ISCOM 2025

THE FUTURE OF PRECISION ONCOLOGY

ASS. PROF. D-R MARIJA KARAKOLEVSKA-ILOVA

STIP, 5/2025

1.PRECISION ONCOLOGY- THE FUTURE OF PERSONALIZED CANCER MEDICINE?

- Along with the discovery of new biomarkers, the development of novel targeted therapies is increased which increased the demand for companion molecular diagnostics to characterize tumors and guide treatment decisions.

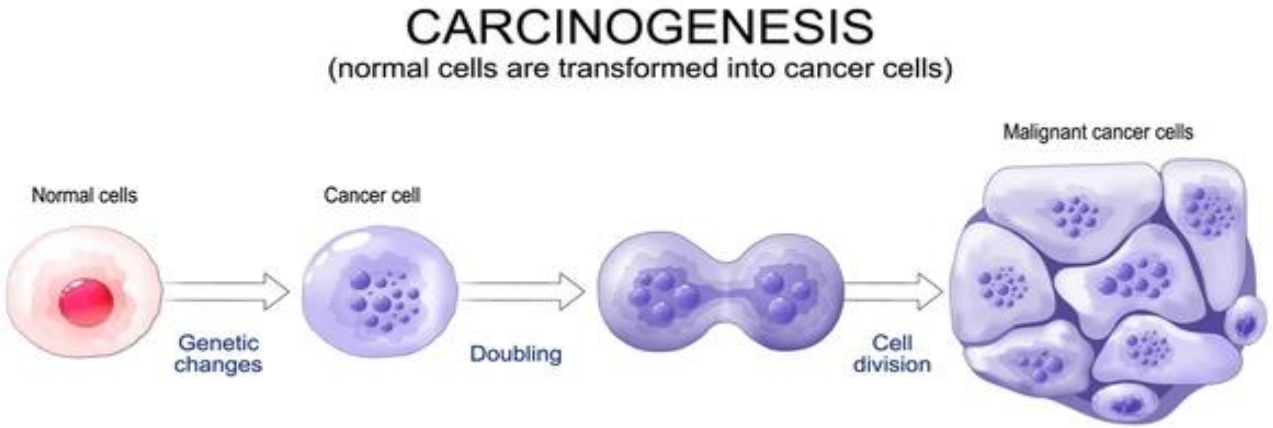
- Chemotherapy has long been the basis for the treatment of cancers, but with the development of molecular diagnostics and the discovery of molecular tumor characteristics, targeted therapy is becoming a new reality.

- There are the series of characteristics that a tumor displays, allowing it to survive, sustain growth and spread to other tissues. As such, they all centre on the different pathways that cancerous cells exploit to proliferate in the native tissue microenviorement including both cell intrinsic and extrinsic mechanisms, and the ways in which tumours respond to and resist to treatment.

There are two “enabling capabilities” that allow cells to acquire these characteristics:

- 1/ *genomic instability*, by which novel DNA aberrations are acquired that can disrupt normal cell function and activate or disable oncogenes and tumor suppressors, respectively, and lead to clone expansion via Darwinian selection, and

- 2/ *tumor promoting inflammation*, which allows different cells to infiltrate the tumor microenvironment including dose that sustain evolution.



- The most promising theme in the development of more specific cancer drugs is the targeting of cancer-specific processes, instead of processes common to all cells.

- Because these drugs are not directly toxic, and because they only affect cancer cells, they offer the hope of being highly specific with few side effects.

- Blocking a single pathway in a cancer cell may be enough to slow it down, but it often does not inhibit the cancer enough to kill it.

- *The combination of a highly specific cancer drug that is able to attack a tumor's weaknesses, and standard chemotherapy to deliver a powerful attack on the tumor, may prove to be an excellent means of treating cancer.*

- Sequencing of individual patient tumors has revolutionized oncology because the genetic information facilitates the elucidation of molecular changes in a specific patient's cancer.

- What this genetic information has provided is the understanding that not only do tumors differ within a sample (tumor heterogeneity), but the information clearly shows that each patient's individual tumor is an assemblage of inimitable molecular irregularities that will require an equally exclusive personalized therapeutic regimen.

- Precision cancer detection was made possible by the discovery of significant gene mutations that promote carcinogenesis.

