Precision medicine in oncology

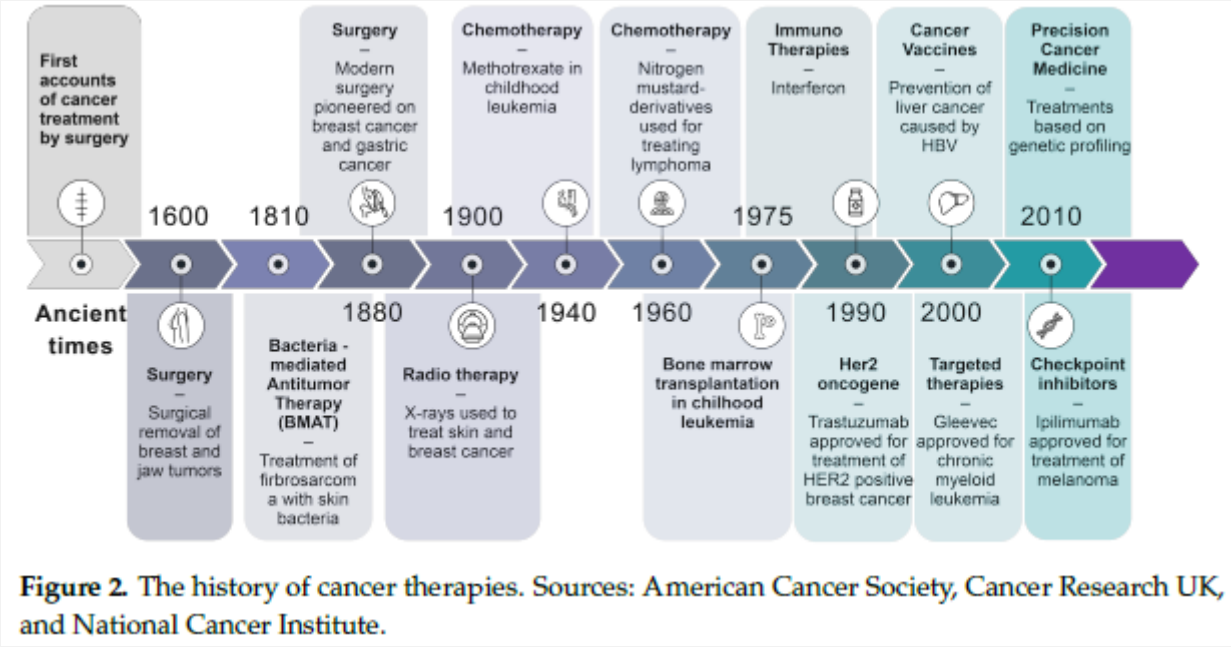
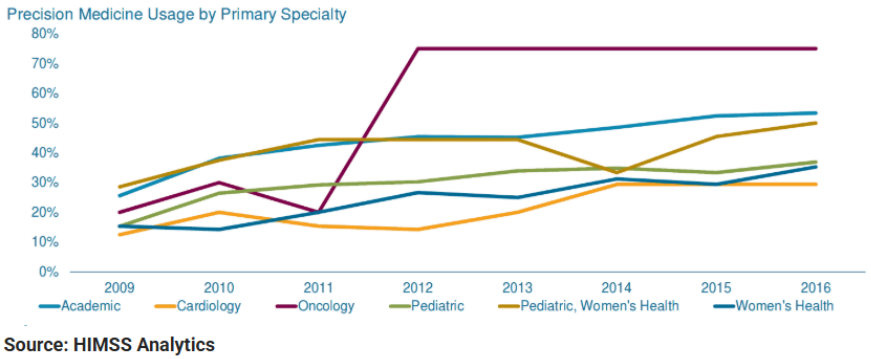


Figure 2. The history of cancer therapies. Sources: American Cancer Society, Cancer Research UK, and National Cancer Institute.

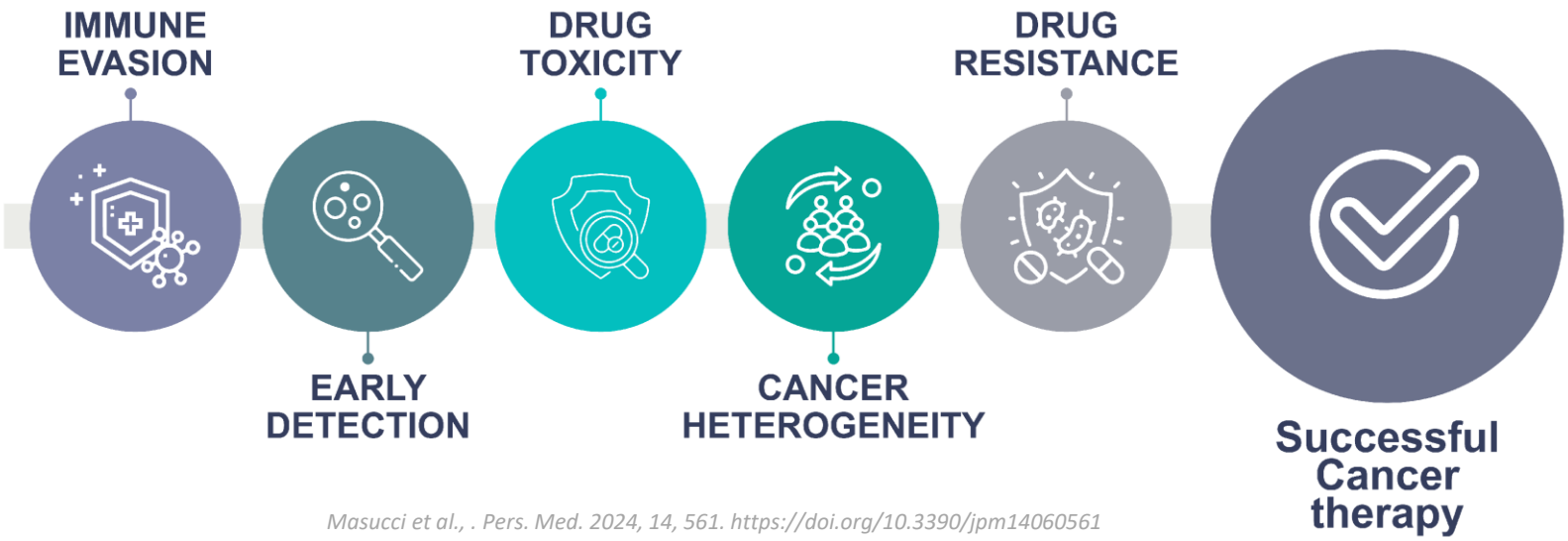
Masucci et al., 2024. Pers. Med. https://doi.org/10.3390/jpm14060561

Cancer treatment has made great progress with the introduction of precision medicine and targeted therapies in clinical practice. They have led to improved survival rates, better clinical outcomes and more effective disease management.



Source: HIMSS Analytics

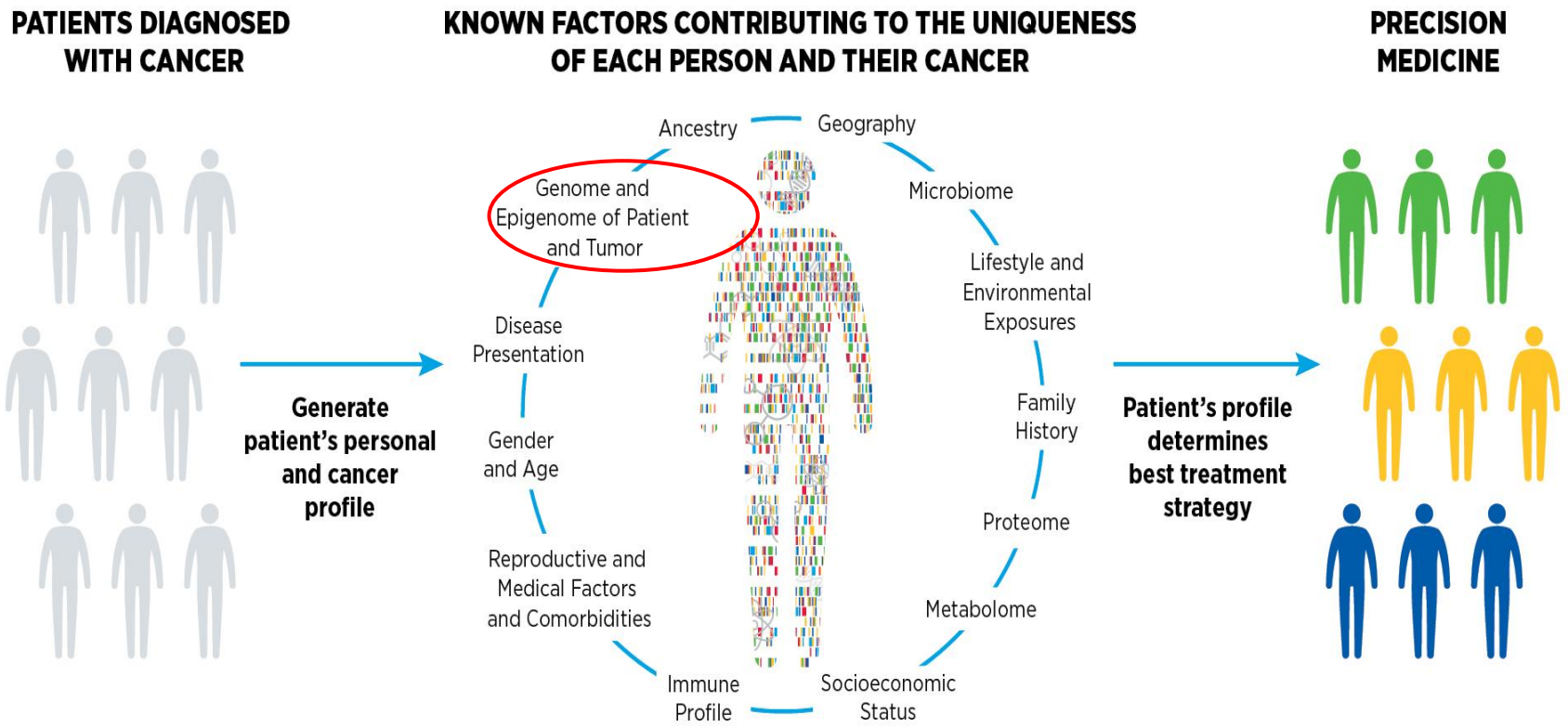
Goals and challenges of personalized cancer medicine



Masucci et al., . Pers. Med. 2024, 14, 561. https://doi.org/10.3390/jpm14060561

- **Tailored treatments**: selecting drugs which acts on specific genetic mutations or protein changes within a tumor (identification of specific tumor's biomarkers).
- **Maximizing effectiveness and reducing side effects:** identifying the treatment most likely to work, reducing the need for trial-and-error and limiting toxic effects.
- **Overcoming treatment resistance:** identifying and targeting the specific subclones within a tumor that drive resistance to therapy
- **Earlier detection and prevention:** genetic profiling to identify individuals at higher risk for specific cancers and implementing personalized screening or preventive strategies

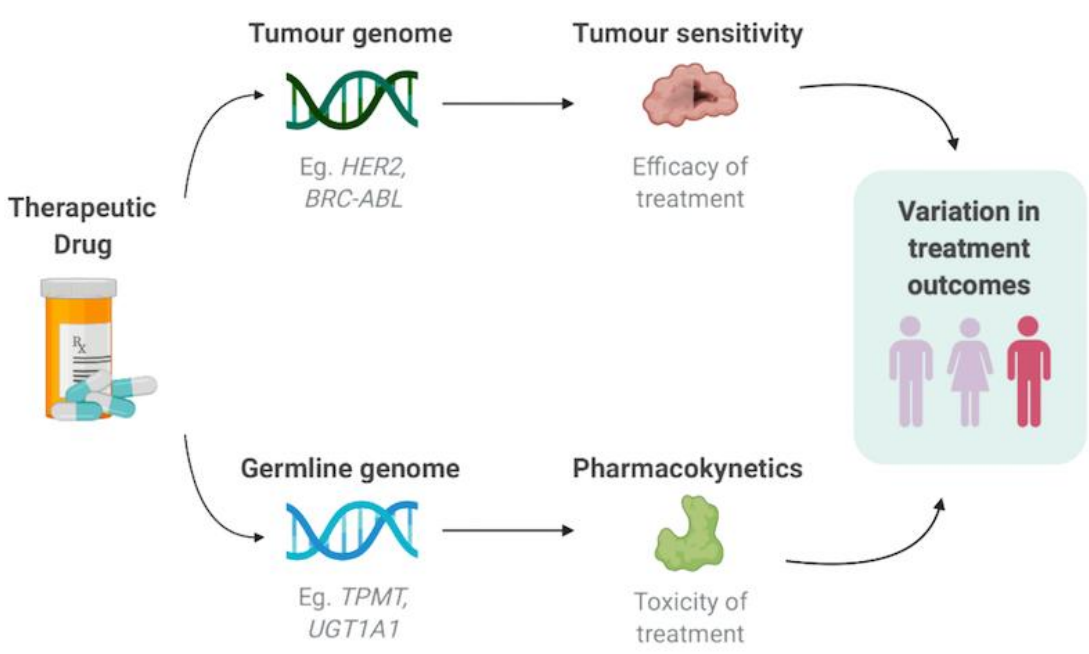
Precision Medicine



© 2024 American Association for Cancer Research®. *AACR Cancer Disparities Progress Report 2024.* 2305052-F6.

