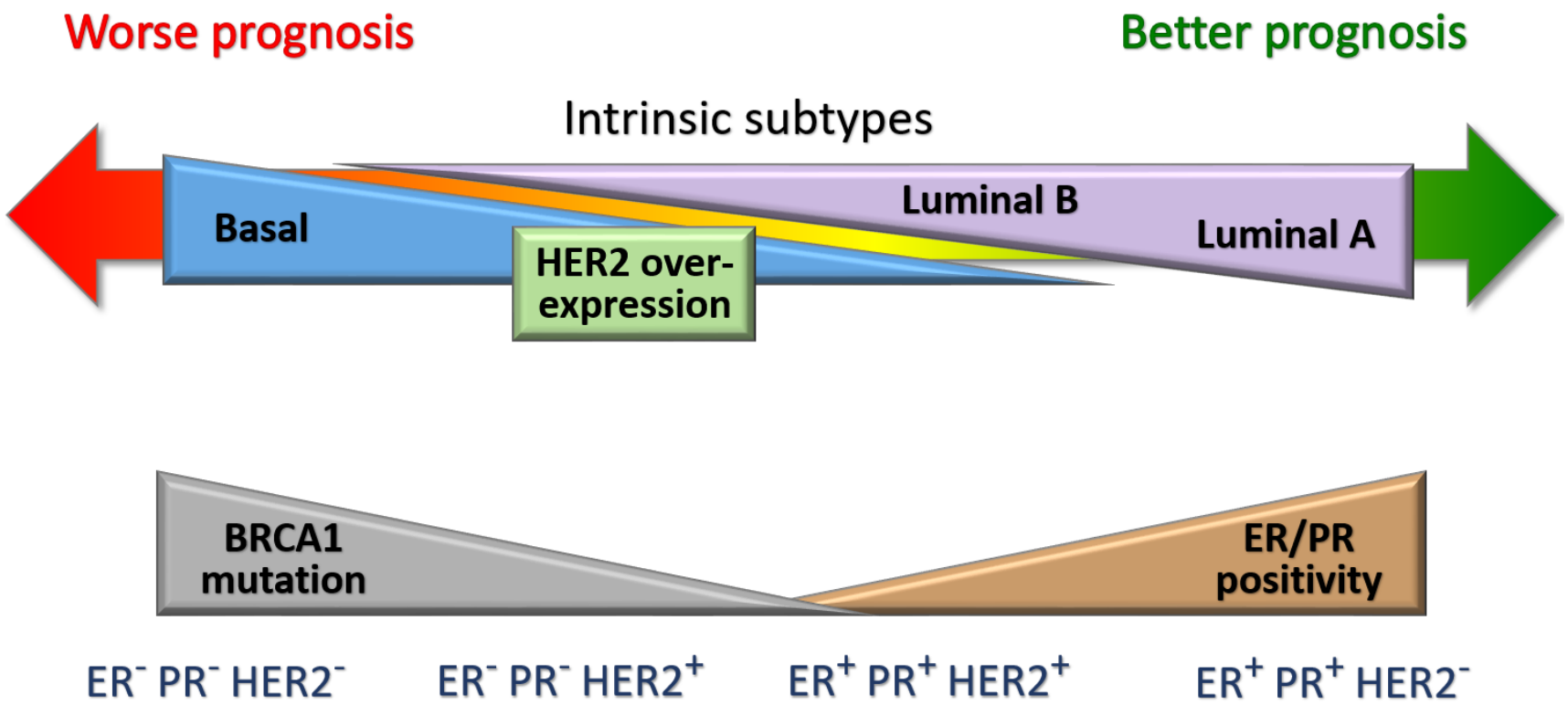


Patient outcomes based on breast cancer intrinsic (molecular) subtypes

Expand information used to stratify patients for prognosis:

Classical clinical parameters age, node status, tumor size, histologic grade.

Pathologic markers ER, PR, and HER2.