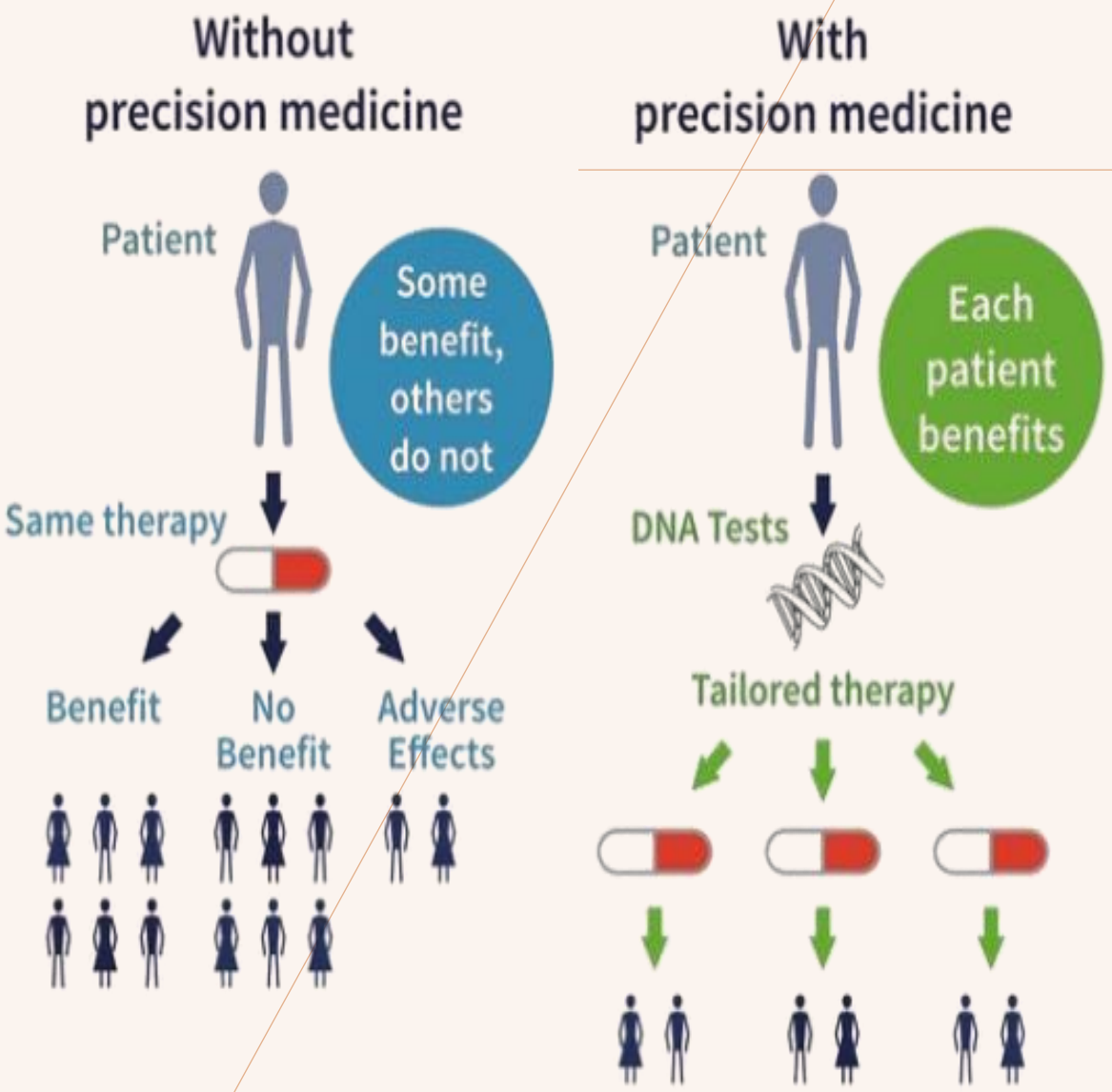
- Due to the substantial research on oncoproteins and associated signaling pathways, target-based precision treatments have been developed to combat a variety of cancer forms.

- Advanced technologies for precision diagnosis and precision therapy will help overcome many of the obstacles that could prevent precision oncology from succeeding.

PRECISION ONCOLOGY

The process of matching each cancer patient with the most precise and efficient therapy is known as **precision oncology!**

The use of a one-size-fits-all strategy for cancer treatment is becoming outmoded!!!!!!!

