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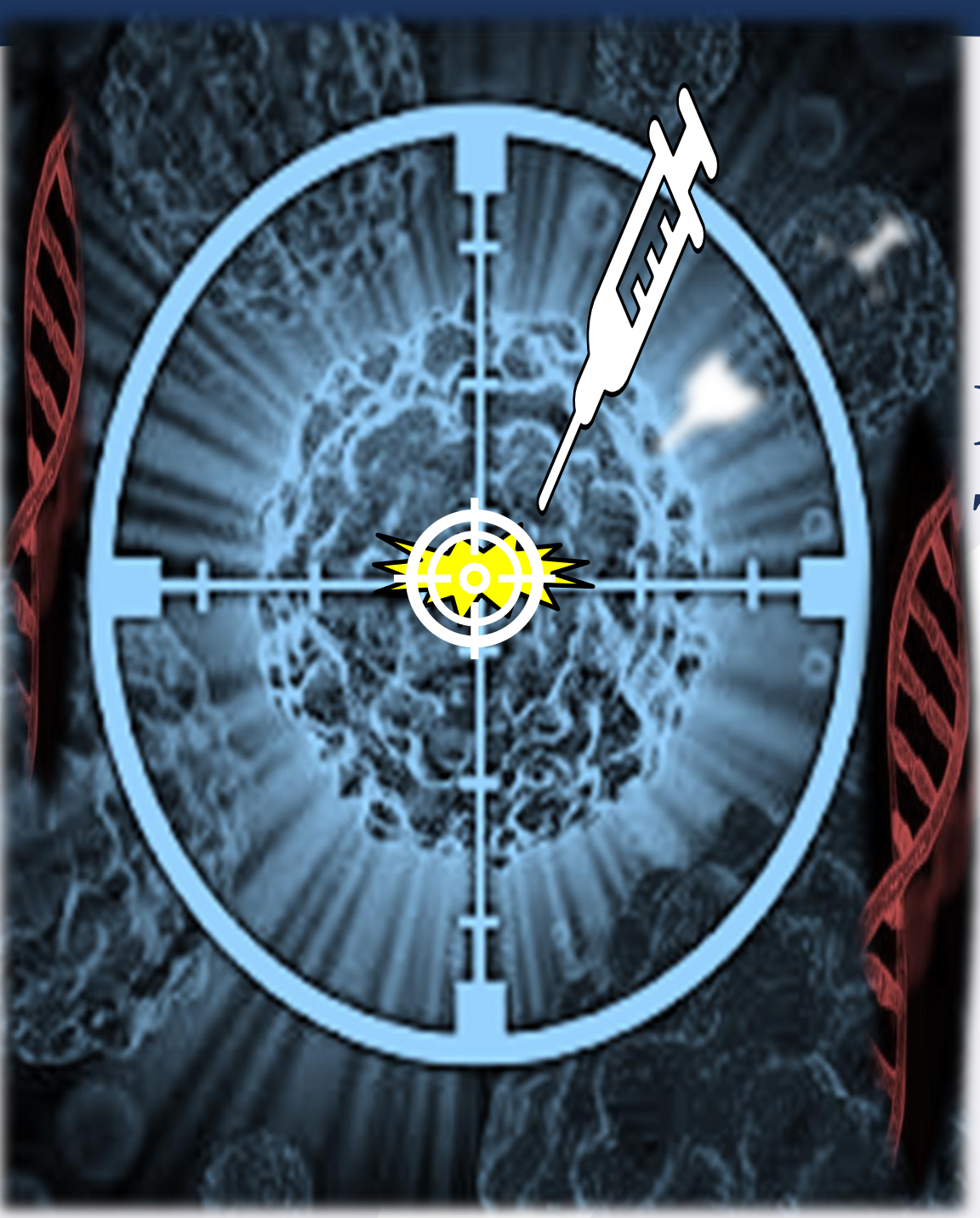


Immunotherapy and Targeted Therapy in Clinical Oncology: Commercial Perspective

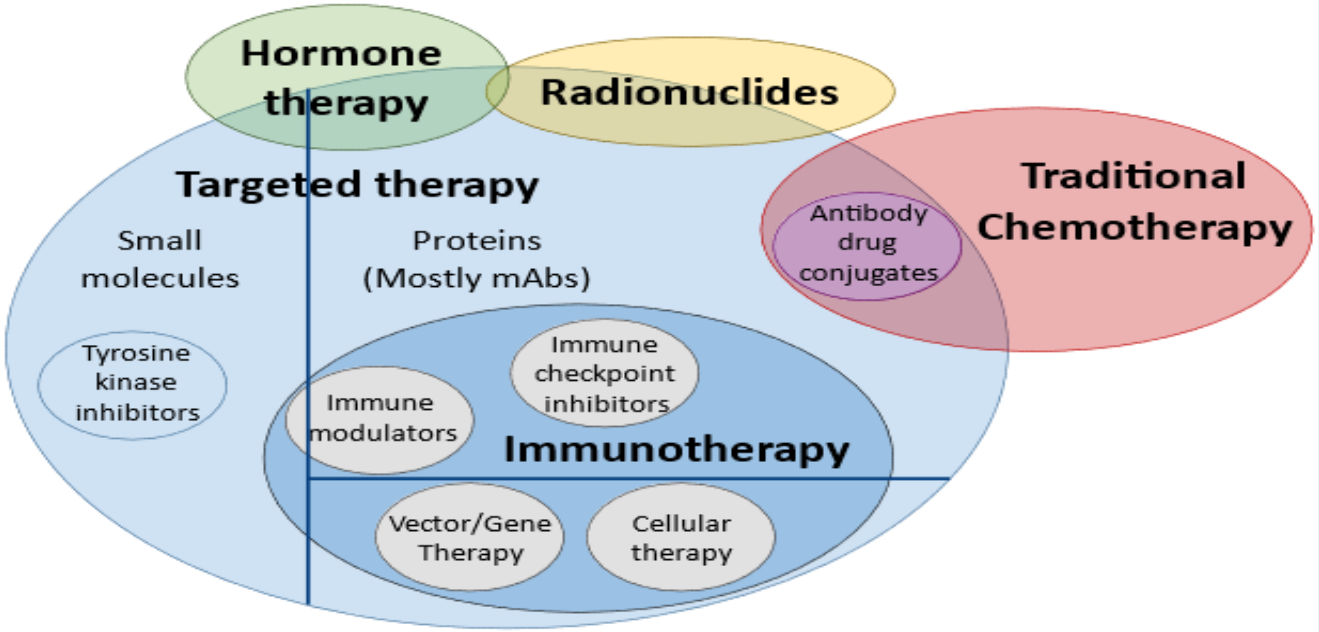
Dr. Bhawna Dubey Ph.D.