PMID 26693050

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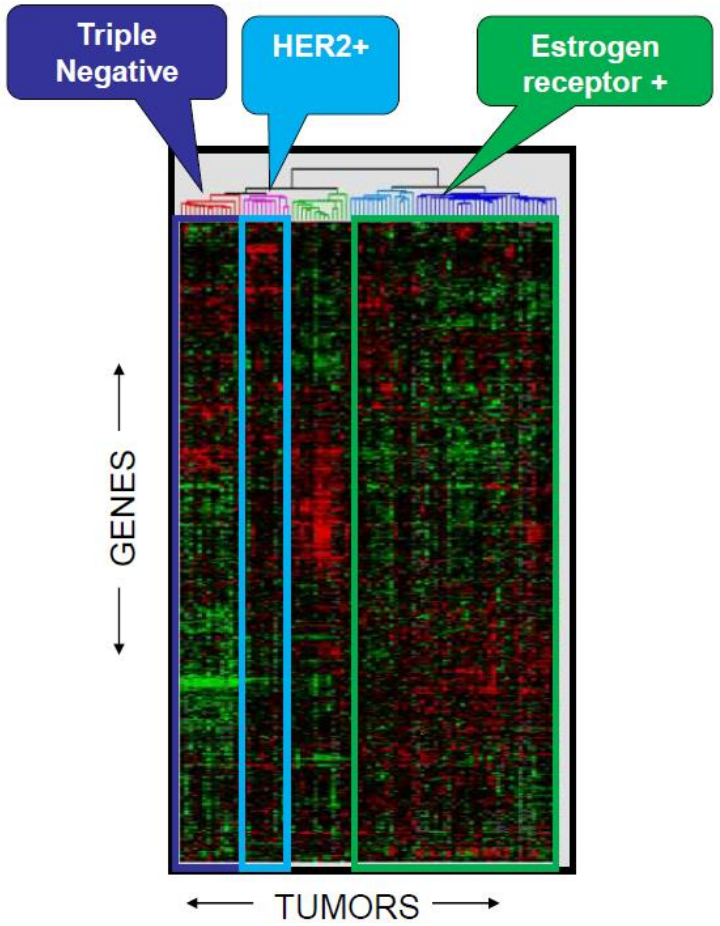