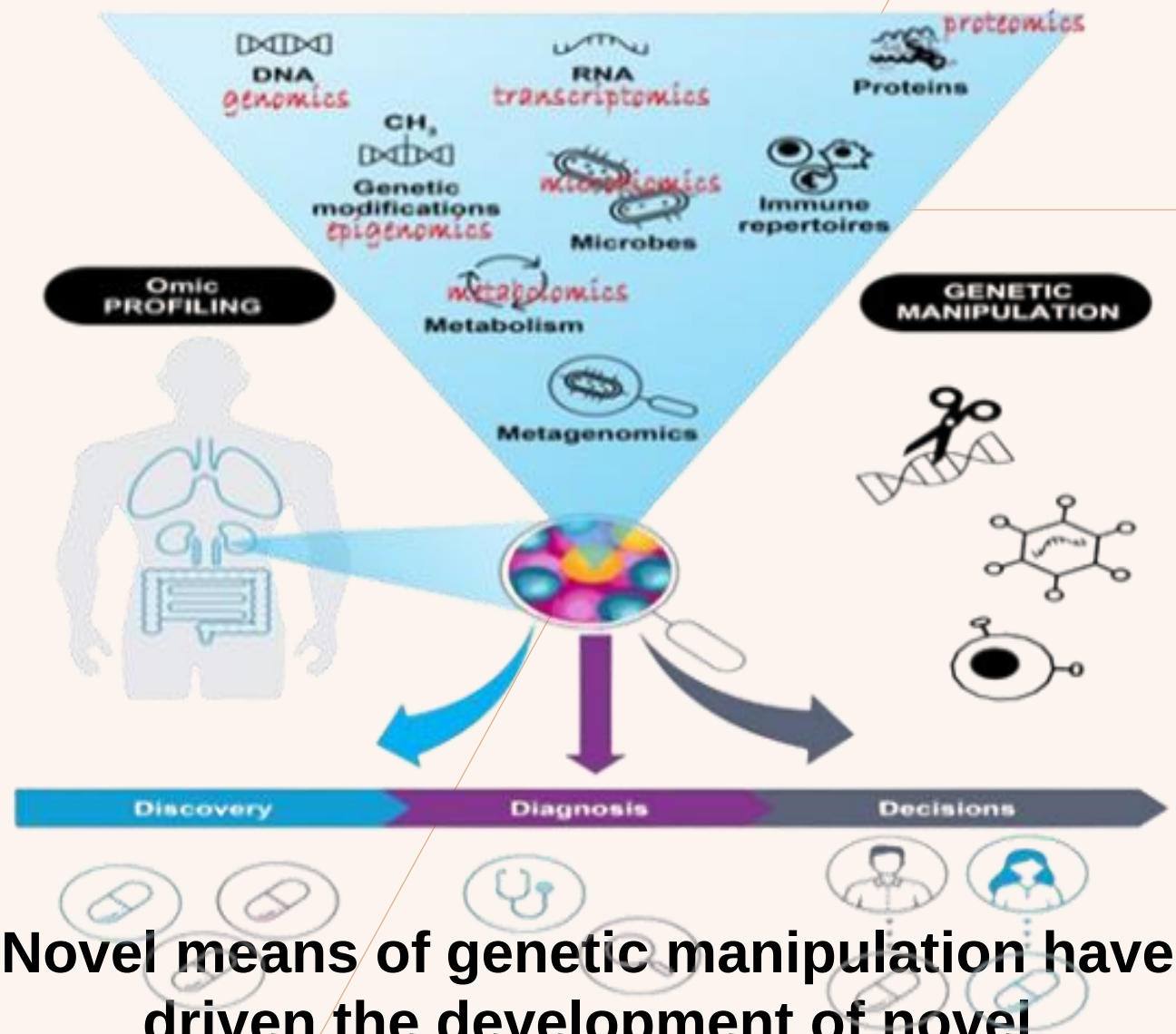


2. FINDING THE TARGET

- The development of increasingly complex “omic” techniques has made it possible to profile complex molecular features of patient tumors, including DNA sequence data, gene expression profiles, protein levels, immune repertoires, and more.

- These techniques are now demonstrating the potential to not only improve our understanding of cancer biology but also to become a crucial component of clinical practice.

- This could fundamentally alter our knowledge of how to care for and treat cancer patients.

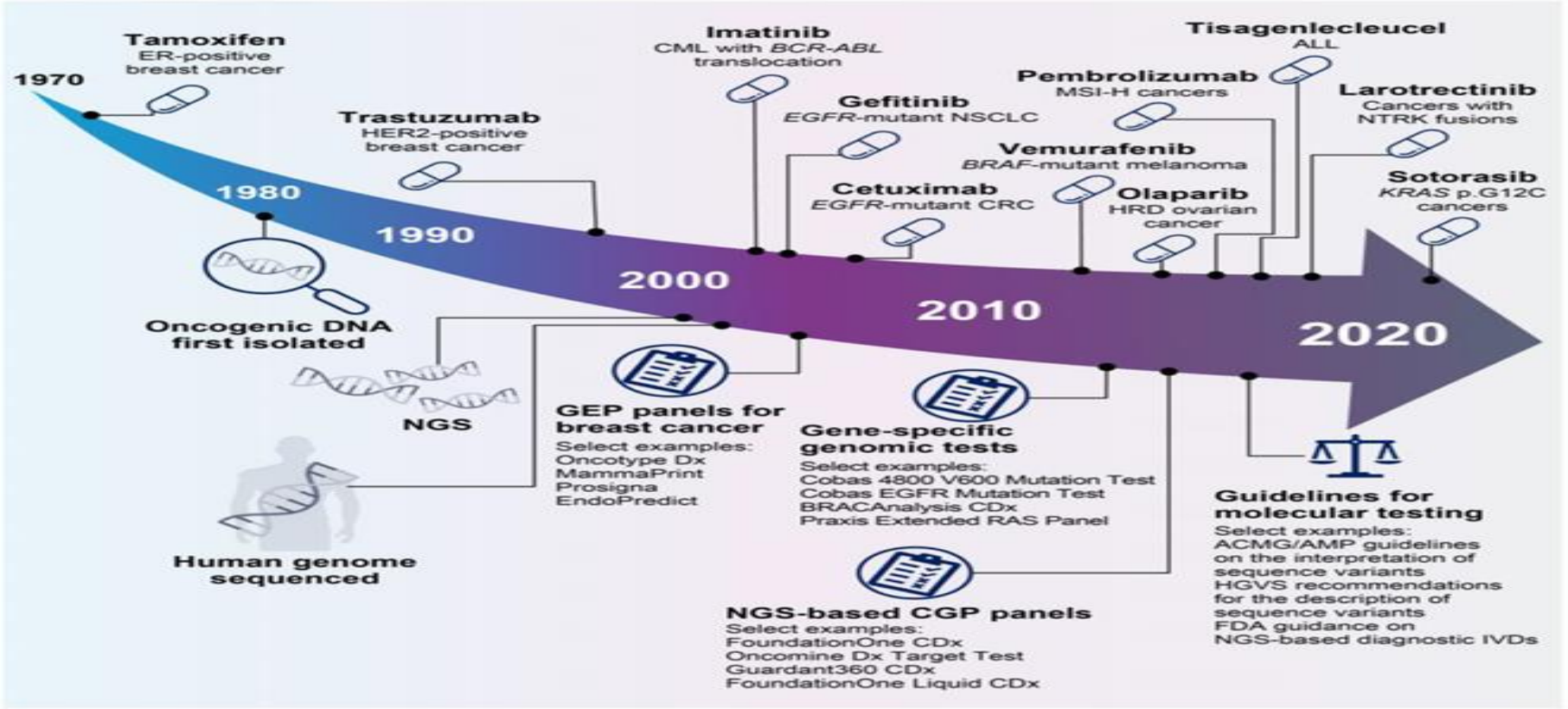


Novel means of genetic manipulation have driven the development of novel therapeutics