Currently, genetic variations represent the predominant factor influencing precision medicine in cancer and pharmacogenomics has become a cornerstone of precision oncology. Cancer pharmacogenomics is the study of how variances in the genome influences an individual's response to different cancer drug treatments.

Cancer pharmacogenomics



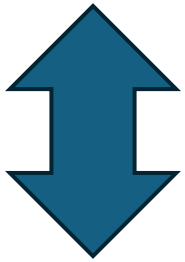
Somatic mutations (Tumor)

Germline mutations (Host)

Modified from: https://www.biocode.org.uk/cancer-pharmacogenomics/

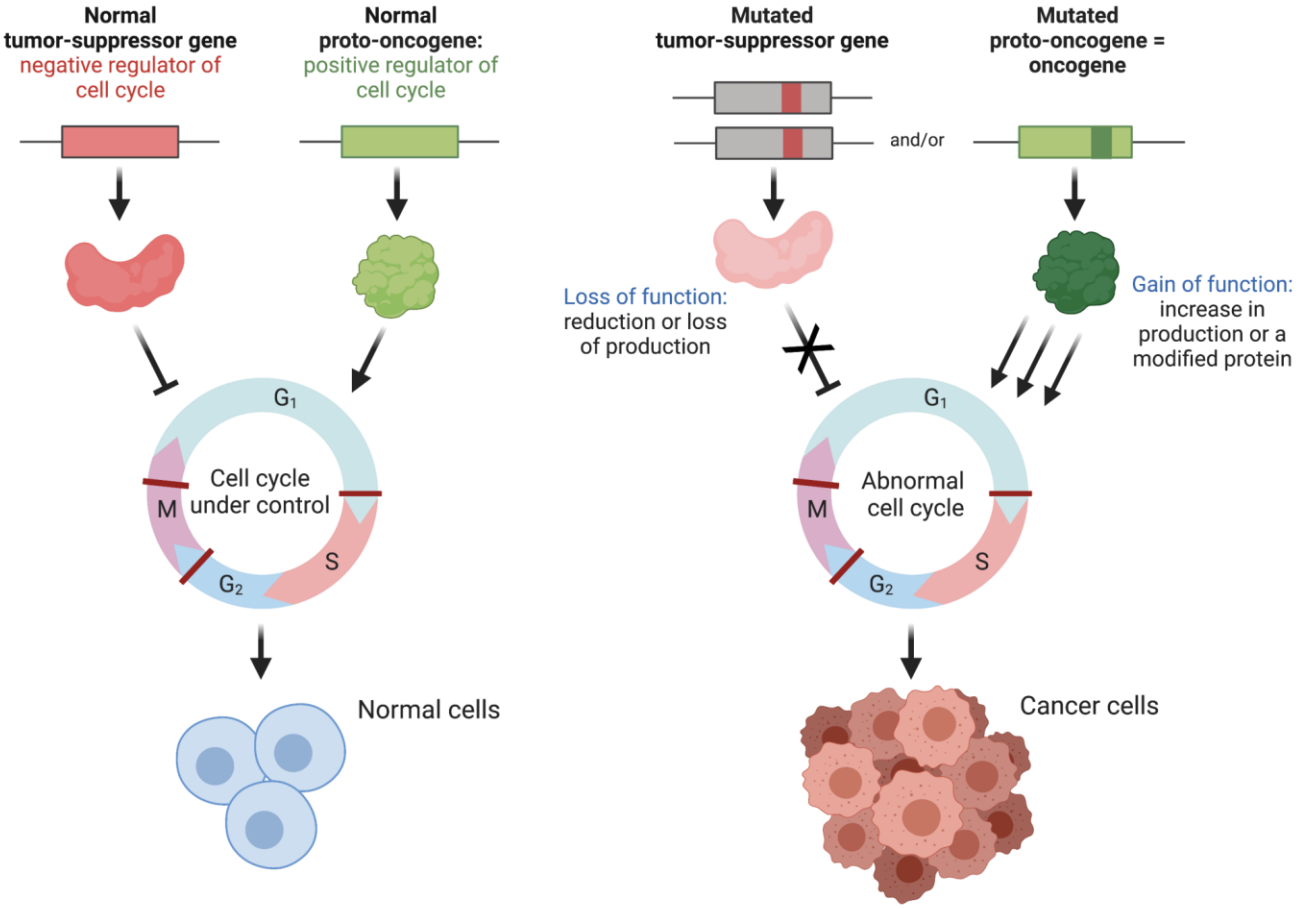
Both the **individual genome** and the **tumor genome** influence the response to cancer drug treatment

Germline pharmacogenetics studies inherited genetic variants that are present in every cell of the body. These variants are passed from parents to offspring and remain constant throughout life. They mainly affect drug absorption, metabolism, distribution and elimination, impacting treatment efficacy and the risk of adverse drug reactions or therapeutic failure.



Somatic pharmacogenetics studies acquired genetic changes that occur in tumor cells. These variants are not inherited and are not present in normal cells. They mainly affects drug targets in cancer and tumor sensitivity or resistance to therapy.

Mutations in cancer cells

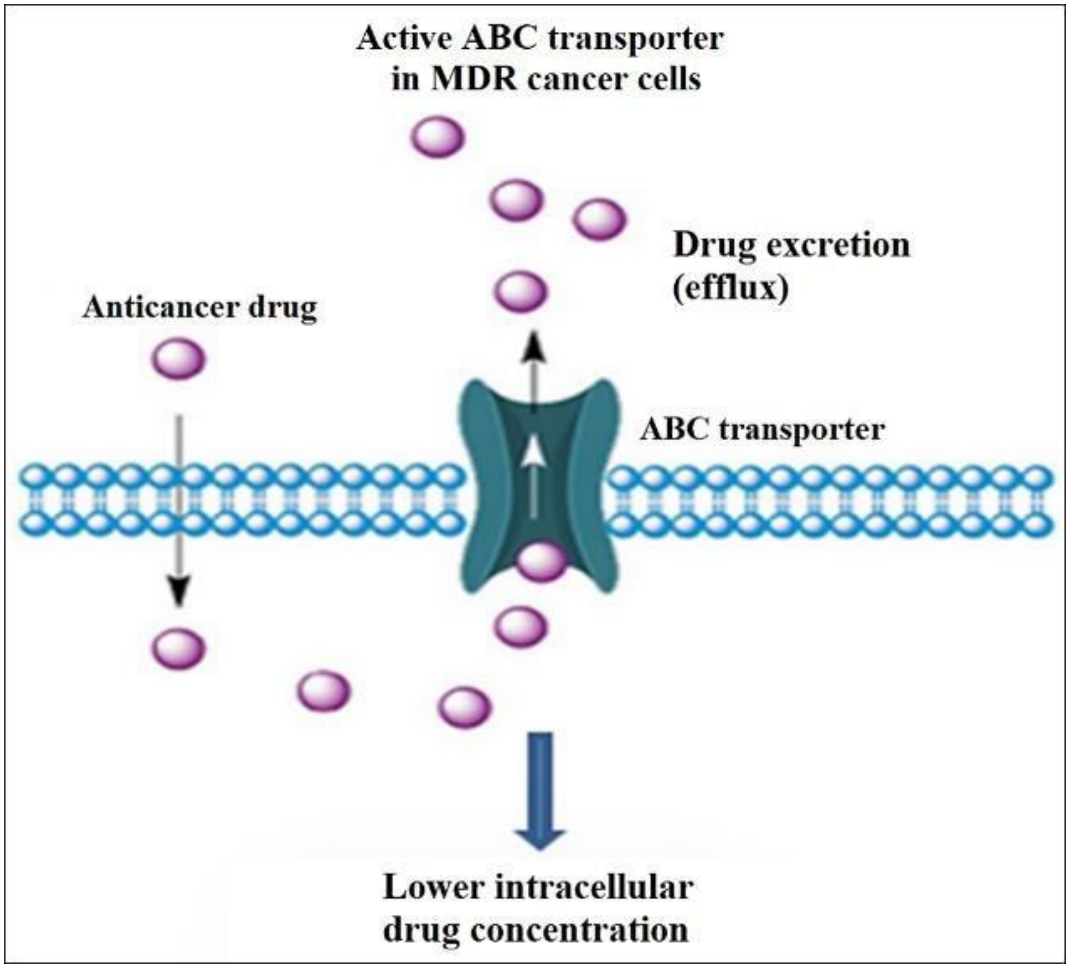


https://slcc.pressbooks.pub/collegebiology1/chapter/cancer-and-the-cell-cycle/

Proto-oncogenes are normal genes involved in cell growth and survival. When activated by mutations, amplifications, or chromosomal translocations, they become **oncogenes** that promote uncontrolled cell proliferation.

Tumor suppressor genes inhibit cell division, repair DNA damage, and promote apoptosis. Cancer arises when both copies of these genes are inactivated, leading to loss of growth control.