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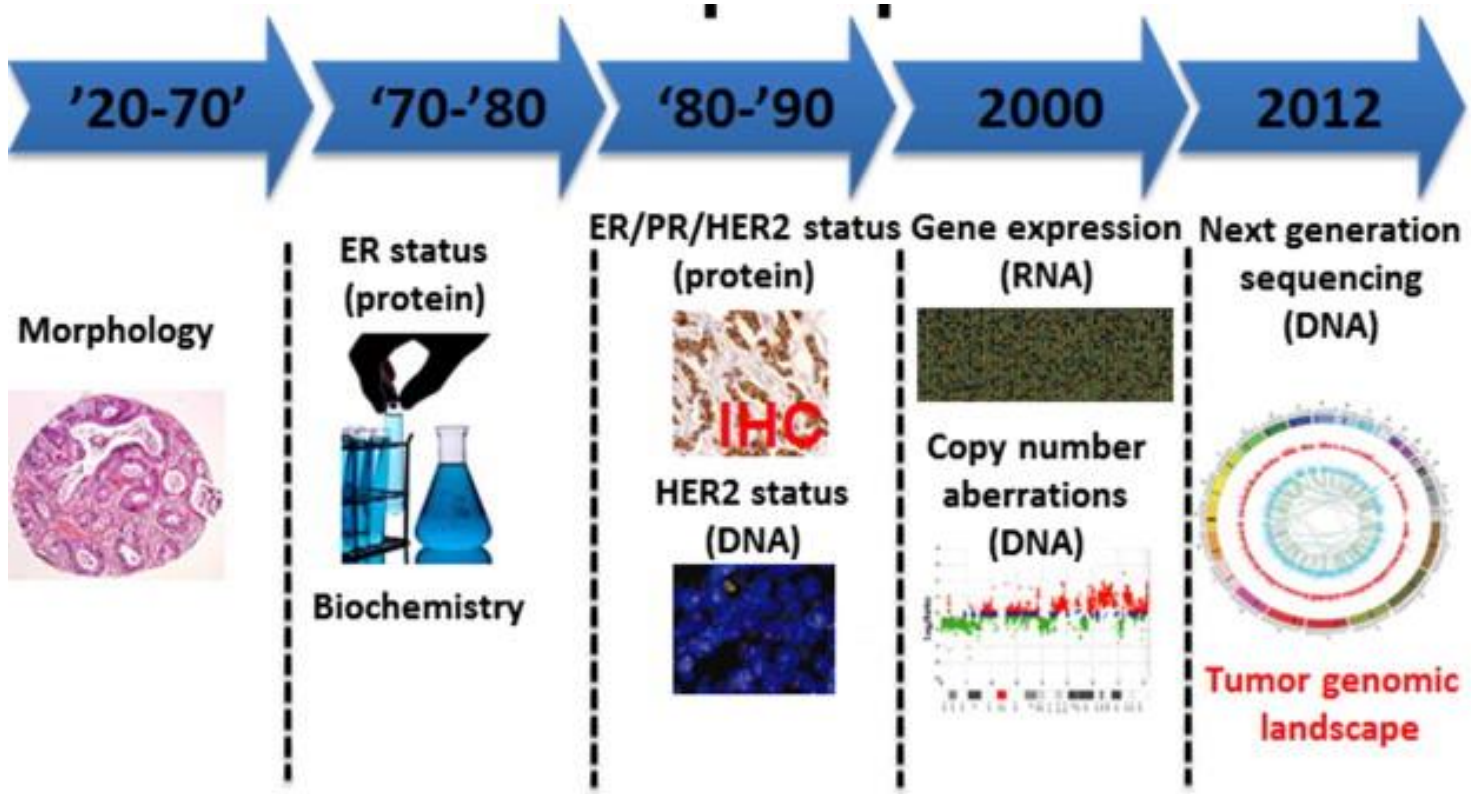
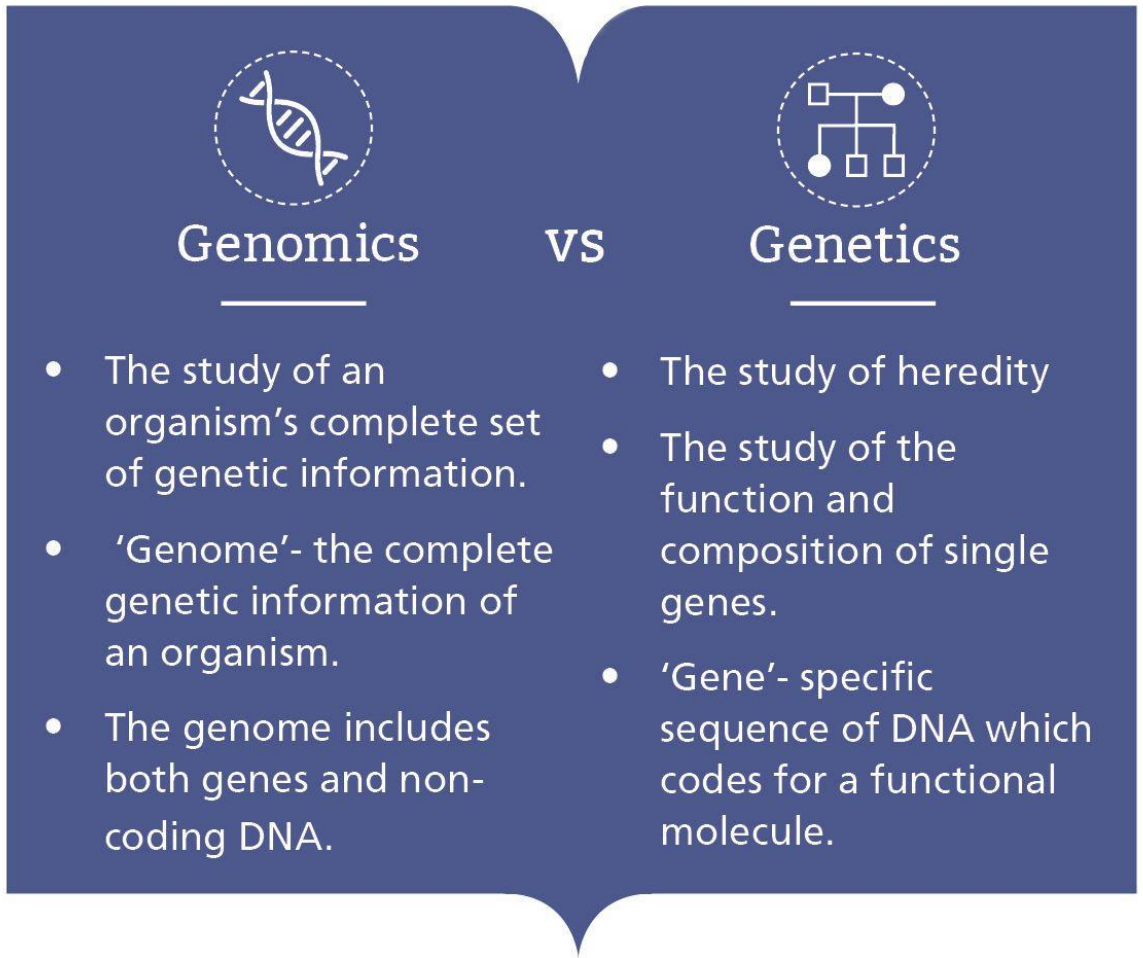