3. Comprehensive Diagnostics for Patients with Cancer

Our knowledge of the biological processes underlying tumor development and patient responses to treatment has greatly expanded since the 1970s, when estrogen-receptor expression was linked to the emergence of specific forms of breast cancer.

This has made it possible to develop a wide range of targeted therapies in clinical settings.



- Molecular profiling for precision cancer therapy uses conventional tests such as IHC and FISH and more advanced techniques such as qPCR and NGS.

- To define molecular alterations and tailor therapy accordingly, a tissue sample is needed, which is delivered to a high-quality laboratory equipped with NGS technology.

- However, even smaller institutions without laboratories can take advantage of commercially available testing platforms to analyse paraffin-embedded tissue samples or plasma samples (ctDNA-liquid biopsy)

- Recent developments in NGS technologies have enabled a transition from single-target diagnostics to comprehensive genomic profiling panels, enabling a one-step testing platform for multiple targeted therapies, despite the fact that the majority of approved molecular tests are limited to single-target assessment within a limited number of tumor types.

- NGS-based gene panels were first approved as companion diagnostics for indications related to lung, skin, and breast cancer.

- Today, they can be used to profile a variety of solid tumor types, although significant *heterogeneity exists in the availability of testing across different countries*.

- *Pharmacogenetic component* (*genetic analysis to predict safety outcomes or response to treatment)* has stayed constant at little over 40%.

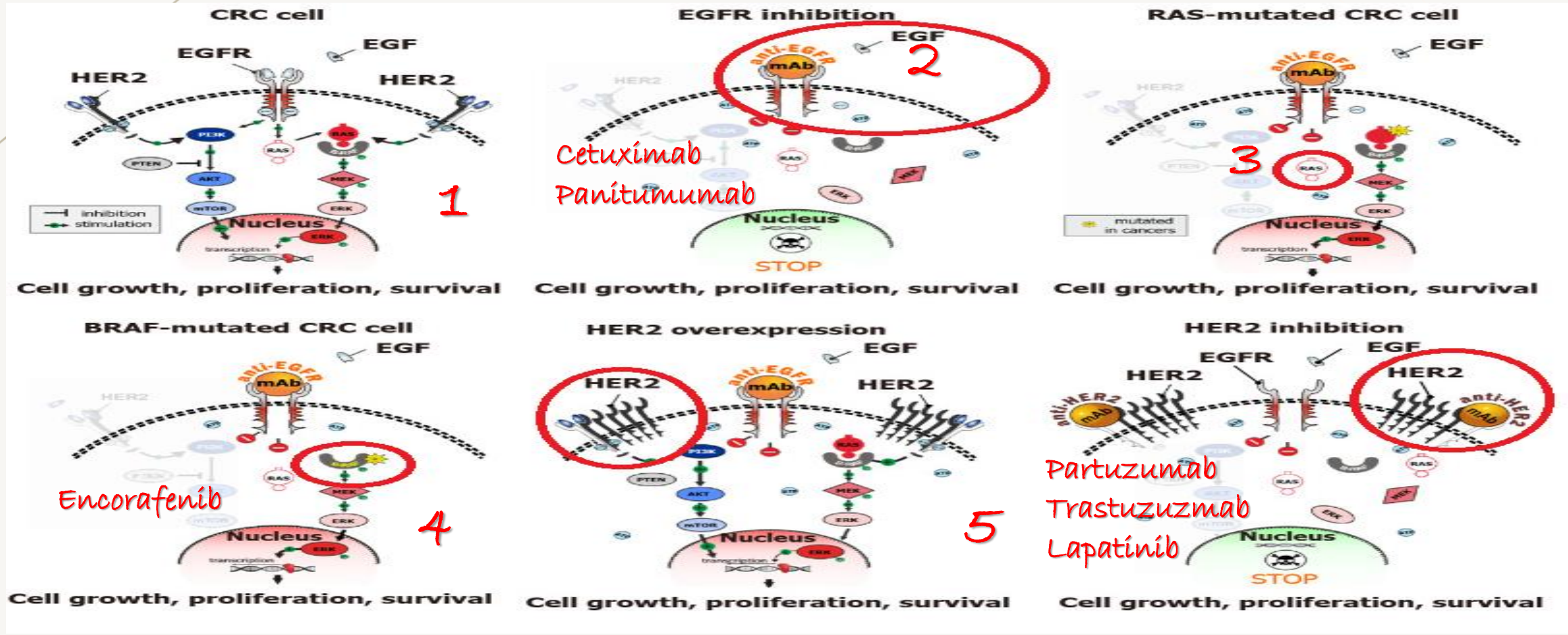
4. Increasing Information to Guide Treatment Decisions

- A growing number of tumor types are now eligible for whole genome sequencing, from which genomic information can be used to further guide therapeutic decisions (e.g. *Homologous recombination deficiency* (HRD mutational signatures) can guide eligibility for poly (ADP-ribose) polymerase (PARP) PARP inhibition, while *tumor mutational burden* (TMB) and *microsatellite instability* (MSI) status can be used to determine patient eligibility for immunotherapy.