REPROCELL

Immunotherapy and Targeted Therapy

Targeted Therapy

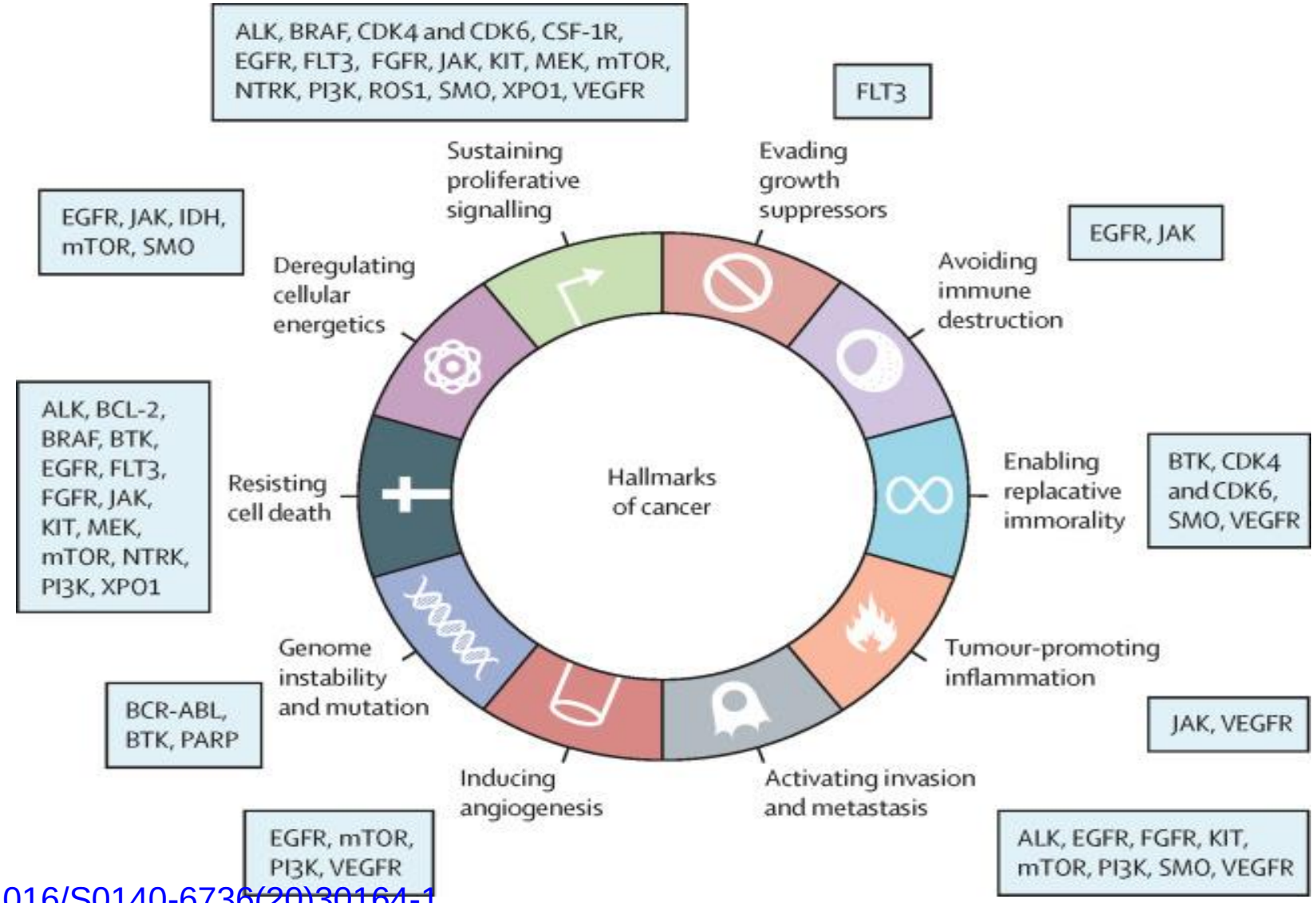
- Targeted therapy- uses drugs to target specific genes and proteins
- Patients with cancer will have a target for a certain drug, so they can be treated with that drug.
- 3 main types: 1. small molecule medicines 2. monoclonal antibodies 3. immunotoxins
- cetuximab (Erbitux) –for advanced bowel cancer and HNC
- trastuzumab (Herceptin) – for breast cancer and stomach cancer.



Immuno- Therapy

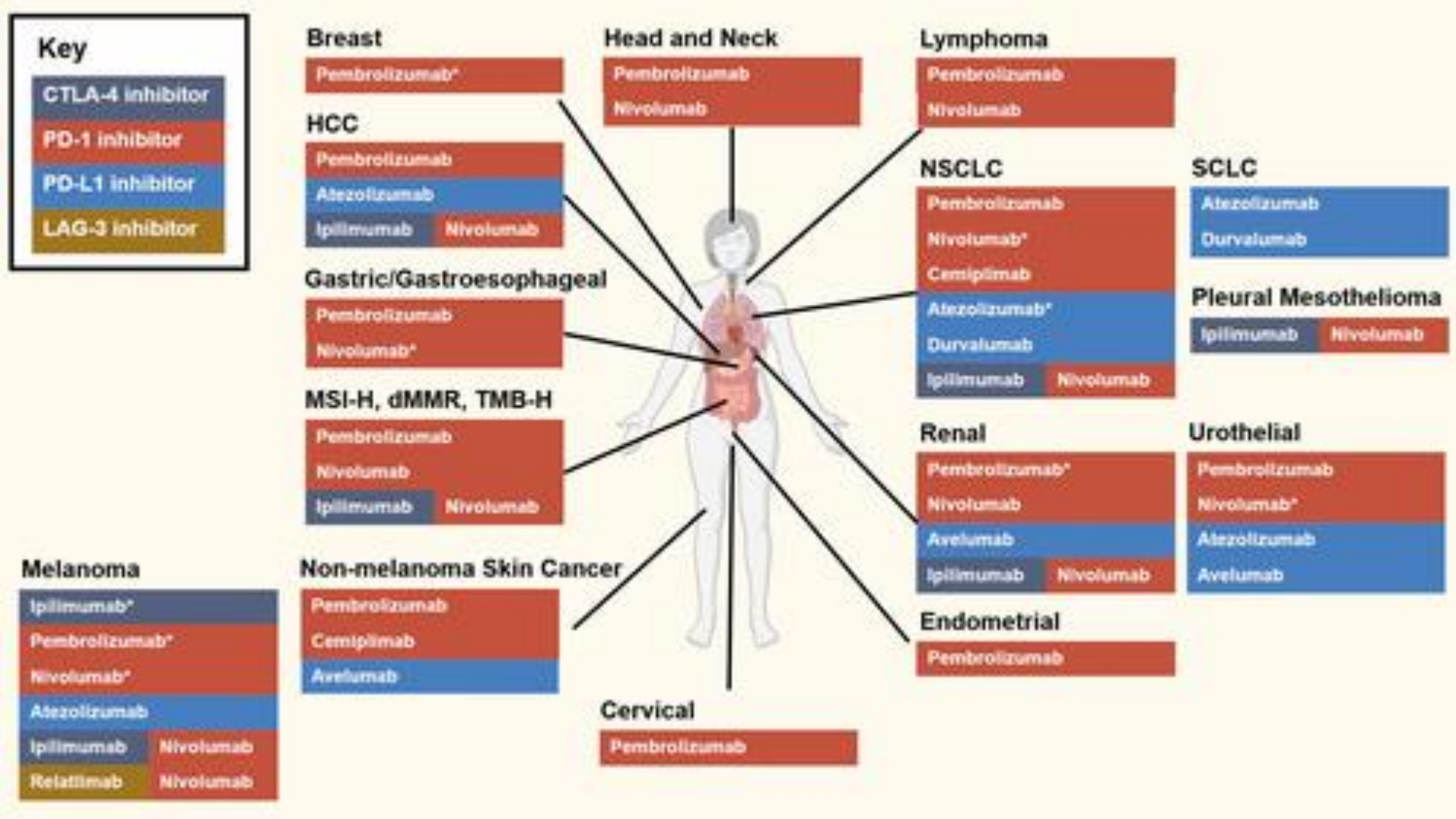
- Some monoclonal antibodies are also immunotherapy because they help turn the immune system against cancer.
- Example: Checkpoint inhibitors block proteins that stop the immune system attacking cancer cells. pembrolizumab (Keytruda)