'20-70'
'70-'80
'80-'90
2000
2012
Morphology
ER status (protein)
Biochemistry
ER/PR/HER2 status (protein)
IHC
HER2 status (DNA)
Gene expression (RNA)
Copy number aberrations (DNA)
Next generation sequencing (DNA)
Tumor genomic landscape

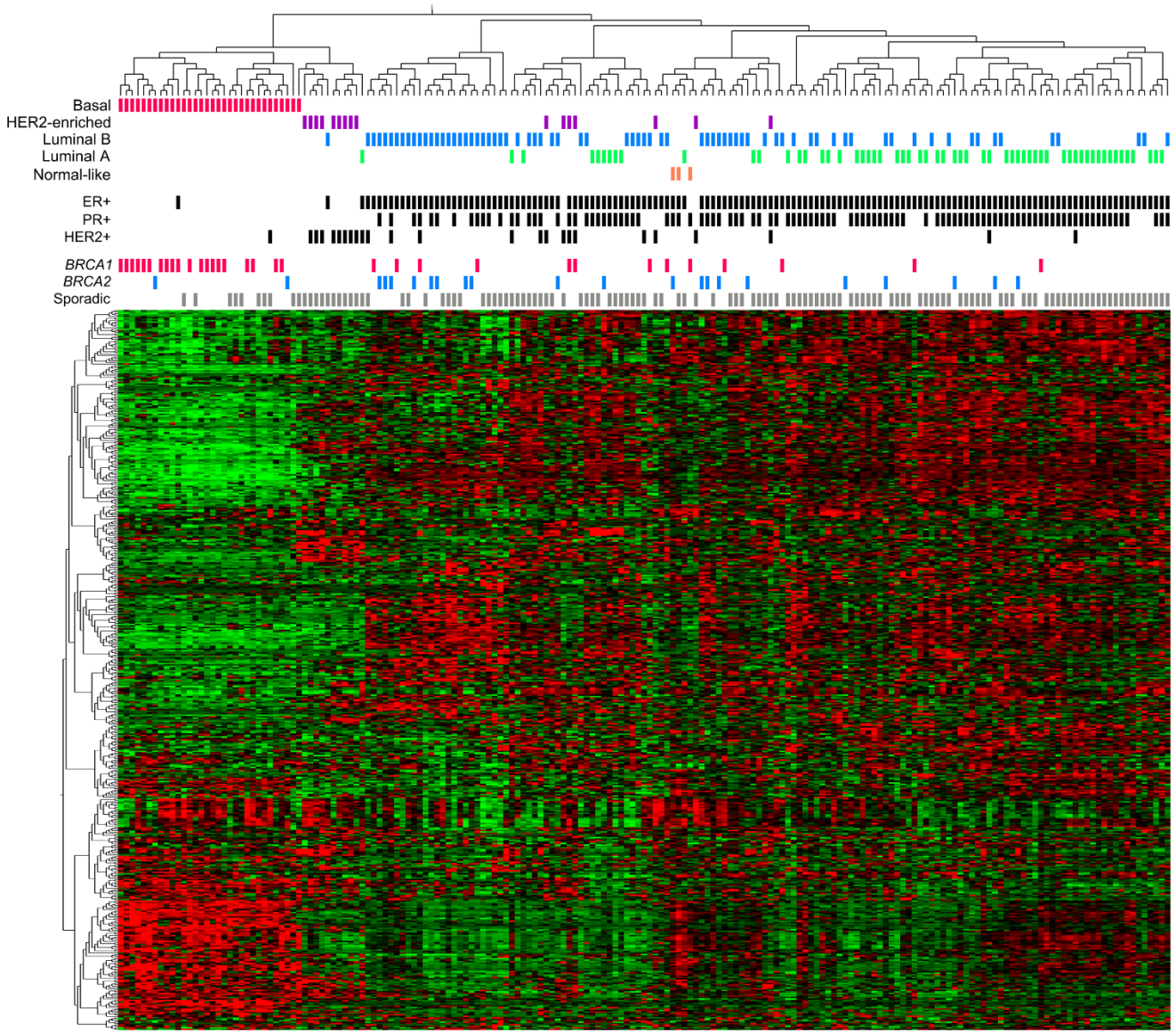
Classical immunohistochemistry (IHC) markers such as ER, PR and HER2, together with traditional clinicopathological variables including, e.g., tumor size, tumor grade and nodal involvement, are conventionally used for patient prognosis and management.

The advent of high-throughput platforms for gene expression analysis has shown that tumor cell response to treatment is not determined by anatomical prognostic factors but rather intrinsic molecular characteristics that can be probed using molecular method.

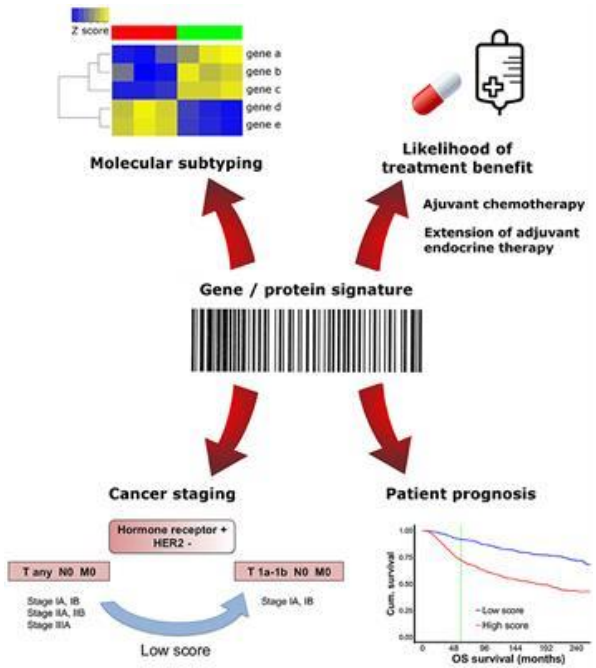
Genomic tests analyze a sample of a cancer tumor to see how active certain genes are. The activity level of these genes affects the behavior of the cancer, including how likely it is to grow and spread. Genomic tests are used to help make decisions about whether more treatments after surgery would be beneficial.