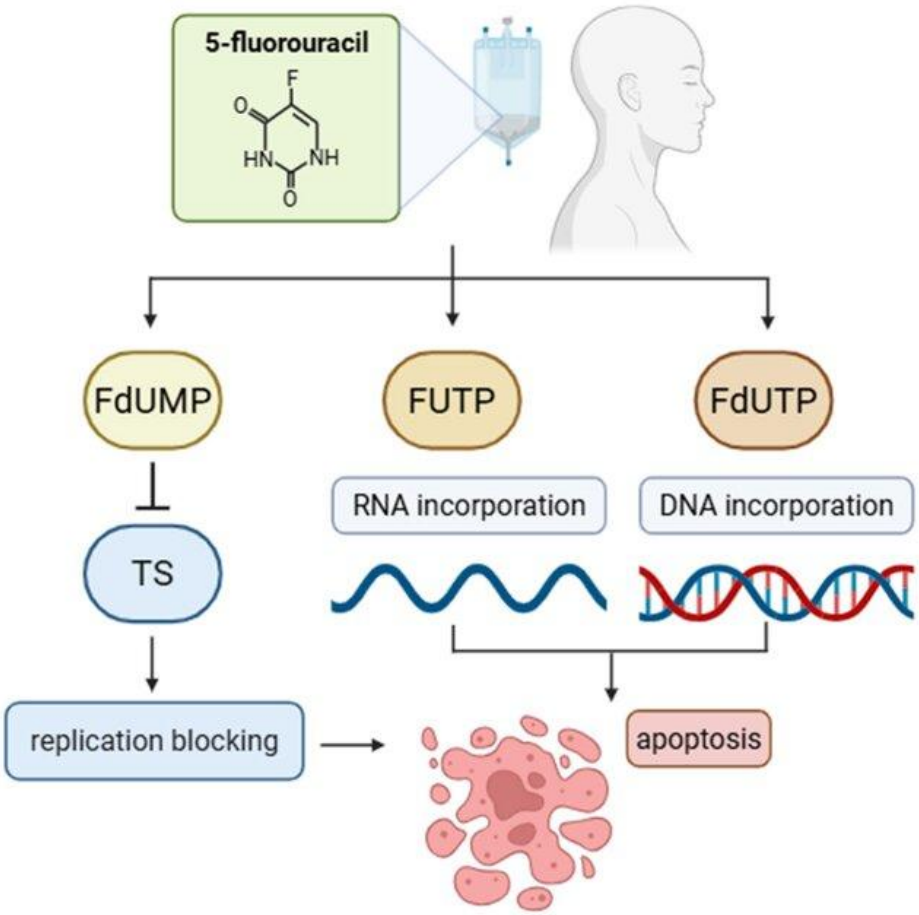
Mutations in cancer cells



Hamed et al., 2019. Bulletin of the National Research Centre. https://doi.org/10.1186/s42269-019-0043-8

Tumor cells often overexpress **ABC transporters**: the increased drug efflux reduces intracellular drug concentration and contributes to multidrug resistance in cancer therapy.

5-Fluorouracil (5-FU) and DPYD gene variants



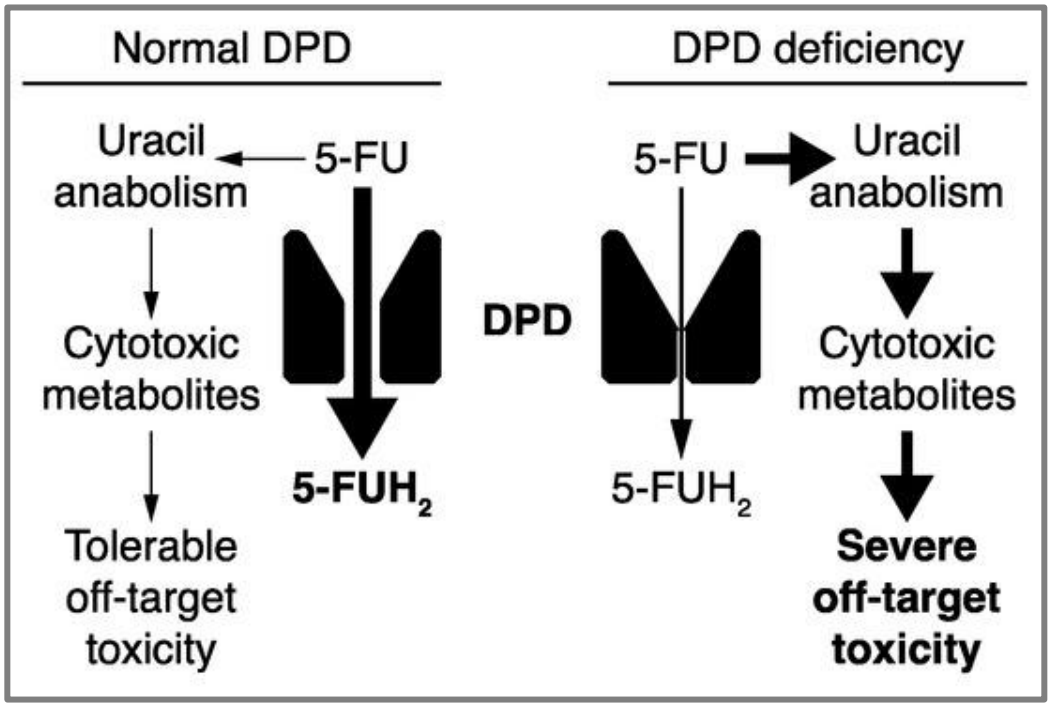
Sarna et al. Curr. Issues Mol. Biol. 2025, 47, 609. https://doi.org/10.3390/cimb47080609

5-FU is a widely used chemotherapeutic drug for the treatment of solid tumors, including colorectal, breast, and gastrointestinal cancers.

5-FU is metabolized into several active forms, including fluorodeoxyuridylate (FdUMP), fluorouridine triphosphate (FUTP), and fluorodeoxyuridine triphosphate (FdUTP). FdUMP inhibits thymidylate synthase (TS), leading to the disruption of DNA synthesis and replication blocking. FUTP is incorporated into RNA, impairing its function, while FdUTP is incorrectly incorporated into DNA.

These combined effects lead to the apoptosis of rapidly dividing cells.

5-Fluorouracil (5-FU) and DPYD gene variants



Diasio and Offer. Cancers 2022, 14, 3207. https://doi.org/10.3390/cancers14133207

80% of 5-FU is inactivated to 5,6-dihydro-5-fluorouracil by **dihydropyrimidine dehydrogenase** (**DPD**), an enzyme encoded by the DPYD gene.

Genetic variants in DPYD can lead to decreased enzyme activity, causing the accumulation of toxic amount of 5-FU and increasing the risk of severe side effects such as myelosuppression, gastrointestinal toxicity (mucositis, nausea and diarrhea) and neurotoxicity.

Table 1. Reference information for commonly tested *DPYD* variants associated with DPD deficiency and increased risk of severe 5-FU toxicity.

rsID	RefSeqGene ID (LRG_722 NG_008807.2)	Transcript Change (NM_000110.3)	Amino Acid Change (NP_000101.2)	Other Names	Functional Impact
rs3918290	g.476002G>A	c.1905+1G>A	N/A [1]	IVS14+1G>A, *2A	Completely deleterious
rs55886062	g.410273T>G	c.1679T>G	p.I560S	*13	Severely deleterious
rs67376798	g.843669A>T	c.2846A>T	p.D949V	-	Partially deleterious
rs75017182	g.346167C>G	c.1129-5923C>G	N/A [2]	HapB3, rs56038477 (c.1236G>A, p.E412E) [3]	Partially deleterious
rs115232898	g.226586A>G	c.557A>G	p.Y186C	-	Partially deleterious

N/A, not applicable. [1] Does not directly encode for an amino acid change but causes alternative splicing and the in-frame deletion of exon 14. [2] Does not directly encode for an amino acid change; causes non-obligate alternative splicing that introduces a frameshift and premature stop codon. [3] The rs56038477 variant is in strong LD with the causal variant (rs75017182), can be assessed using exome-level data, and is often used as a proxy for rs75017182.

Diasio and Offer. Cancers 2022, 14, 3207. https://doi.org/10.3390/cancers14133207

Intermediate metabolizers are individuals carrying one normal and one decreased function allele (2846A>T and 1129-5923C<G) or two decreased function alleles.
Poor metabolizers carry two nonfunctioning alleles (190511G>A and 1679T>G) or one nonfunctioning allele and one decreased function allele.

The prevalence of partial DPD deficiency (IM) is approximately 3-5% in the population. Complete DPD deficiency is rare (-0.2% of individuals) but in these patients standard dose of 5-FU can be fatal.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 July 2020
EMA/367286/2020

EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine

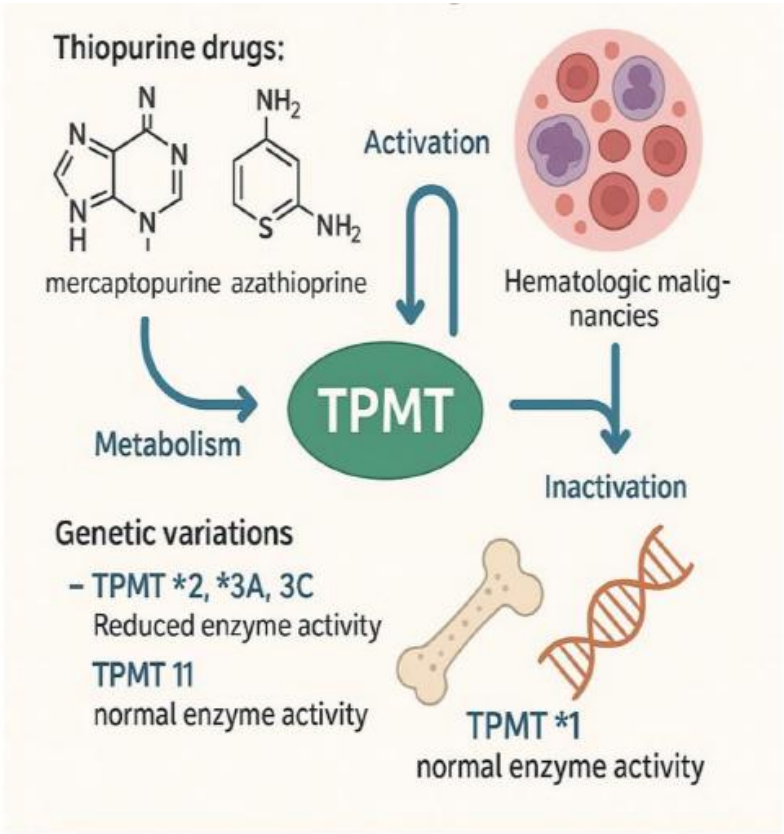
On 30 April 2020, EMA recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur.

Information for patients

Treatment with fluorouracil, capecitabine or tegafur

- Before starting cancer treatment with fluorouracil given by injection or infusion (drip), capecitabine or tegafur, your doctor should do a test to check whether you have a working DPD enzyme.
- If you have a known complete lack of DPD, you will not be given these treatments as they will increase the risk of severe and life-threatening side effects.
- If you have a partial DPD deficiency, your doctor may start treatment at low doses, which can be increased if there are no serious side effects.
- If you know that you have a partial DPD deficiency or if you have a family member who has partial or complete DPD deficiency, talk to your doctor or pharmacist before taking these medicines.
- If you are using fluorouracil applied to the skin for conditions such as actinic keratosis and warts you do not need a DPD test, as the level of fluorouracil absorbed through the skin into the body is very low.
- If you have any questions about your treatment or about DPD testing, talk to your doctor or pharmacist.