Small Molecules- Targeted Therapy



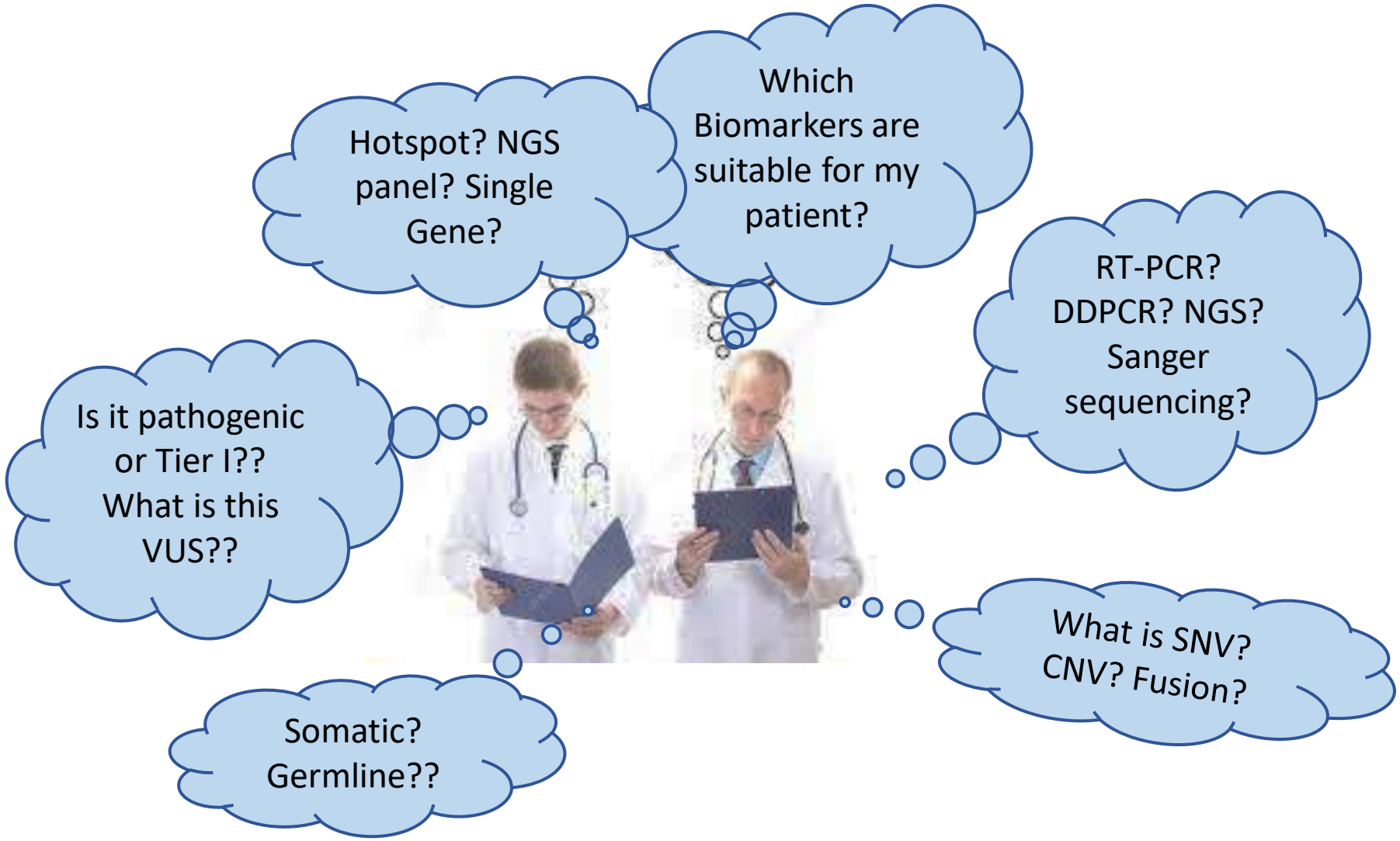
https://doi.org/10.1016/S0140-6736(20)30164-1