Subtypes of breast cancer, defined by differential expression of a panel of genes, have been shown to be predictive of risk of recurrence and benefit of hormonal therapy and chemotherapy.



Goal: Better inform treatment decisions



Oncotype Dx and Oncotype DCIS

Estrogen receptor: ESR1, PGR, BLC2, SCUBE2
Proliferation: Ki67, STK15, Survivin, CCNB1, MYBL2
Related: HER-2, GRB7, MMP11, CTSL2, GSTM1, CD68, BACG1
Reference Genes: ACTB, GAPDH, RPLPO, GUS, TFRC

Proliferation: Ki67, STK15, Survivin, CCNB1, MYBL2
Hormone Receptor Group: PR, GSTM1
Reference Genes: ACTB, GAPDH, RPLPO, GUS, TFRC

Prosigna

PGR, NAT1, BCL2, ESR1, MAPT, MDM2, CXXC5, GPR160, FOXA1, MLPH, SLC39A6, ACTR3B, BLVRA, TMEM45B, CDH3, MMP11, SFRP1, FOXC1, MIA, KRT14, MYC, BAG1, ERBB2, GRB7, PHGDH, PTTG1, KRT5, KRT17, UBE2C, CDC6, ANLN, ORC6L, TYMS, BIRC5, CEP55, CENPF, CCNB1, RRM2, MK167, CCNE1, KIF2C, CDC20, UBE2T, MYBL2, EX2O1, MELK, EGFR, FGFR4

Breast Cancer Index

BUB1B, CENPA, NEK2, RACGAP1, RRM2
HOXB13:IL17BR (H/I or MGI ratio)

MammaPrint

AL0B005D, COMBIG63649RC, LOC5120CJ, COMBIG45216RC, COMBIG38288RC, AA555029RC, CONBIG2655, 26552RC, FLT9, MMP9, DC13, EXT1, AL137718, PK428, HEC, ECT2, GMPS, CONBIG22185RC, UCH37, CONBIG35251RC, DCK, CENPA, SM20, MCM6, AKAP2, CONBIG5645, TRC, RFC4, DKFZP584D062, SLC2A3, NP1, CONBIG46831RC, CONBIG24252RC, FLJ11180, CONBIG51464RC, IGFBPS, IGFBPS
CCNE2, ESM1, COMBIG28217RC, DECI, AP2B1, CFFM4, PEC1, TOFB3, COMBIG45223RC, COMBIG55377RC, HSA250830, GSTM3, BBC3, CEGP1, COMBIG48328RC, WISP1, ALDH4, KAA1442, CONBIG32125RC, FGF10

EndoPredict

Cancer genes: BIRC5, UBE2C, DHCR7, RBBP8, IL6ST, AZGP1, MGP, and STC2
House keeping genes: CALM2, OAZ1, and RPL37A

Videssa Breast

SPBs: IL-6, IL-8, TNF-α, INF-γ, CEA, ErbB2, OPN, HGF, FasL, VEGF-C, VEGF-D
TaaBs: ALG10, ATF3, ATP6AP1, BAT4 (GPANK1), BDNF, BMX, C15orf48 (NMES1), CSNK1E, CTAG1A, CTAG2, CTBP1, DBT, EIF3E, FRS3, GPR157, HOXD1, IGFBP2, MUC1, MYOZ2, p53, PDCD6IP, RAB5A, RAC3, SELL, SERPINH1, SF3A1, SLC33A1, SOX2, TFCP2, TRIM32, UBAP1, ZMYM6, ZNF510

Biological samples

Condition 1 (e.g. tumor)

Condition 2 (e.g. normal)

Isolate RNA

Poly(A) tail

Generate cDNA, Construct fragment library

High-throughput sequencing platform

100s of millions of paired reads
10s of billions bases of sequence

Generate reads

Unsequenced RNA

RNA reads

Short insert

Align reads to reference genome

Intron

pre-mRNA

Exon

Transcript

Short reads

Downstream analysis