- The successful clinical development of a variety of precision medicines for cancer patients has been facilitated by advancements in technologies to couple precision companion diagnostics to targeted therapies, the development of novel treatment modalities like *Chimeric antigen receptor (CAR-T cell) therapy*, and new discoveries in disease biology, such as the relationship between genome instability and anti-tumor immune responses.

- Patients with a variety of tumor types, such as breast, colorectal, lung, ovarian, skin, and hematological cancers, have reported Improved outcomes

COLON CANCER



Virtually all colorectal cancers (CRCs) are characterized by upregulation of ***mitogen-activated protein kinases (MAPK) signaling pathway***

* Imyanitov E., E Kuligina E. Molecular testing for colorectal cancer: Clinical applications. World J Gastrointest Oncol . 2021 Oct 15;13(10):1288–1301. doi: 10.4251/wjgo.v13.i10.1288

BREAST CANCER

Cancer biomarkers can be prognostic (associated with disease progression and outcome irrespective of treatment) or predictive (associated with disease response and survival in patients receiving a particular therapy).

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NCCN Guidelines Version 4.2025
Invasive Breast Cancer

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PRINCIPLES OF BIOMARKER TESTING
HR TESTING

- HR testing (ER and PR) by IHC should be performed on any new primary or newly metastatic breast cancer using methodology outlined in the latest ASCO/CAP HR testing guideline.[g] DCIS should be tested for ER (PR not required).
- ER testing should be used to determine if a patient is a candidate for endocrine therapies.
  - Cancers with 1%–100% of cells positive for ER expression are considered ER-positive. Patients with these results are considered eligible for endocrine therapies (applies to DCIS and invasive cancers).
  - Invasive cancers with between 1%–10% ER positivity are considered ER-low–positive. There are more limited data on the benefit of endocrine therapies in this group, but they suggest possible benefit from endocrine treatment, so patients are considered eligible for this treatment (as above). However, this group is noted to be heterogeneous and the biologic behavior of ER-low–positive cancers may be more similar to ER-negative cancers. This should be considered in decision-making for other adjuvant therapy and overall treatment pathway.
  - Cancers with <1% staining are considered ER-negative. Patients with cancers with these results have not been shown to benefit from endocrine therapies.
- Laboratories should have standard operating procedures to maximize accuracy and reproducibility of results for cases with <10% ER staining or weak intensity staining (to avoid false negatives). The status of controls should be reported for cases with these results.
- PR testing by IHC on invasive cancers can aid in the prognostic classification of cancers and serve as a control for possible false-negative ER results. Patients with ER-negative, PR-positive cancers may be considered for endocrine therapies, but the data on this group are noted to be limited. The same overall interpretation principles apply but PR should be interpreted as either positive (if 1%–100% of cells have nuclear staining) or negative (if <1% or 0% of cells have nuclear staining).
- Interpretation of any ER result by pathology should include evaluation of the concordance with the histologic findings of each case. Clinicians should be aware of when results are unusual and work with pathologists to attempt to resolve (eg, repeat testing, consultative review) or explain atypical reported findings. See table below.

Summary of ER IHC Scoring/Interpretation

Results (following ER testing by validated IHC assay)		Interpretation/ Report As:
0% to <1% of nuclei stain		ER-negative
1%–100% of nuclei stain	1%–10% of nuclei stain	ER-low–positive (with recommended comment)
	>10% of nuclei stain	ER-positive

Correlation of ER and Histology: Highly Unusual Results

Highly Unusual ER-Negative Results	Highly Unusual ER-Positive Results
Low-grade invasive carcinomas of no special type (also known as invasive ductal carcinoma)	Metaplastic carcinomas of all subtypes
Lobular carcinomas (classic type)	Adenoid cystic carcinomas and other salivary gland-like carcinomas of the breast
Pure tubular, cribriform, or mucinous carcinomas	Secretory carcinoma
Encapsulated papillary and solid papillary carcinomas	Carcinomas with apocrine differentiation (apocrine carcinoma)

[g] Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. J Clin Oncol 2020;38:1346-1366; Arch Pathol Lab Med 2020;144:545-563.

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PRINCIPLES OF BIOMARKER TESTING
HER2 TESTING[a,b]

- HER2 testing should be performed on all new primary or newly metastatic breast cancers using methodology outlined in the ASCO/CAP HER2 testing guideline.[a]
- A re-review of the pathology with consideration for repeat or consultative HER2 testing should be made if a Grade 1 (any histologic type), pure mucinous, pure tubular, or pure cribriform carcinoma tests HER2-positive.[a]
- After a negative HER2 test result on initial biopsy sample, consider retesting on subsequent surgical or other additional sample if the initial sample was suboptimal (eg, minimal invasive cancer was present, cold ischemic time or fixation was suboptimal), testing error is expected, additional samples contain higher grade morphologically distinct cancer from the biopsy, to rule out heterogeneity in a high grade cancer, or if it will otherwise aid in clinical decision-making.[a]

HER2 testing by validated immunohistochemistry (IHC) assay[b,c]