Immunotherapy: Immune checkpoint inhibitors



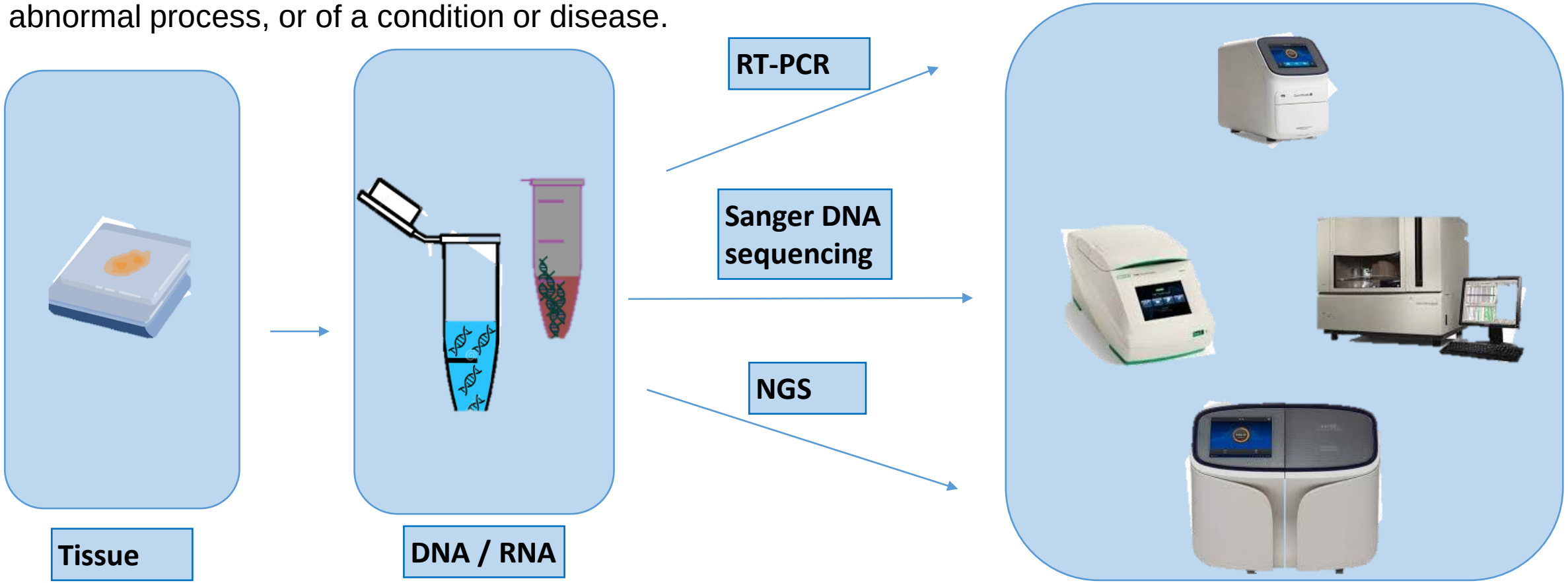
https://www.jacc.org/doi/10.1016/j.jaccao.2022.09.004

Detection of Biomarkers- Physician's Conundrum



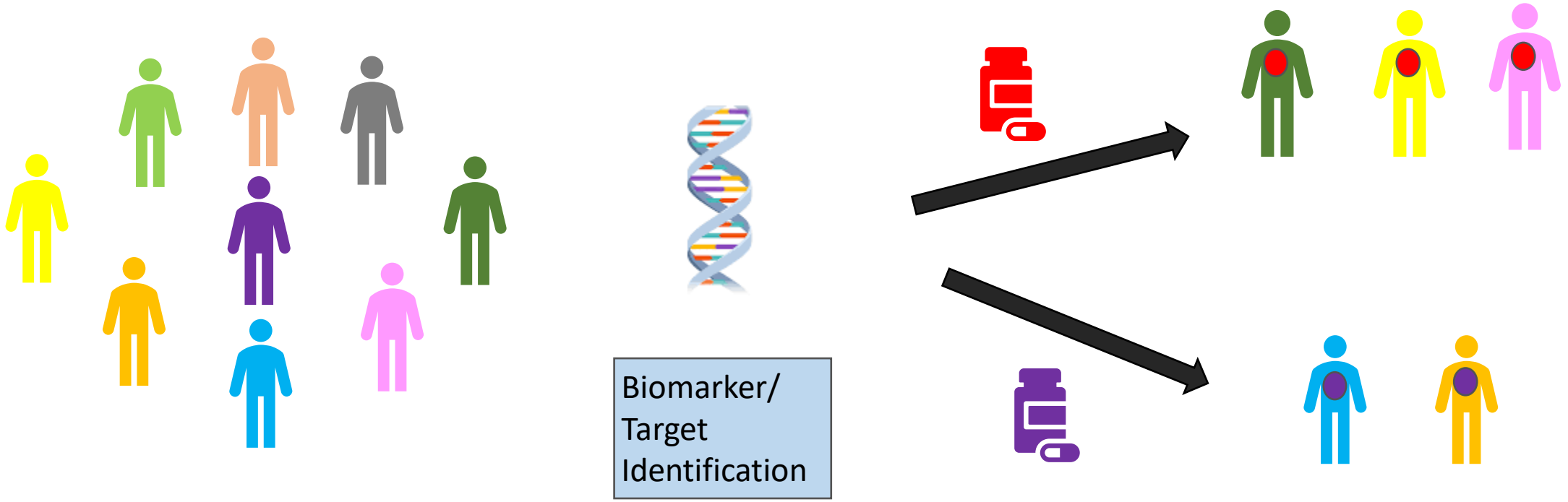
Molecular Diagnostics

- **Molecular Diagnostics:** The process of identifying a disease by studying molecules, such as proteins, DNA, and RNA, in a tissue or fluid.
- **Bio-Marker:** A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.