Thiopurines and TMPT



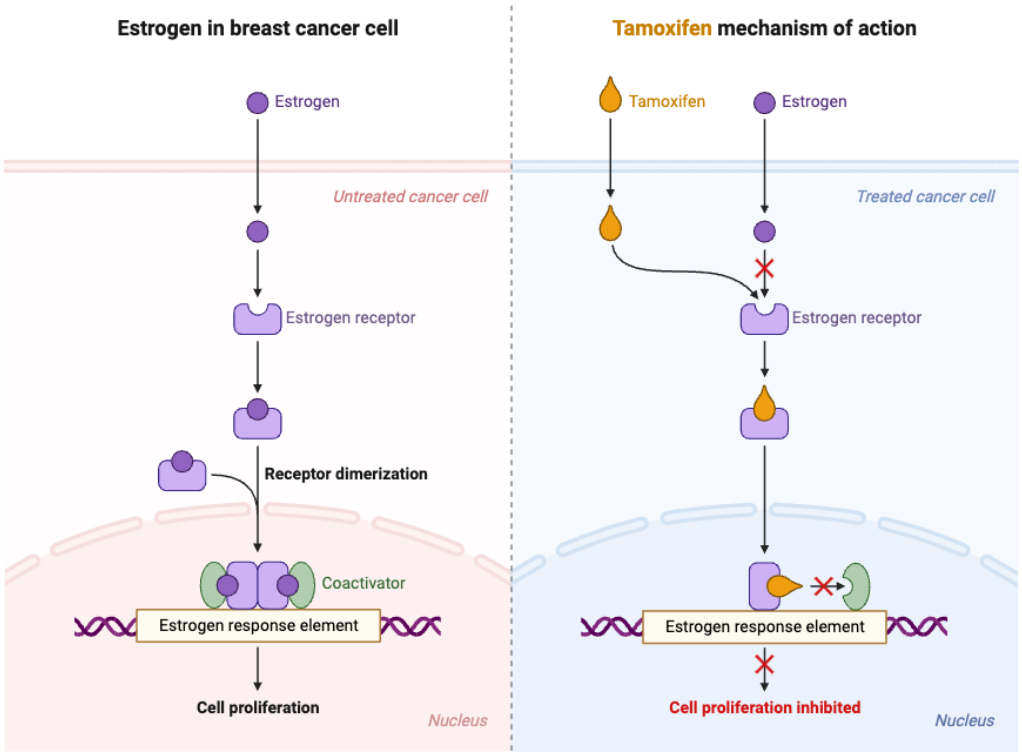
Nafchi et al., 2025. Mol Biol Rep 52, 785 (2025). https://doi.org/10.1007/s11033-025-10887-4

Thiopurine drugs, such as mercaptopurine and azathioprine, are commonly used to treat leukemia and other hematologic tumors.
Their pharmacological effects depend on intracellular activation to thioguanine nucleotides which incorporate into nucleic acids and exert cytotoxic effects in rapidly dividing cellls.

Thiopurine drugs are metabolized by the enzime **thiopurine S-methyltransferase (TPMT).**
Genetic variations in TPMT (*2, *3 A and 3C) result in reduced enzyme activity.
Patients carrying TPMT loss-of-function alleles have an increased risk of severe myelosuppression due to accumulation of thioguanine nucleotides in erythrocytes.

Less than 1% of individuals have complete TPMT deficiency and about 10% have intermediate TPMT activity (heterozygotes).
Guidelines recommend genotyping and dose reduction for TPMT heterozygotes or alterative therapy for TPMT-deficient patients.

Tamoxifen and CYP2D6

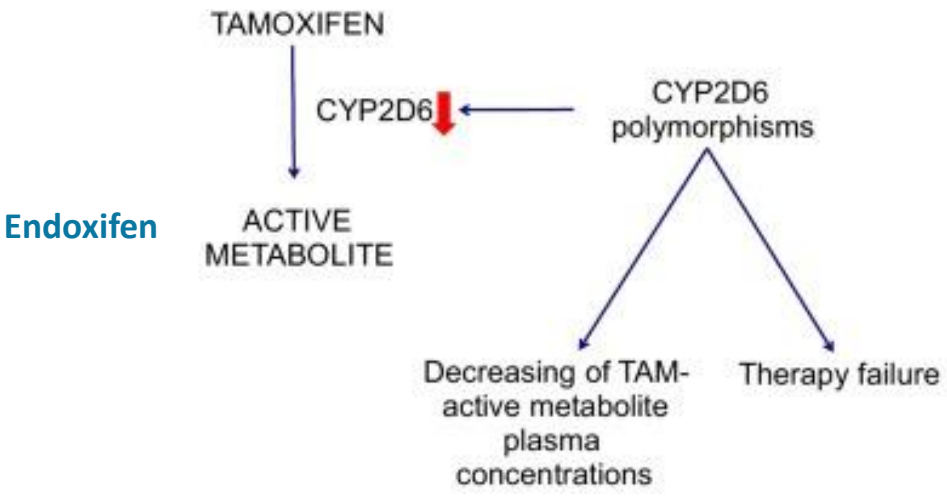


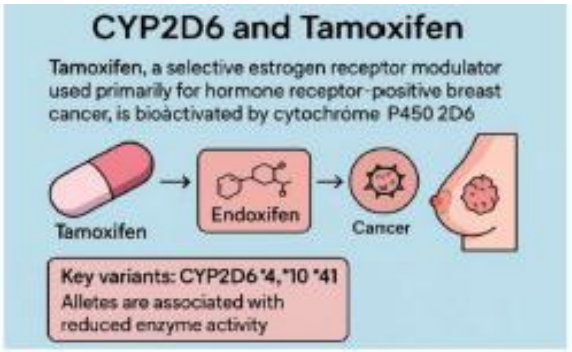
https://www.biorender.com/template/tamoxifen-mechanism-of-action-in-breast-cancer

Tamoxifen is a selective estrogen receptor (ER) modulator used primarily for the treatment of hormone-receptor-positive breast cancer. In breast tissue, tamoxifen acts as an ER antagonist and prevents estrogen-mediated transcription of genes involved in cell proliferation.

Approximately 30-50% of patients treated with tamoxifen show no therapeutic benefit.

Tamoxifen and CYP2D6





Del Re et al., 2016. Pharmacological research. 107, 398-406. https://doi.org/10.1016/j.phrs.2016.03.025.
Nafchi et al., 2025. Mol Biol Rep 52, 785 (2025). https://doi.org/10.1007/s11033-025-10887-4

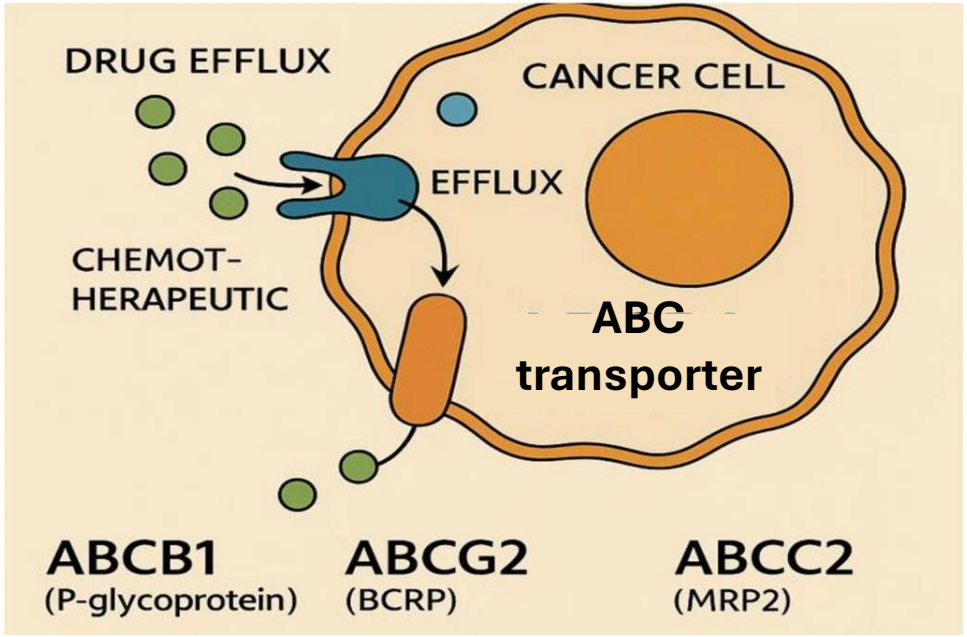
Tamoxifen is administered as a prodrug and bioactivated by CYP2D6 to the active metabolite endoxifen.

Variations in the CYP2D6 gene can drastically affect tamoxifen activation to endoxifen. CYP2D6 poor metabolizers may experience significantly reduced therapeutic benefit from tamoxifen and have a higher risk of breast cancer recurrence.

Higher tamoxifen doses

Alternative endocrine therapy (e.g. aromatase inhibitors)

ABC transporters and drug resistence



Modified from Nafchi et al., 2025. Mol Biol Rep 52, 785 (2025). https://doi.org/10.1007/s11033-025-10887-4

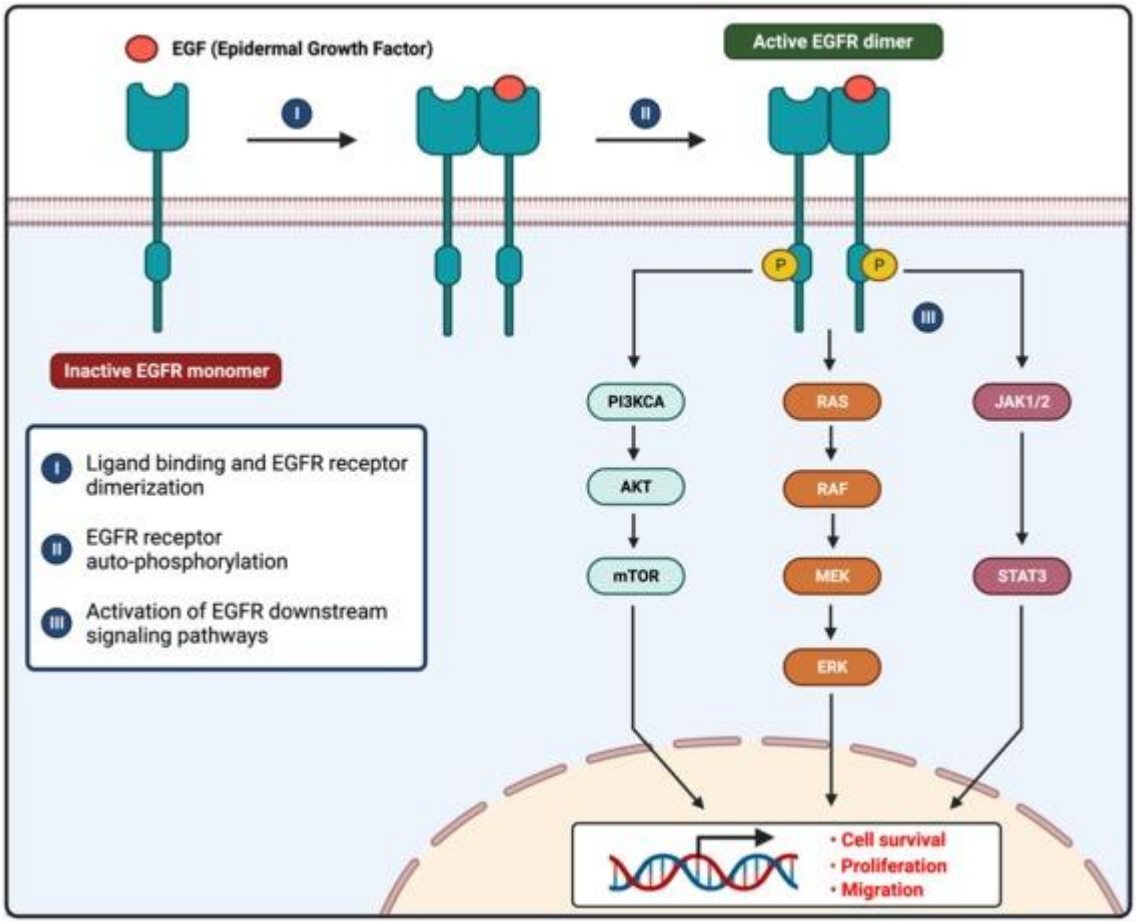
ABCB1 (P-gp)
Variants: 3435 C>T and 2677G>T/A
Poor response to taxanes, anthracyclines and vinca alkaloids
Resistence in leukemia and breast cancers

ABCG2 (BCRP)
Poor response to topotecan, methotrexate and anthracyclines
Resistence in breast, lung and colorectal cancer

ABCC2 (MRP2)
Variants: 24 C>T
Poor response to cisplatin, oxaliplatin, methotrexate and irinotecan
Resistence in ovarian, lung and bladder cancer

Overexpression of specific ATP-binding cassette (ABC) trasporters in cancer cells can lead to chemotherapy resistence through increase drug efflux. ABC transporters actively pump chemotherapeutic drugs by reducing intracellular drug concentrations and their cytotoxic effects.