- IHC 0,1+[d] → HER2 (-)
- IHC 2+ → Equivocal result → Must reflex test with ISH (if same specimen), or order new test with IHC or dual probe ISH (if new specimen available).
- IHC 3+ → HER2 (+)

HER2 testing by validated dual-probe[e] ISH assay[b,c]

- HER2-Negative:
  - (Group 5) HER2/CEP17 ratio <2.0 AND average HER2 copy number <4.0 signals/cell
- HER2-Negative[f] (Determined by concurrent IHC and ISH results):
  - (Group 2) HER2/CEP17 ratio ≥2.0 AND average HER2 copy number <4.0 signals/cell and concurrent IHC 0-1+ or 2+
  - (Group 3) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥6.0 signals/cell and concurrent IHC 0-1+
  - (Group 4) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 0-1+ or 2+
- HER2-Positive[f] (Determined by concurrent IHC and ISH results):
  - (Group 2) HER2/CEP17 ratio ≥2.0 AND average HER2 copy number <4.0 signals/cell and concurrent IHC 3+
  - (Group 3) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥6.0 signals/cell and concurrent IHC 2+ or 3+
  - (Group 4) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 3+
- HER2-Positive:
  - (Group 1) HER2/CEP17 ratio ≥2.0 AND average HER2 copy number ≥ 4.0 signals/cell

[a] NCCN endorses the ASCO/CAP HER2 testing guideline. "Principles of HER2 Testing" modified with permission from Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018;36:2105-2122.
[b] Laboratory must participate in a quality assurance accreditation program for HER2 testing. Otherwise, tissue specimen should be sent to an accredited laboratory for testing. Health care systems and providers must cooperate to ensure the highest quality testing.
[c] Evidence from trastuzumab adjuvant trials show that HER2 testing by ISH or IHC have similar utility to predict clinical benefit from HER2-targeted therapy.
[d] The distinction between HER2 IHC 0/absent membrane staining, IHC 0+/with membrane staining (faint, partial membrane staining in ≤10%), IHC 1+, or 2+/ISH negative results (on primary or metastatic samples) is currently clinically relevant since patients with metastatic disease may be eligible for treatment targeting non-amplified levels of HER2 expression.
[e] Single-probe ISH assays are not preferentially recommended but if used, cases with average HER2 copy number ≥4.0 and <6.0 signals/cell should base final results on concurrent IHC and if 2+ reflexed to dual probe ISH testing.
[f] For ISH Groups 2–4 final ISH results are based on review of concurrent IHC, with recounting of the ISH test by a second reviewer if IHC is 2+ (per 2018 CAP/ASCO Update recommendations). Additional report comments are recommended for negative final results in these ISH groups.

Note: All recommendations are category 2A unless otherwise indicated.

BINV-A

BREAST CANCER

CASE REPORT 1.

- 43 years old patient, unmarred,premenopausal
- No family history of cancer
- **15/9/2022** : Ca ductale mammae lat dex. Mastectomam cum dissectio axilae lat. dex.
- Pathohistological findings: pTNM= pT1a (11mm) pN0 (16/0) G3
- **IHC : ER 85%, PR 95%, Ki67 15%, p53/ neg, Her2/neu 1+ (Luminal A)**

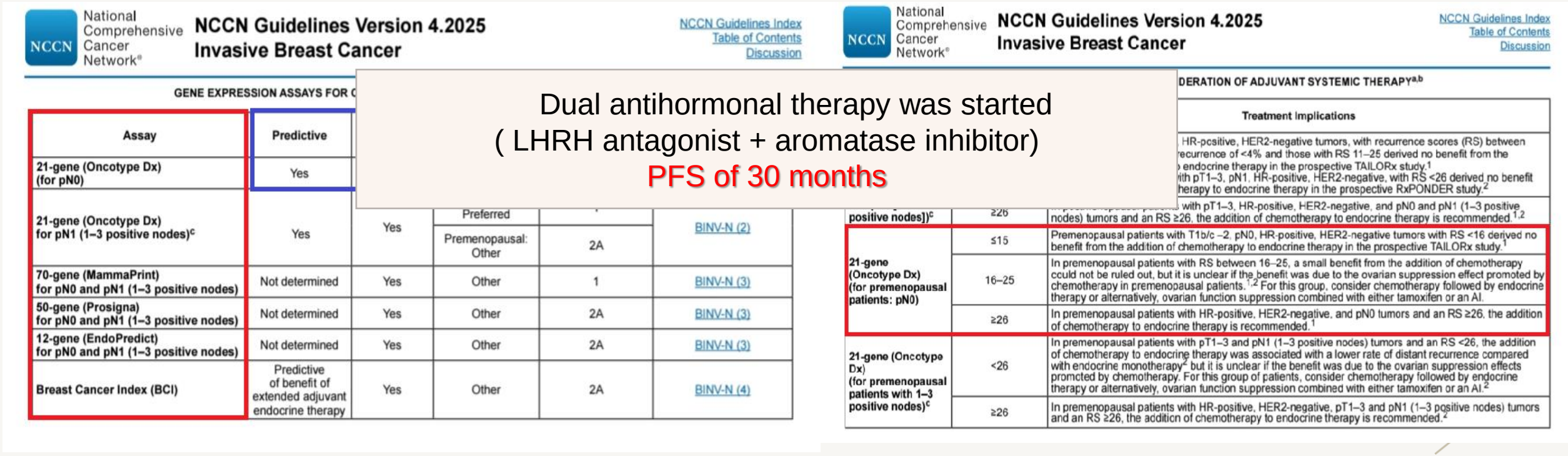
Chemotherapy v.s. hormonal therapy???