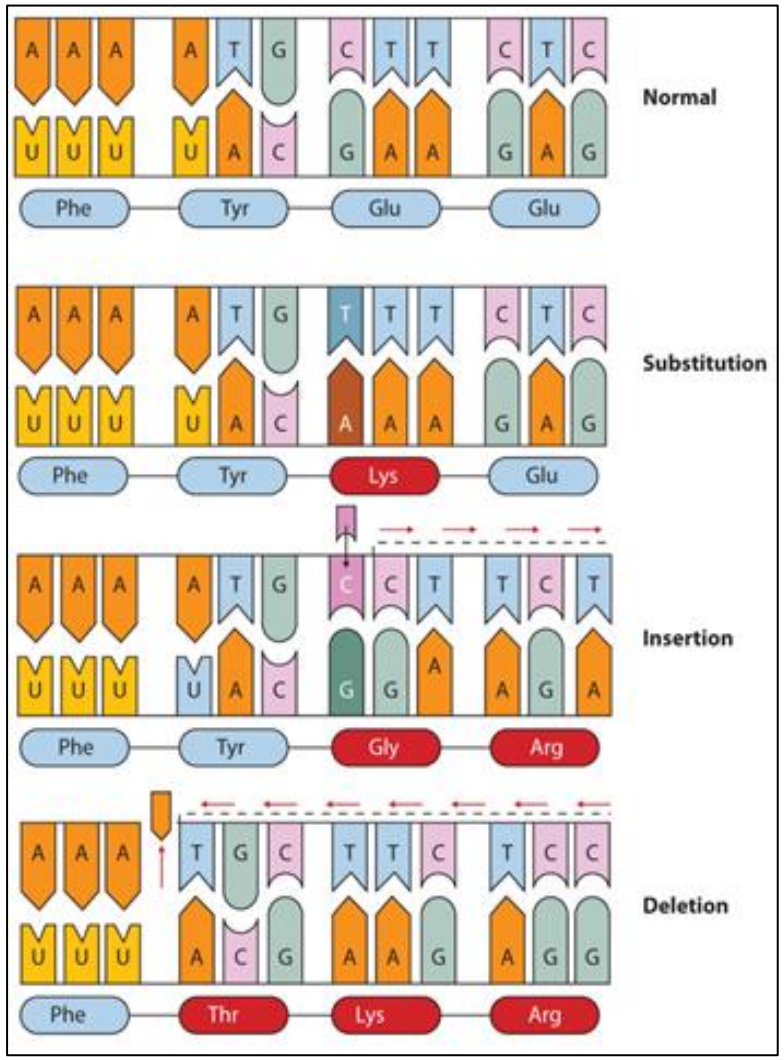


Why Target Testing

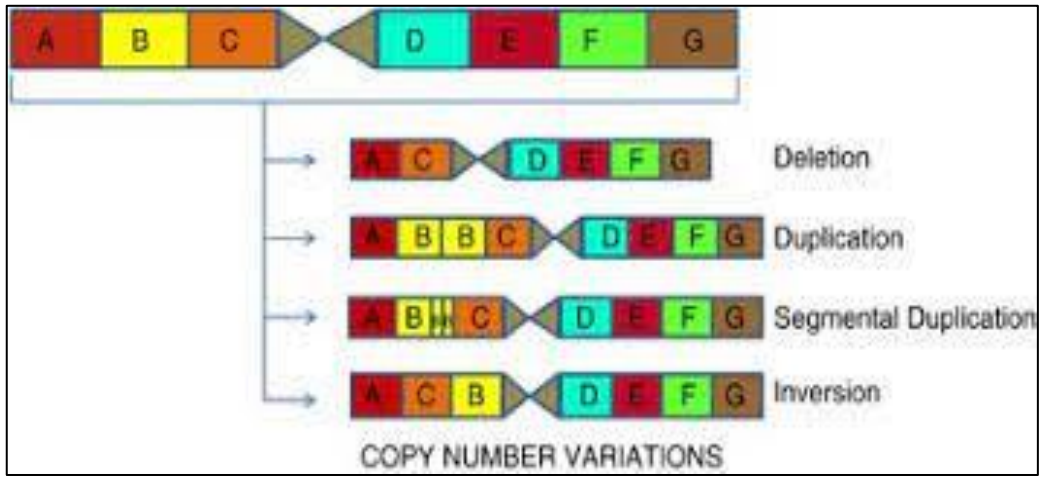
- Identify target in the patient to decide therapy options
- Enrich Patient pool which can benefit from target therapy



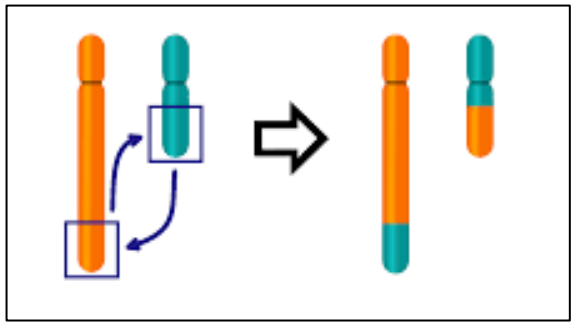
What are these “Targets”? What are their types?



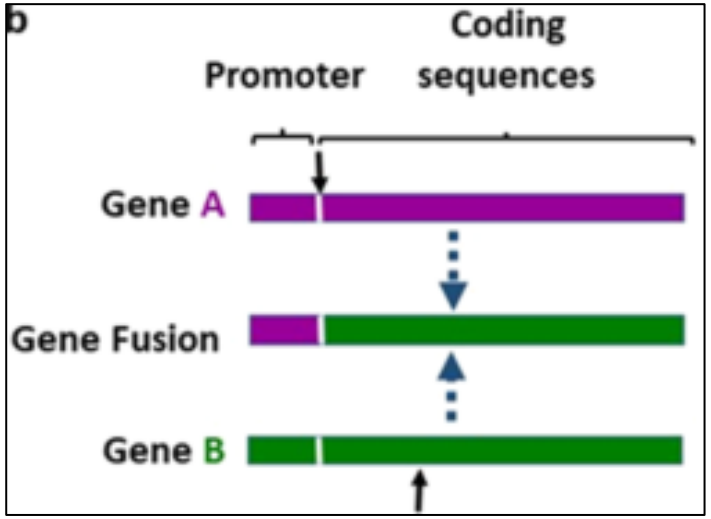
Single nucleotide Mutation (SNV) or Point mutations
Ex: EGFR T790M



CNV –Copy Number Variants
Ex: MET amplification



Translocations
Ex: BCR-ABL (Ph chromosome)



Gene Fusion
Ex: ALK/ROS

Targets/ Biomarkers for Immunotherapy

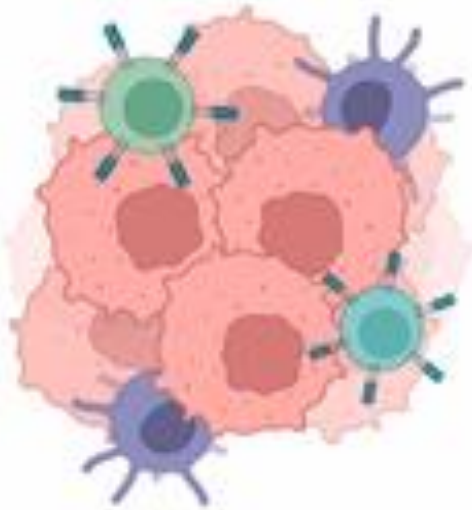
Biomarkers in Use

PD-L1 Expression
- Useful only in certain tumors
- Predictive for anti-PD-1/PD-L1

Tumor Mutational Burden
- Increases neoantigen expression
- Predictive for anti-CTLA-4 and anti-PD-1/PD-L1

Microsatellite Instability
- Reflects hypermutability
- Predictive for anti-CTLA-4 and anti-PD-1/PD-L1