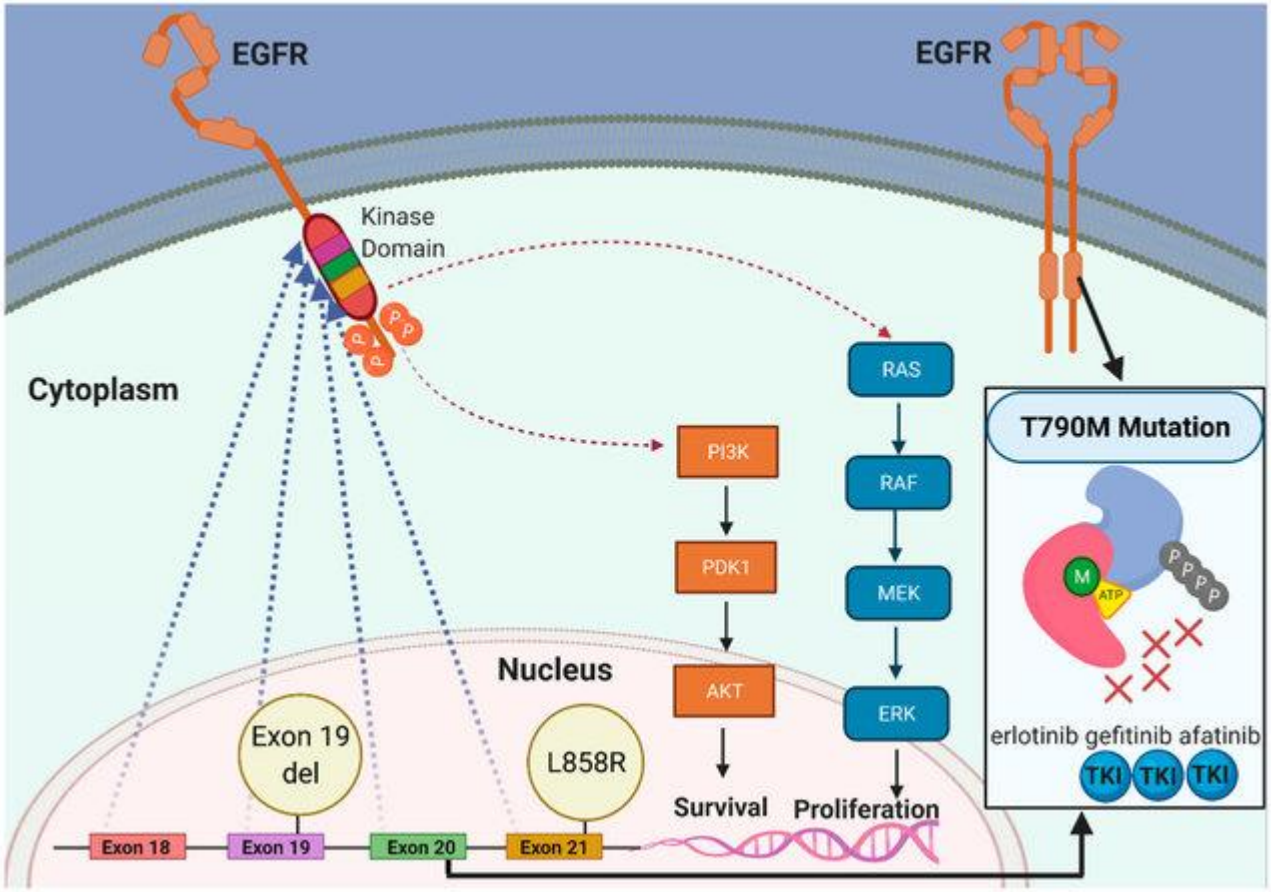
EGFR mutations and tyrosine kinase inhibitors

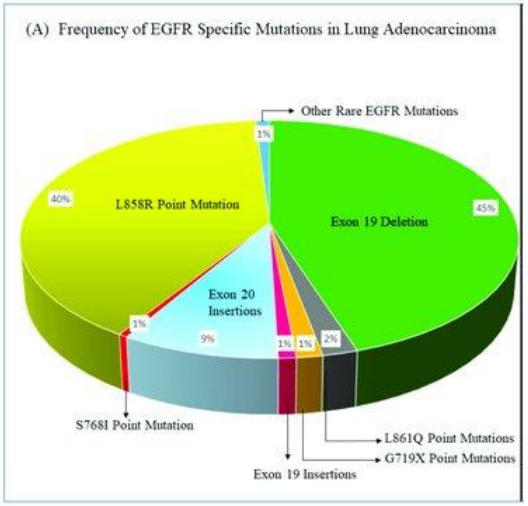


Papini et al., 2021. Crit Rev Oncol Hematol. doi: 10.1016/j.critrevonc.2021.103454.

Epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kynase. In normal cells, ligand binding causes EGFR dimerization which in turn activates the intracellular tyrosine kinase domain and downstream signaling pathways such as RAS/MAPK and PI3K/AKT. These pathways regulate cell proliferation, survival and resistence to apoptosis.

EGFR mutations and tyrosine kinase inhibitors

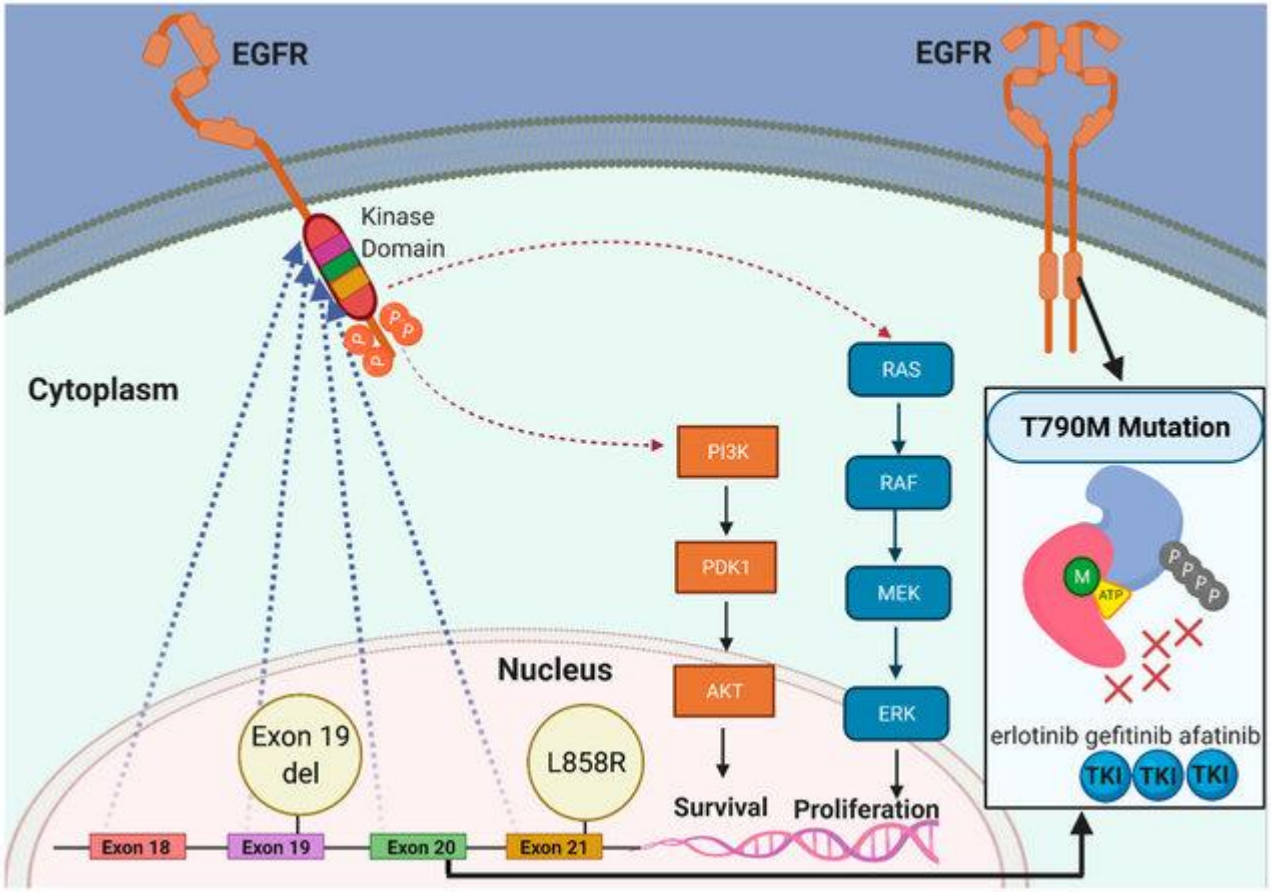


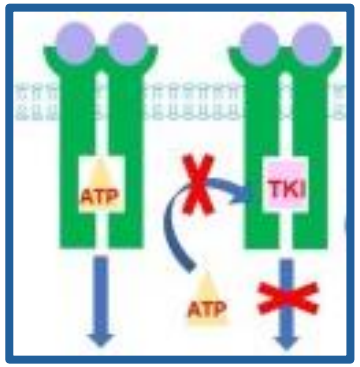


Khaddour et al., 2021.Cancers. 24;13(13):3164. doi: 10.3390/cancers13133164.

EGFR mutations are common in non-small cell lung cancer. The most frequent mutations are **exon 19 deletions** and the **L858R point mutation in exon 21**, which lead to constitutive activation of the receptor and uncontrolled tumor cell proliferation.

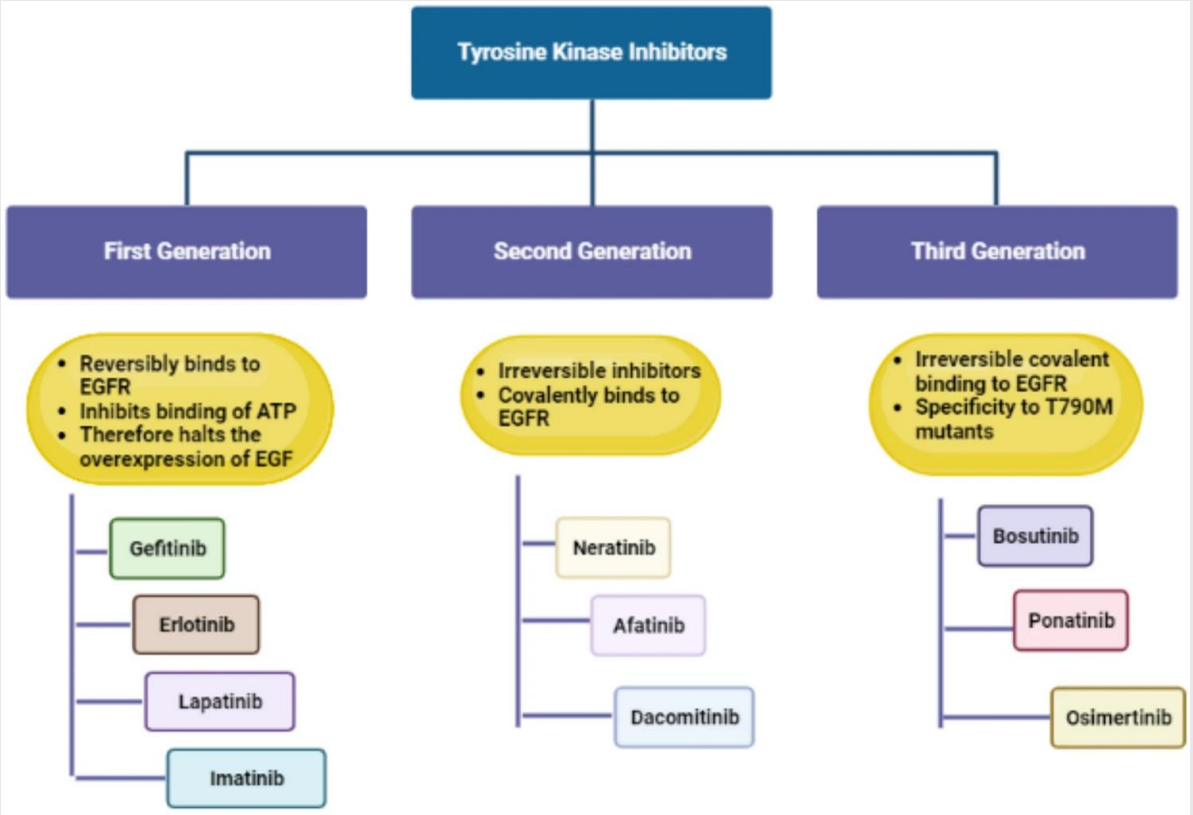
EGFR mutations and tyrosine kinase inhibitors