Overtreated v.s subtreated???

BREAST CANCER

CASE REPORT 1.

- A variety of clinical molecular tests have been approved as a result of strong clinical trial evidence to help with disease characterisation, prognostication, and treatment selection. For instance, clinical judgments regarding the use of adjuvant chemotherapy or endocrine therapies are guided by multigene expression profiles, which are used to categorize breast tumors.



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GENE EXPRESSION ASSAYS FOR C

Assay	Predictive				
21-gene (Oncotype Dx) (for pN0)	Yes				
21-gene (Oncotype Dx) for pN1 (1–3 positive nodes)[c]	Yes	Yes	Preferred		BINV-N (2)
			Premenopausal: Other	2A	
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	1	BINV-N (3)
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3)
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3)
Breast Cancer Index (BCI)	Predictive of benefit of extended adjuvant endocrine therapy	Yes	Other	2A	BINV-N (4)

Dual antihormonal therapy was started
(LHRH antagonist + aromatase inhibitor)
PFS of 30 months

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DERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

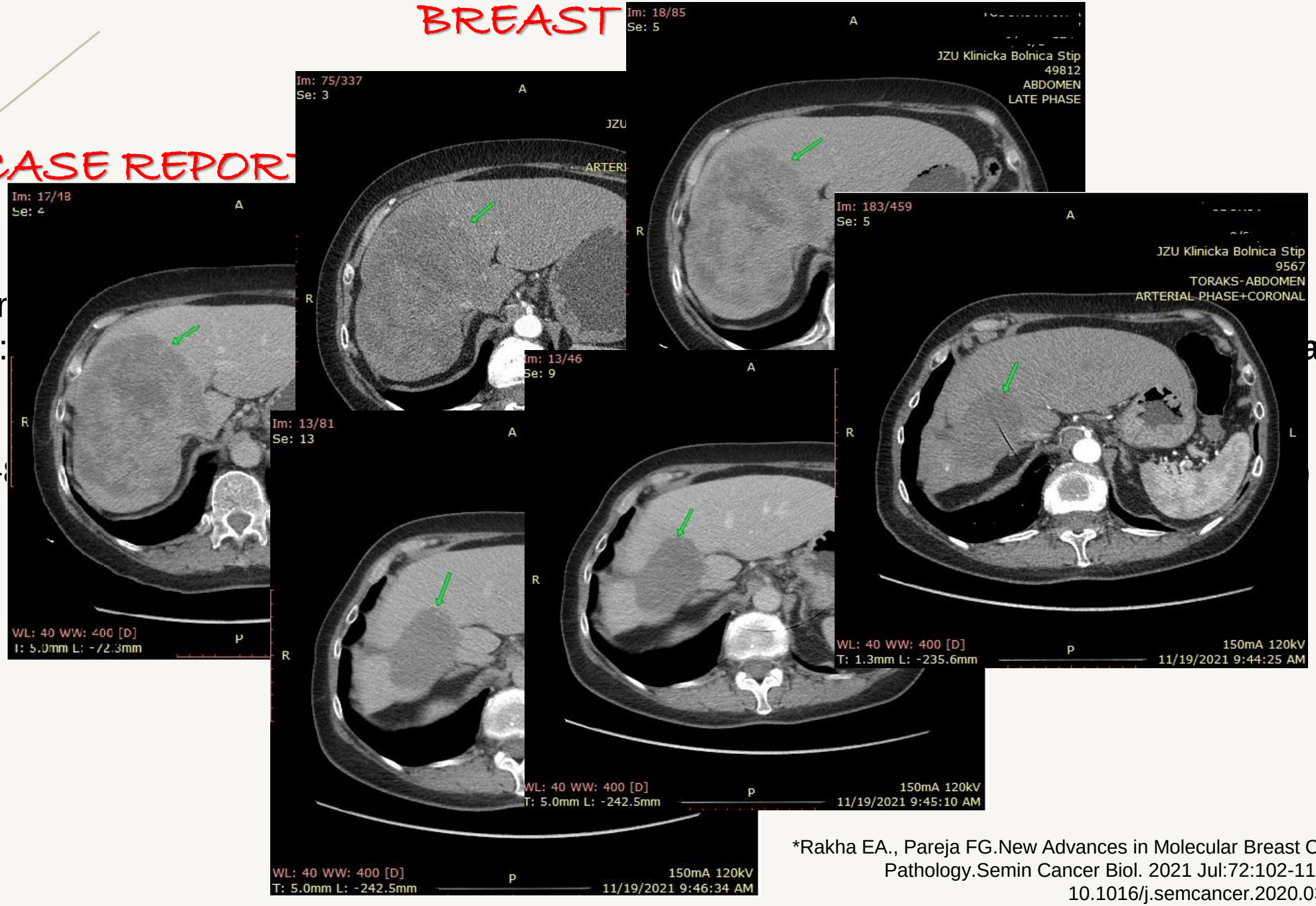
		Treatment Implications
		HR-positive, HER2-negative tumors, with recurrence scores (RS) between recurrence of <4% and those with RS 11–25 derived no benefit from the endocrine therapy in the prospective TAILORx study.[1] ith pT1–3, pN1, HR-positive, HER2-negative, with RS <26 derived no benefit herapy to endocrine therapy in the prospective RxPONDER study.[2]
positive nodes])[c]	≥26	with pT1–3, HR-positive, HER2-negative, and pN0 and pN1 (1–3 positive nodes) tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[1,2]
21-gene (Oncotype Dx) (for premenopausal patients: pN0)	≤15	Premenopausal patients with T1b/c –2, pN0, HR-positive, HER2-negative tumors with RS <16 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study.[1]
	16–25	In premenopausal patients with RS between 16–25, a small benefit from the addition of chemotherapy could not be ruled out, but it is unclear if the benefit was due to the ovarian suppression effect promoted by chemotherapy in premenopausal patients.[1,2] For this group, consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI.
	≥26	In premenopausal patients with HR-positive, HER2-negative, and pN0 tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[1]
21-gene (Oncotype Dx) (for premenopausal patients with 1–3 positive nodes)[c]	<26	In premenopausal patients with pT1–3 and pN1 (1–3 positive nodes) tumors and an RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy[2] but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy. For this group of patients, consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI.[2]
	≥26	In premenopausal patients with HR-positive, HER2-negative, pT1–3 and pN1 (1–3 positive nodes) tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[2]