Predictive Biomarkers of ICI Response



Biomarkers Under Investigation

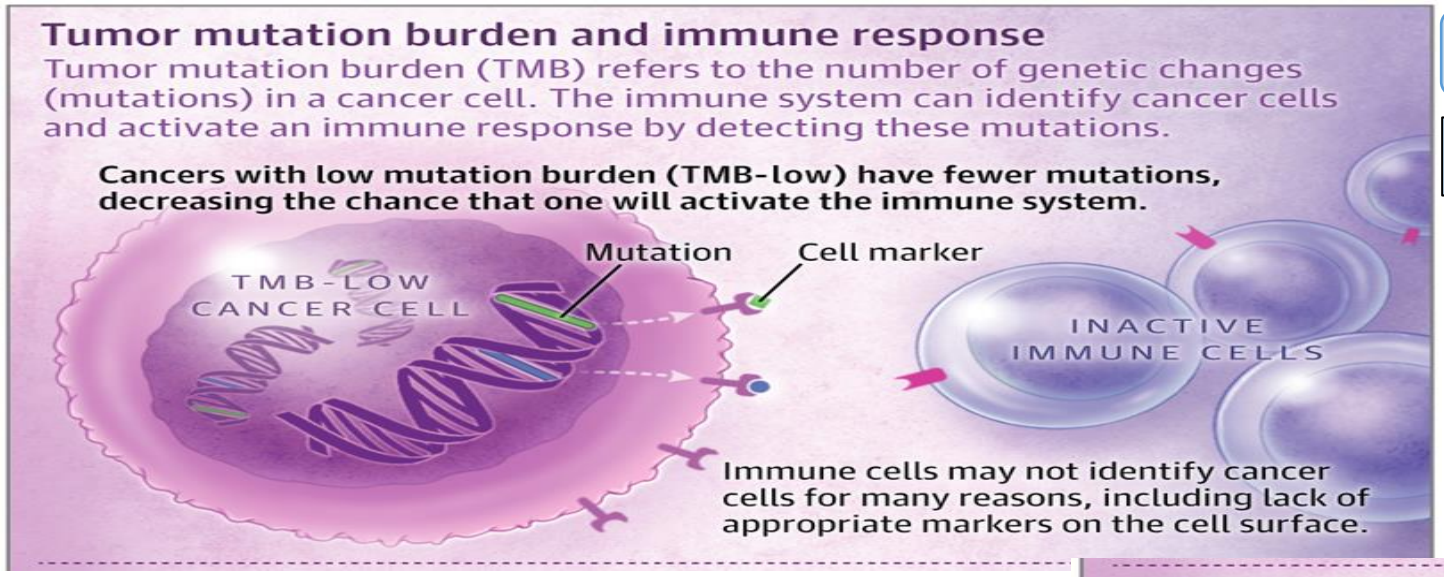
Tumor Microenvironment
- Immune and angiogenesis profiles around tumor cells

Genomic Mutational Profile
- Defects in oncogenes, tumor suppressors and signalling

Gut Microbiome
- Better response with increased diversity, anabolic pathways and specific bacteria

Neutrophil/Lymphocyte Ratio
- Obtained from peripheral blood
- Imperfect and lacks standardized threshold