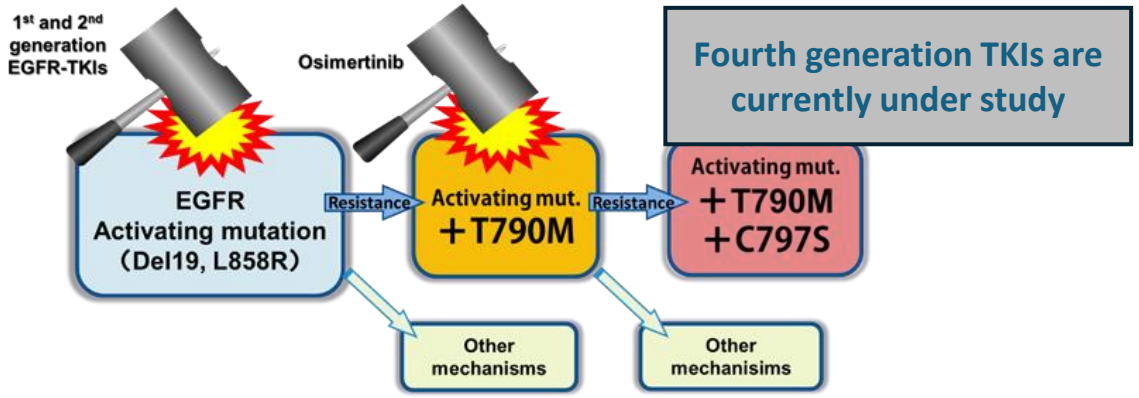


Khaddour et al., 2021.Cancers. 24;13(13):3164. doi: 10.3390/cancers13133164; Liang et al., 2020. Pharmacol Res.. doi: 10.1016/j.phrs.2020.105164.

Tyrosine kinase inhibitors (TKIs) are targeted therapies that block the activity of the mutated receptor, inhibiting downstream signaling pathways involved in cancer grow. They block the activity of kinase domain binding the ATP-binding site, preventing the autophosphorylation of the receptor. The presence of the point **mutation T790M in exon 20** leads to resistance to first and second generation EGFR TKIs

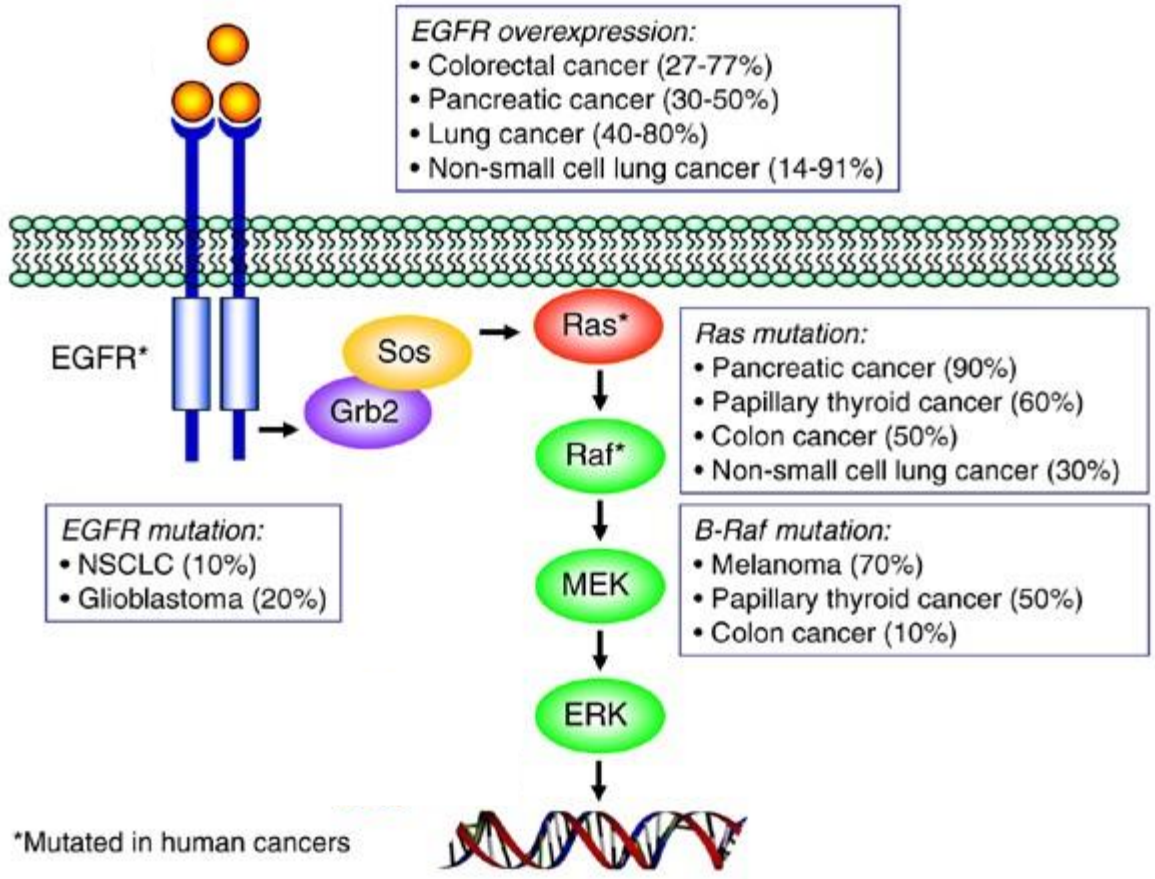


Mangla et al., 2024. Med Oncol. doi: 10.1007/s12032-024-02414-5.



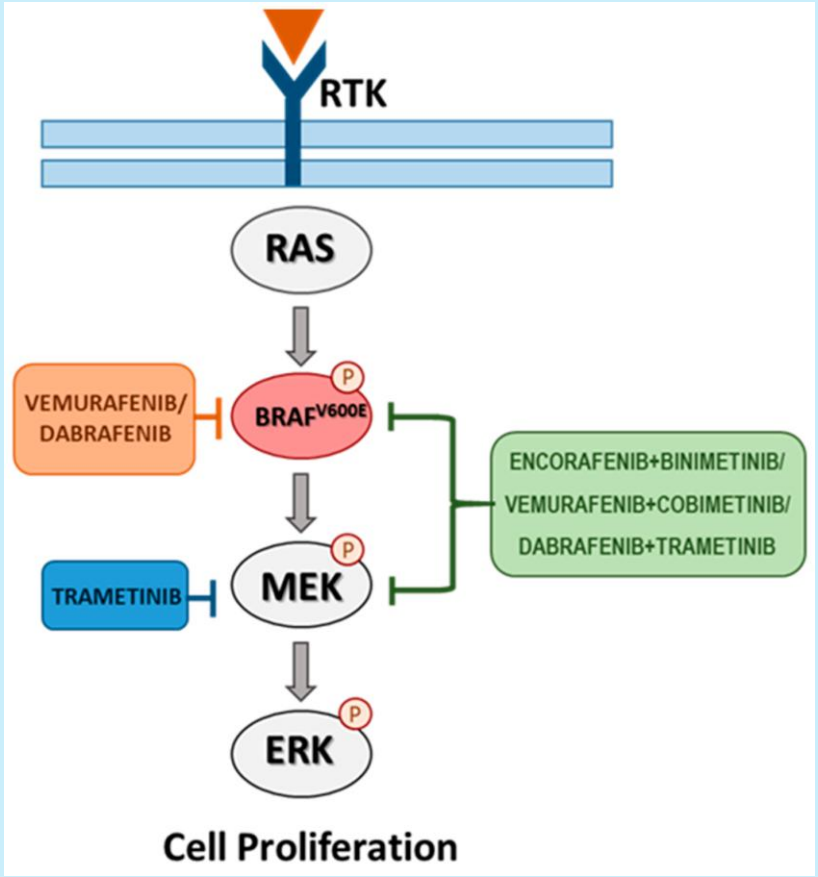
Modified from Uchibori et al., 2017. Nat Commun. doi: 10.1038/ncomms14768.

RAS and RAF mutations



Modified from: https://www.onkologik.com/adenocarcinoma-e-ia/

BRAF mutations and melanoma



Castellani et al., 2023. Cancers (Basel). doi: 10.3390/cancers15164026.

In melanoma, mutations in BRAF gene, in particular the **mutation V600E**, leads to a constitutive activation of the BRAF-MEK-ERK pathway, leading to increased proliferation and cell growth.

Targeted therapy with combinations of **BRAF and MEK inhibitors** represent the standard treatment in patients with BRAF V600-mutant metastatic melanoma.

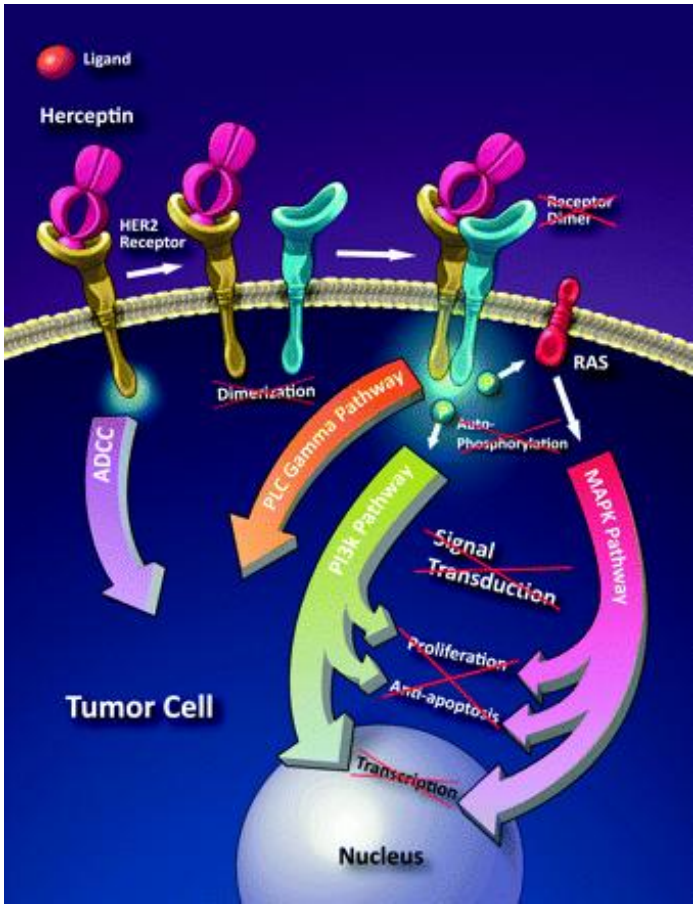
BRAF inhibitors (vemurafenib, dabrafenib, encorafenib) block mutant BRAF and MEK inhibitors (trametinib, binimetinib, cobimetinib) regulate the activation of MEK. Combination therapies inhibit both BRAF and MEK to improve efficacy and reduce resistance.

HER2 and breast cancer

Human epidermal growth factor receptor 2 (HER2) is overespressed in 20-25% of breast tumors and is associated with an unfavorable clinical outcome.
Trastuzumab (Herceptin) is a monoclonal antibody which target the extracellular domain of HER2 receptor.