*Yang T., Li W., Huang T., Zhou J. Genetic Testing Enhances the Precision Diagnosis and Treatment of Breast Cancer. Int J Mol Sci. 2023 Nov 22;24(23):16607. doi: 10.3390/ijms242316607.

BREAST

CASE REPORT

- 66 year
- 3/2021:
- (3/2021-



*Rakha EA., Pareja FG.New Advances in Molecular Breast Cancer Pathology.Semin Cancer Biol. 2021 Jul:72:102-113. doi: 10.1016/j.semcancer.2020.03.014.

8/2022: Mastectomia radicalis lat dex,pT1b (0.8cm) G2 ypN0 (0/9)

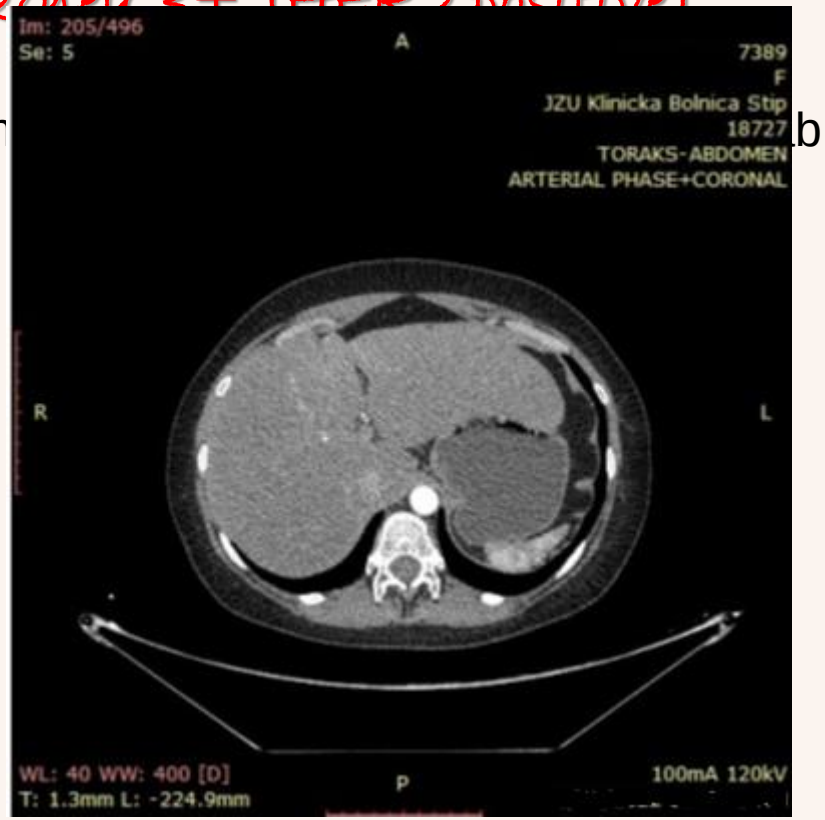
IHC: Er neg PR neg Her2/neu 3+ (HER2 positive)

(8/2022-12/2024) Second line chemotherapy + Second lin b emtasine)

12/2024: Ms cerebri / RT (10fr/30Gy)

1/2025 - Bilogical therapy (**Trastuzumab 600mg/sc**)

OS 48 MONTHS



5. Future Directions for Molecular Profiling of Patients with Cancer and Target the tumor

- Despite significant advances in the molecular characterization of a wide range of cancers, and the development of novel precision oncology therapies, prognostic and predictive assessments for many tumor types are still largely dependent on histopathological and radiological assessments, and precision medicine currently remains unavailable for many patients.

- Even though recent trials with targeted therapies have demonstrated encouraging response rates, a consequence of ever-more precise patient selection is that biomarker-positive populations can be very small, and the most effective targeted therapies may only benefit a small number of patients with specific tumor types, while targeted therapies are not yet available for the majority of patients.

- Novel approaches to drug development and patient testing, the integration of multi-omic data from preclinical experiments and clinical trials, communication across all disciplines, and global collaboration will ensure that as many patients as possible can benefit from precision-based treatments

THANK YOU