1. Tumor Mutation Burden- TMB

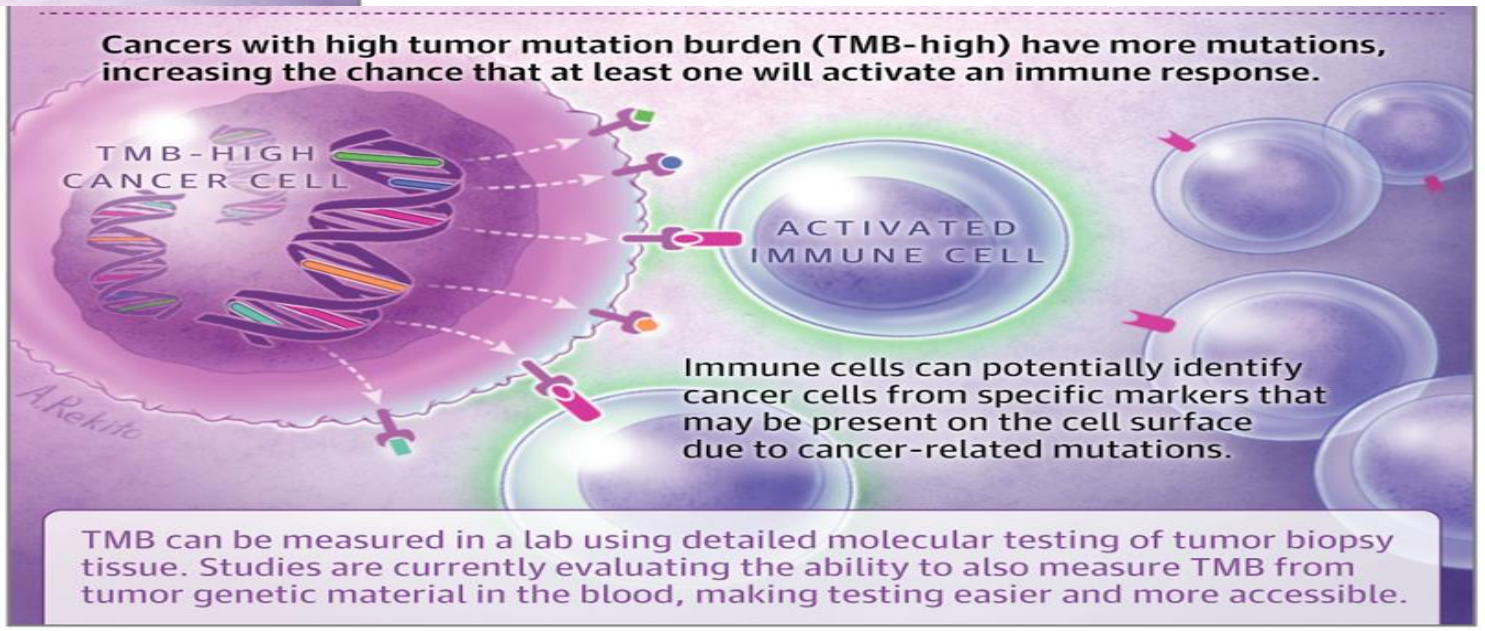


Cold Tumor

Low TMB

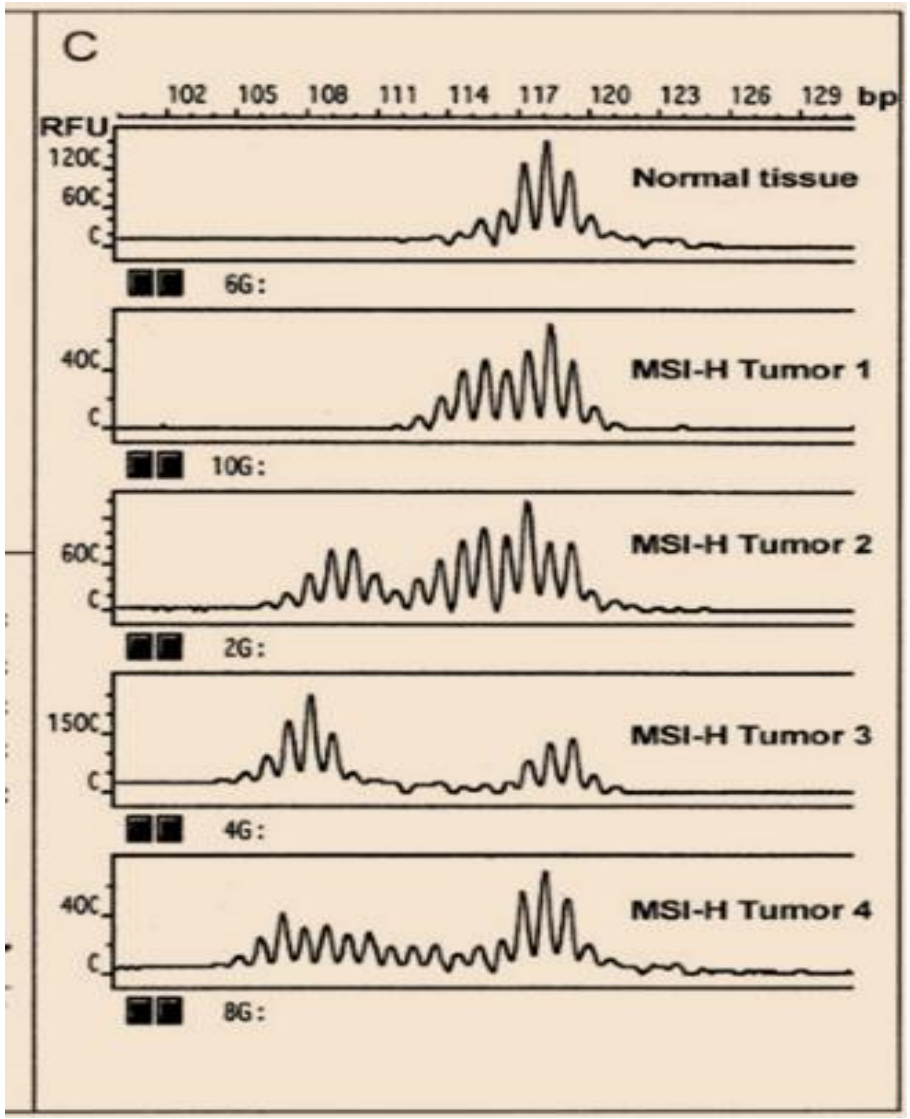
Hot Tumor

High TMB – Better ICI response

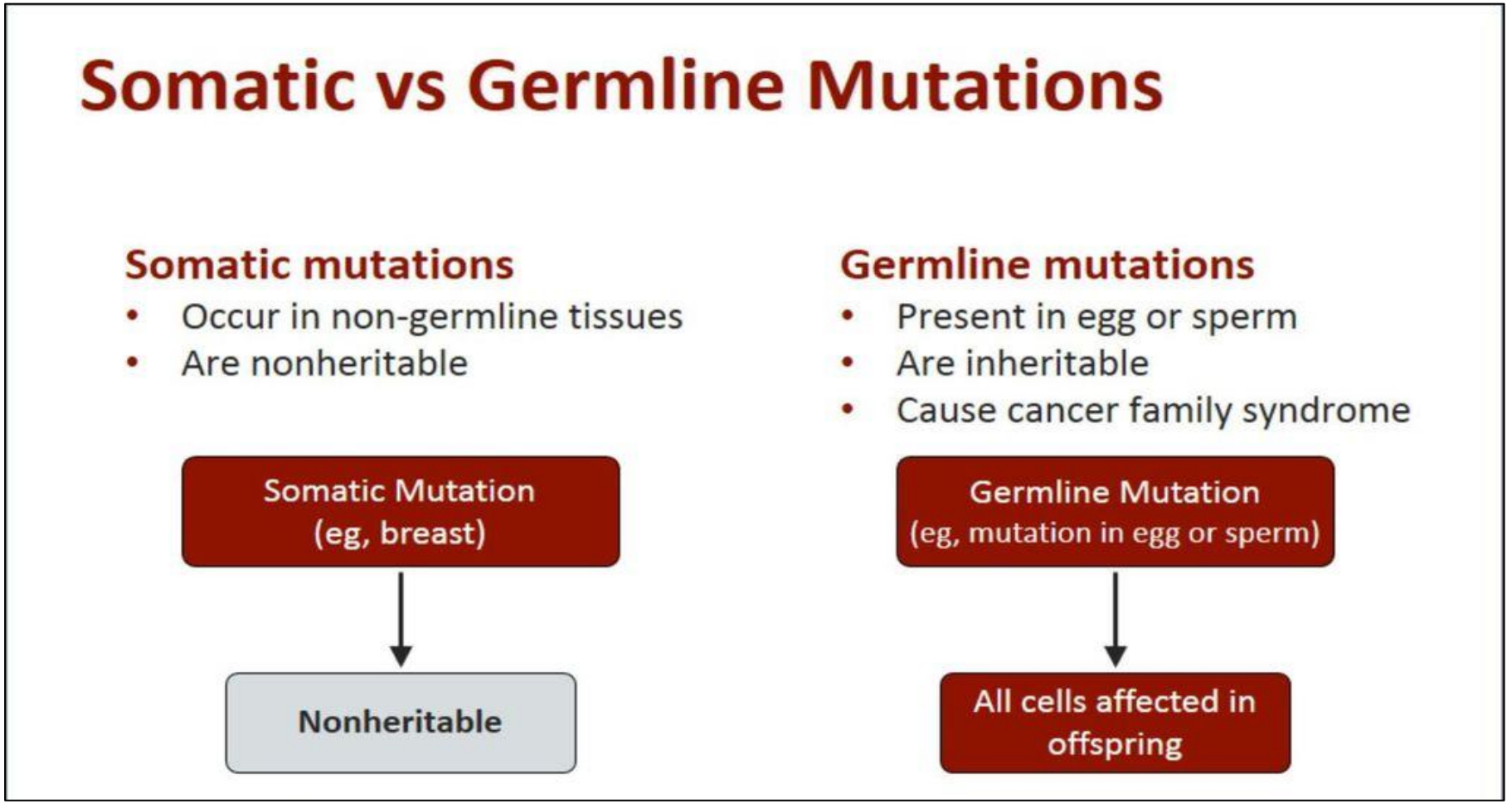


2. Microsatellite Instability (MSI)

- Microsatellites are regions of repeated DNA that change in length (show instability) when mismatch repair is not working properly.
- MSI – High / low/ stable
- MSI-H: Predictive for ICI therapy
- MSI-H: eligibility to Pembrolizumab, ipilimumab, nivolumab treatment of colorectal cancer patients
- MSI-H: Diagnostic- Lynch Syndrome
- MSI-H = mismatch repair deficient (dMMR)
- dMMR is defined as at least 1 protein (MSH 2, MSH 6, PMS 2 and MLH 1) showing loss of expression- IHC