It abrogates intracellular HER-2 signalling and it induces antibody-dependent cell-mediated cytotoxicity (ADCC) driving immune cells-mediated cancer death.

Trastuzumab improves survival and prognosis in early and metastatic breast cancer

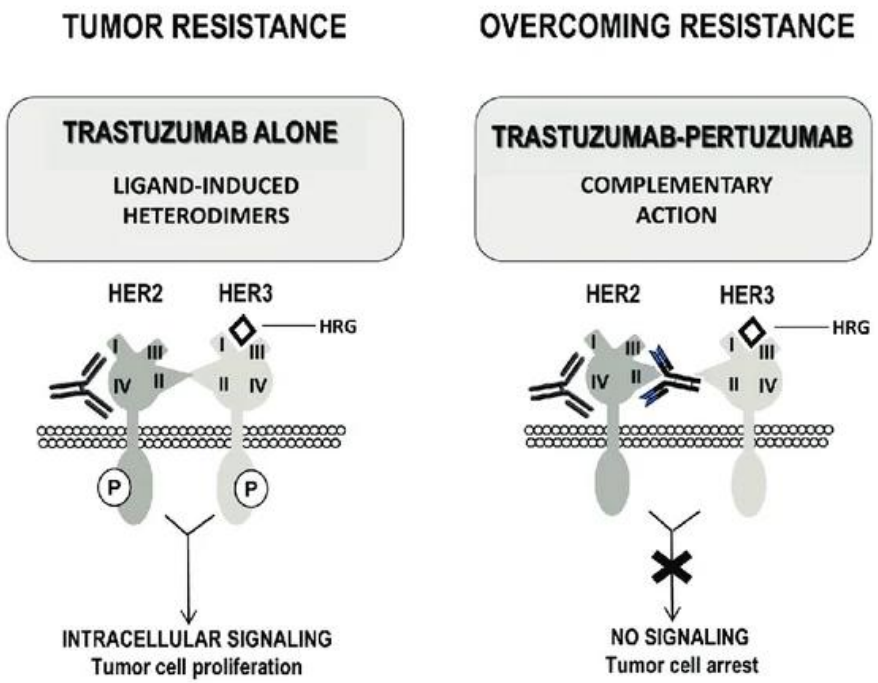


Gemmete and Mukherji, 2011. American Journal of Neuroradiology. Doi: https://doi.org/10.3174/ajnr.A2619

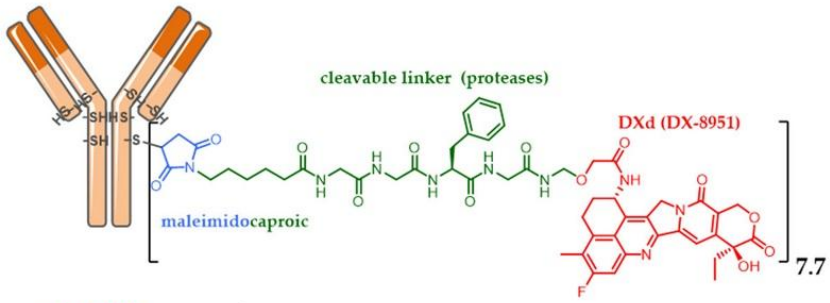
HER2 and breast cancer

However, 50% of patients with a HER2-positive tumor do not respond to trastuzumab therapy (HER2-low tumors, drug resistance due to HER2-HER3 dimers or HER2 mutation). New drugs have been developed to overcome therapeutic failure.

Trastuzumab-Pertuzumab combination therapy



Richard et al., 2016. Pertuzumab and trastuzumab: the rationale way to synergy. doi: 10.1590/0001-3765201620150178.

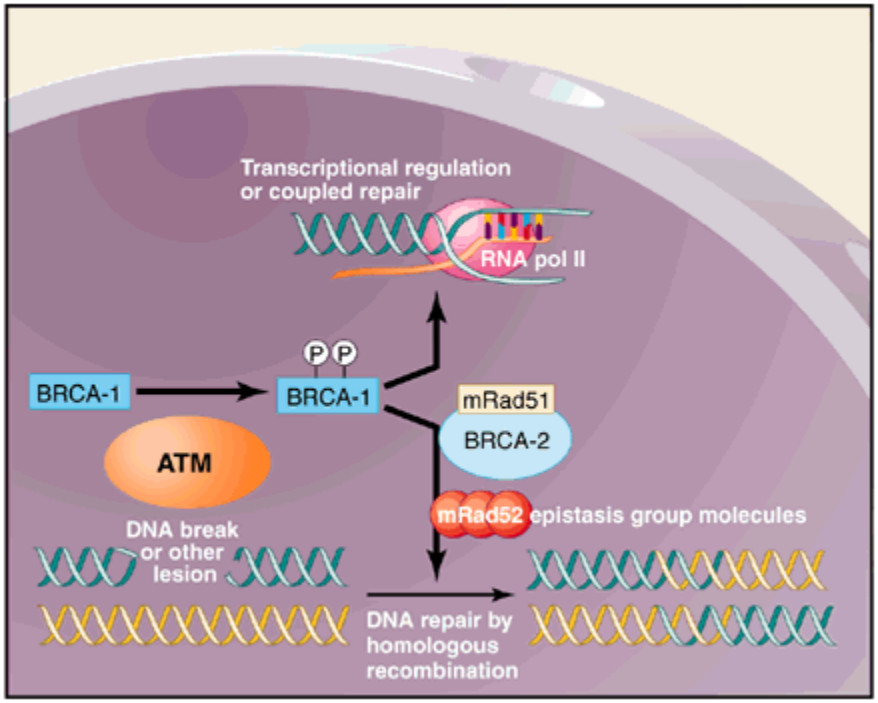


anti-HER2 Enhertu® (fam-trastuzumab deruxtecan-nxki or DS-8201a)

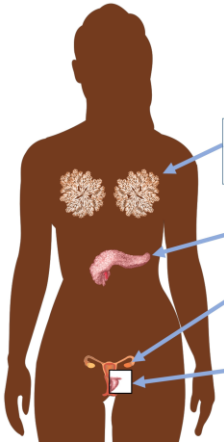
https://www.biochempeg.com/article/348.html

Trastuzumab deruxtecan is an **antibody-drug conjugate** composed of the anti-HER2 monoclonal antibody linked to a potent cytotoxic topoisomerase I inhibitor.

BRCA mutations



Ashok R. Venkitaraman. 1999. Science DOI: 10.1126/science.286.5442.1100



	BRCA1	BRCA2
Breast cancer:	**50% to 65%** Males: 1.2%	**40% to 55%** Males: Up to 9%
Pancreas cancer:	1-3%	2-7%
Ovarian cancer:	**40% to 65%**	**15% to 25%**
Prostate cancer:	9%	15%

GENE	MUTATION[a]
BRCA1	c.116G > A (p.Cys39Tyr)
BRCA1	c.181T > G (p.Cys61Gly)
BRCA1	c.676delT (p.Cys226Valfs*8)
BRCA1	c.1687C > T (p.Gln536*)
BRCA1	c.5266dupC (p.Gln1756Profs*74)
BRCA2	c.5682C > G (p.Tyr1894*)
BRCA2	c.7806-2A > G (p.Ala2603_Arg2659del)
BRCA2	c.8878C > T (p.Gln2960*)

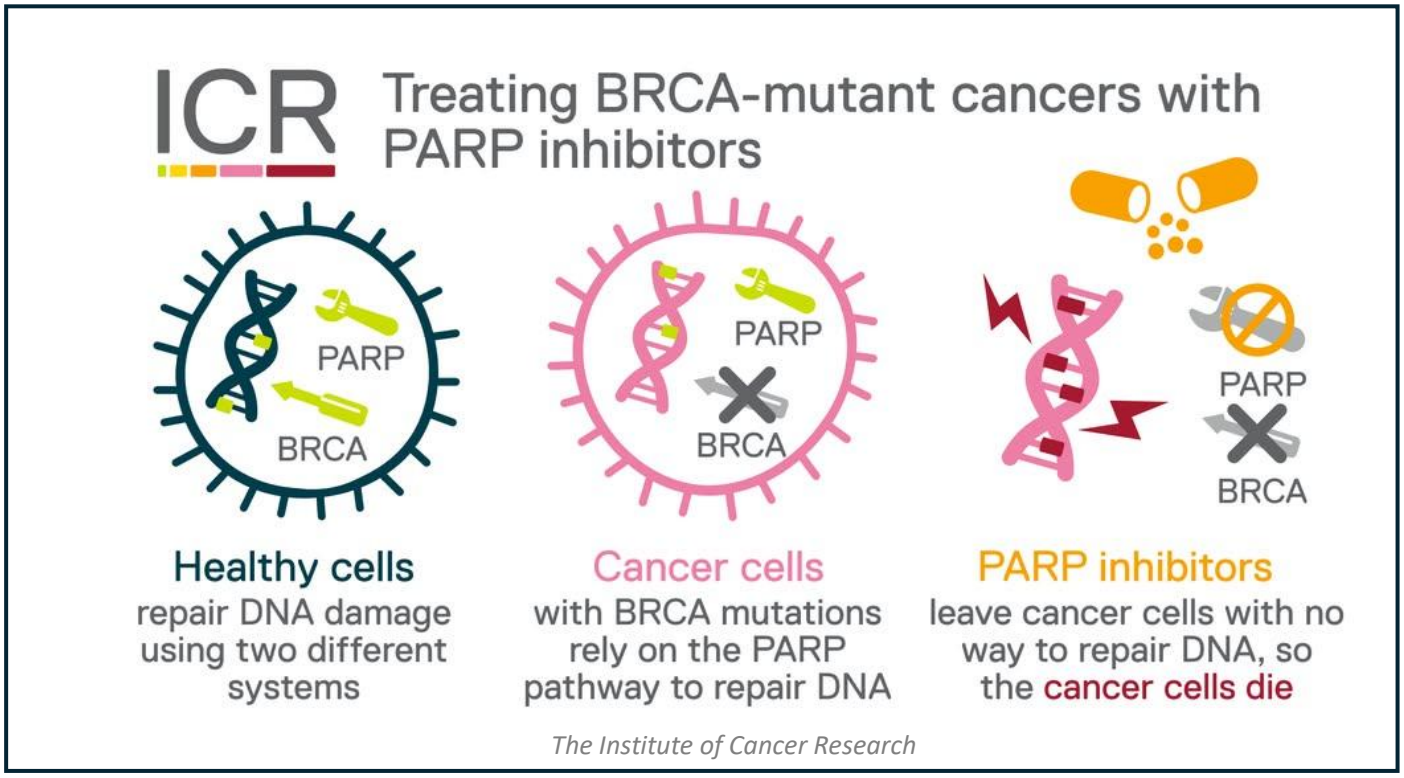
[a]The mutations are defined according to the Human Genome Variati

BRCA1 and BRCA2 genes encode for proteins that repair double-stranded breaks in DNA, which can occur when cells replicate. Mutations in either of these two genes can compromise the cell's ability to repair DNA damage. Individuals who carry these mutations have an increased risk of developing cancer.

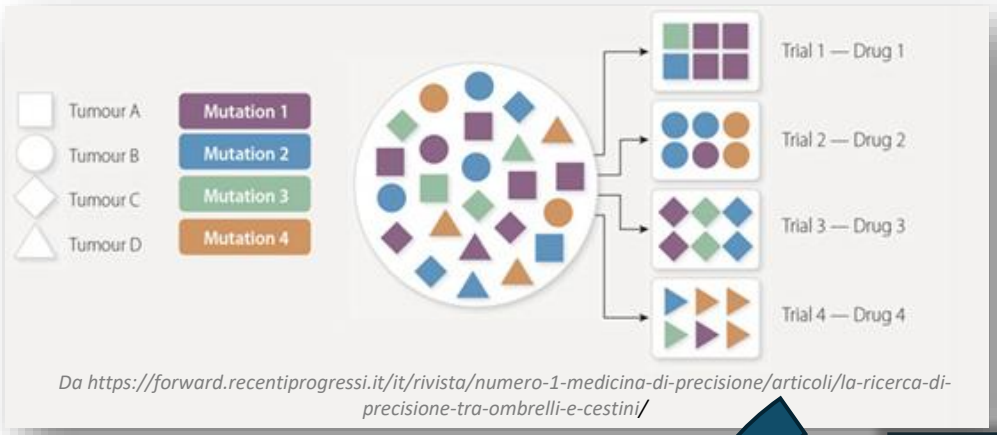
BRCA mutations and PARP inhibitors

Poly-ADP ribose polymerase (PARP) is an enzyme involved in repairing single-strand DNA breaks.

PARP inhibitors are targeted cancer therapies that block the PARP enzyme. In cancer cells with defective DNA repair pathways (such as BRCA-mutated cells), PARP inhibition causes the accumulation of DNA damage, leading to selective cancer cell death, while normal cells are relatively spared (**synthetic letality**).



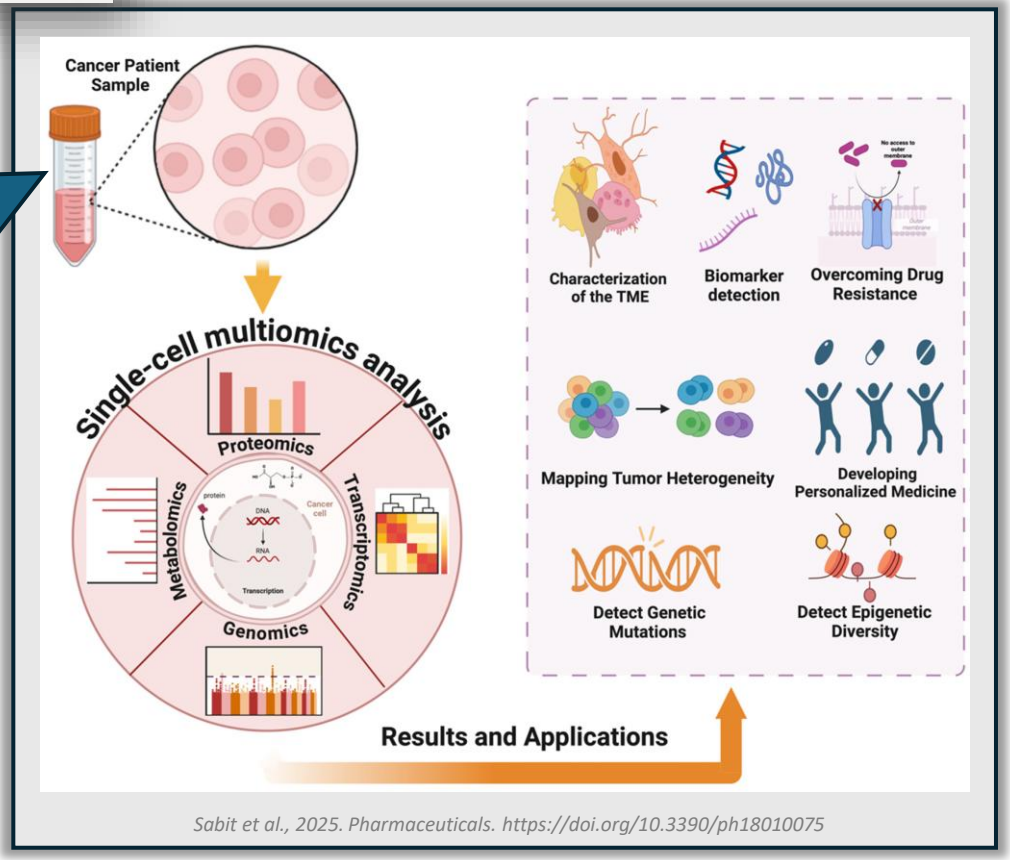
Precision cancer medicine clinical trials



Da https://forward.recentiprogressi.it/it/rivista/numero-1-medicina-di-precisione/articoli/la-ricerca-di-precisione-tra-ombrelli-e-cestini/

In the past, cancer drugs were tested and approved for specific tumor types based on tumor location and histomorphological features of the cancer cells.

In contrast, precision/personalized oncology relies on data from trials selecting patients on the basis of their genomic/biologic/immune markers.

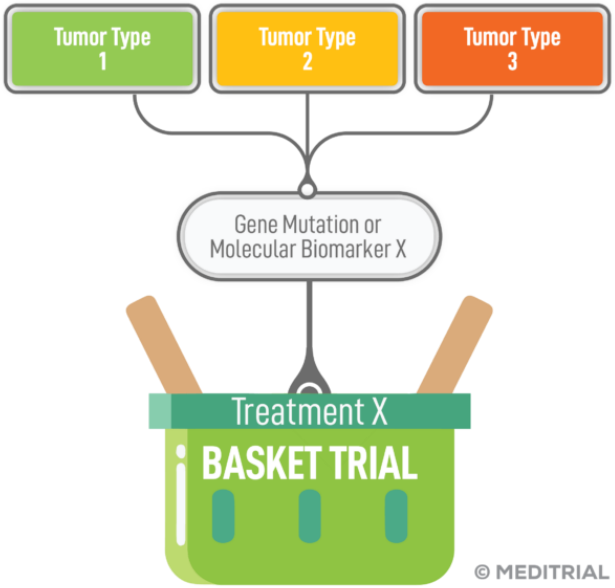


Sabit et al., 2025. Pharmaceuticals. https://doi.org/10.3390/ph18010075

Precision cancer medicine clinical trials

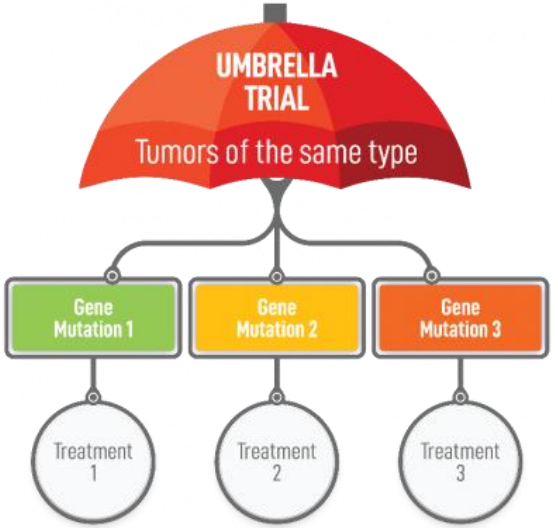
BASKET TRIAL

A targeted therapy is tested on patients with a specific genetic mutation across a variety of tumor types.



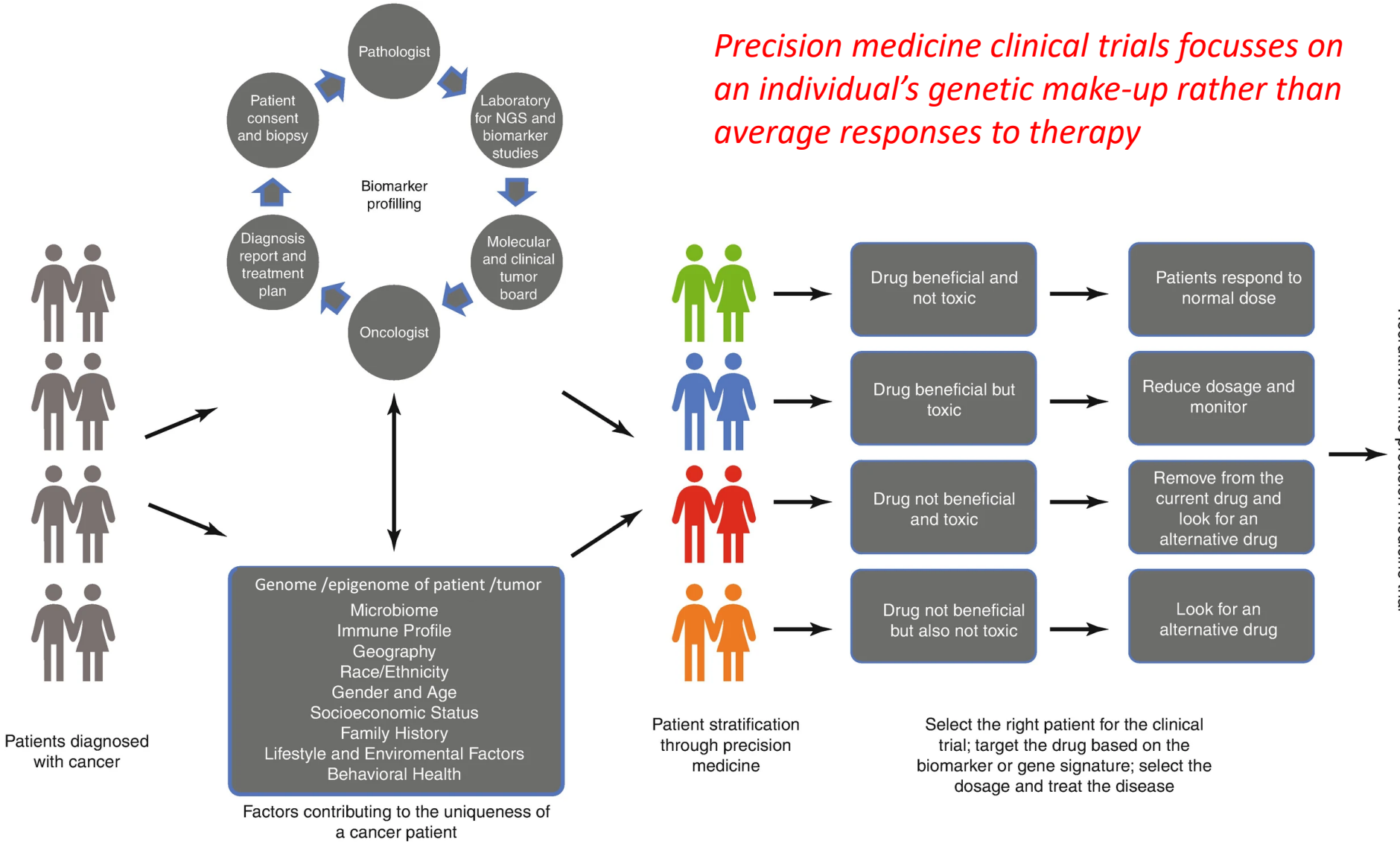
UMBRELLA TRIAL

Patients are enrolled based on the same tumor type (i.e. the same organ). Within this group, patients are tested for the presence of different mutations and assigned to different treatment arms.



Precision cancer medicine clinical trials

Precision medicine clinical trials focusses on an individual's genetic make-up rather than average responses to therapy



Kumar, G.L. (2019). Prominent Precision Medicine Clinical Trials in Oncology Around the World. Predictive Biomarkers in Oncology. https://doi.org/10.1007/978-3-319-95228-4_52

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Pan-cancer analysis of whole genomes

The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium

Nature **578**, 82–93 (2020) | Cite this article

More than 1300 researchers and clinicians from 37 countries collaborated on this project, making it a milestone in cancer research

The scientists involved in the PCAWG project completed the analysis of 2658 whole tumor genomes across 38 tumor types.
The project identify:

- shared and cancer-specific genetic alterations, including mutations in coding and non-coding regions
- chronology of mutations
- chromothripsis as frequent early event in tumour evolution
- common and rare germline variants affecting patterns of somatic mutations

Data are available via platforms such as cBioPortal for Cancer Genomics, allowing clinicians to compare individual patient mutations with a global reference dataset.