Mutations Types based on Origin

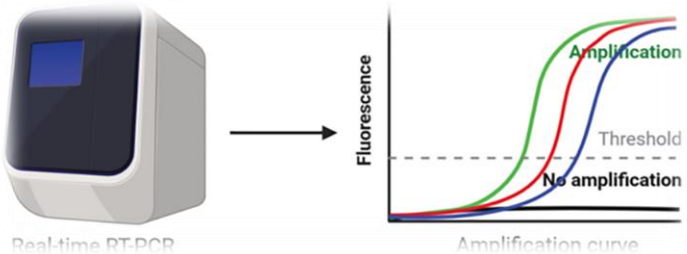


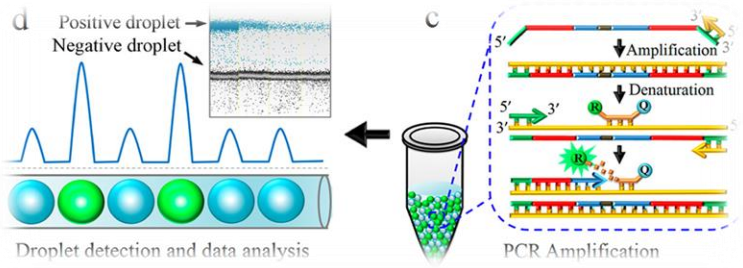
Somatic Testing = Tumor testing. Samples: FFPE block, FFPE slides, Liquid biopsy, Whole blood in streck/paxgene tube for ctDNA analysis

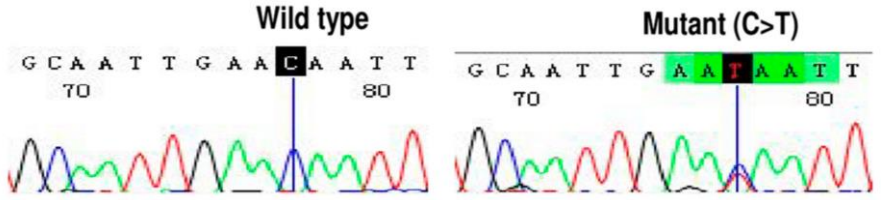
Germline Testing: Testing for heredity. Sample: Blood in EDTA tube

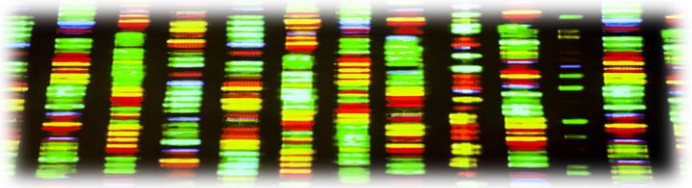
How are these Targets detected: Molecular Techniques

Technique	Application
RT-PCR	Detection/ Quantification of a marker eg. BCR/ABL IS %
DD-PCR	Highly sensitive detection/ Quantification of a marker eg. EGFR T790M mutation
Sanger Sequencing	Detection multiple mutations on a gene eg. JAK2 Exon 12, KRAS mutations
Next Generation Sequencing	Detection multiple mutations on multiple genes eg. All genes involved in lung cancer

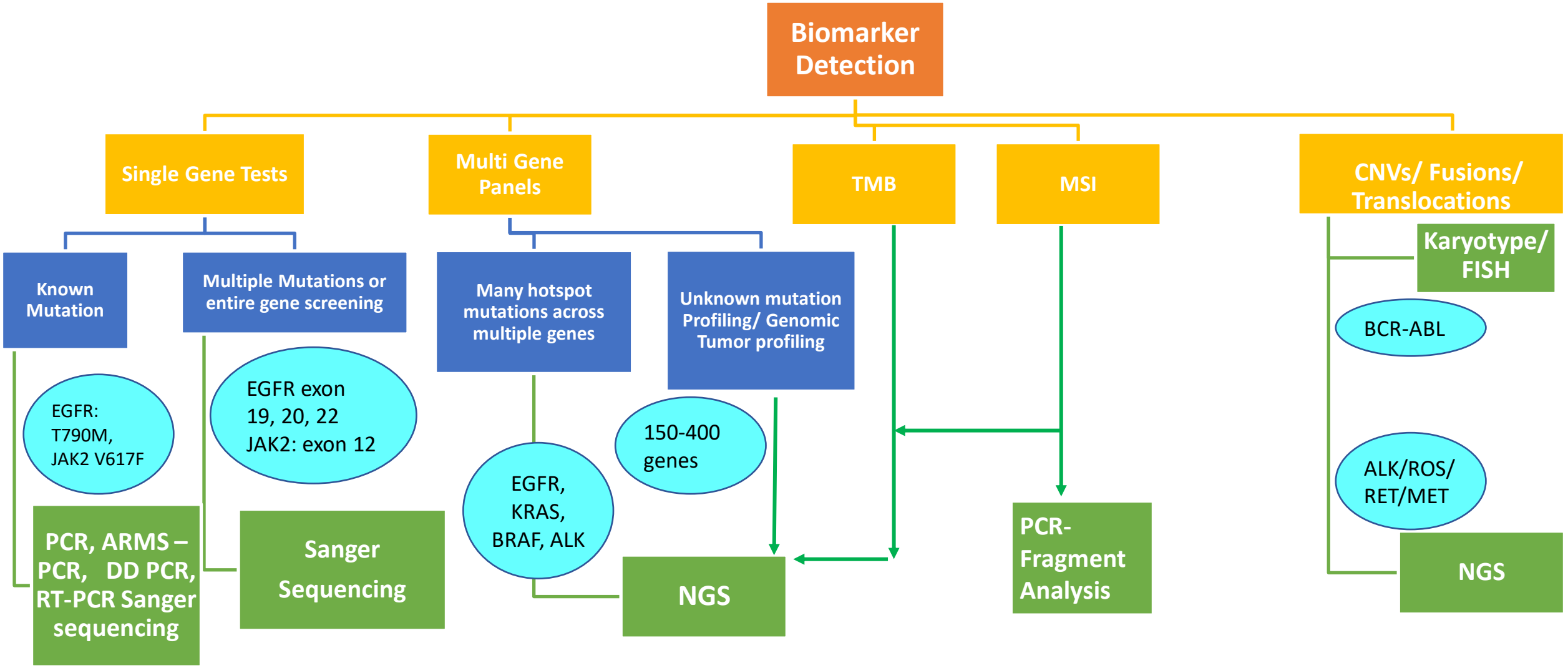






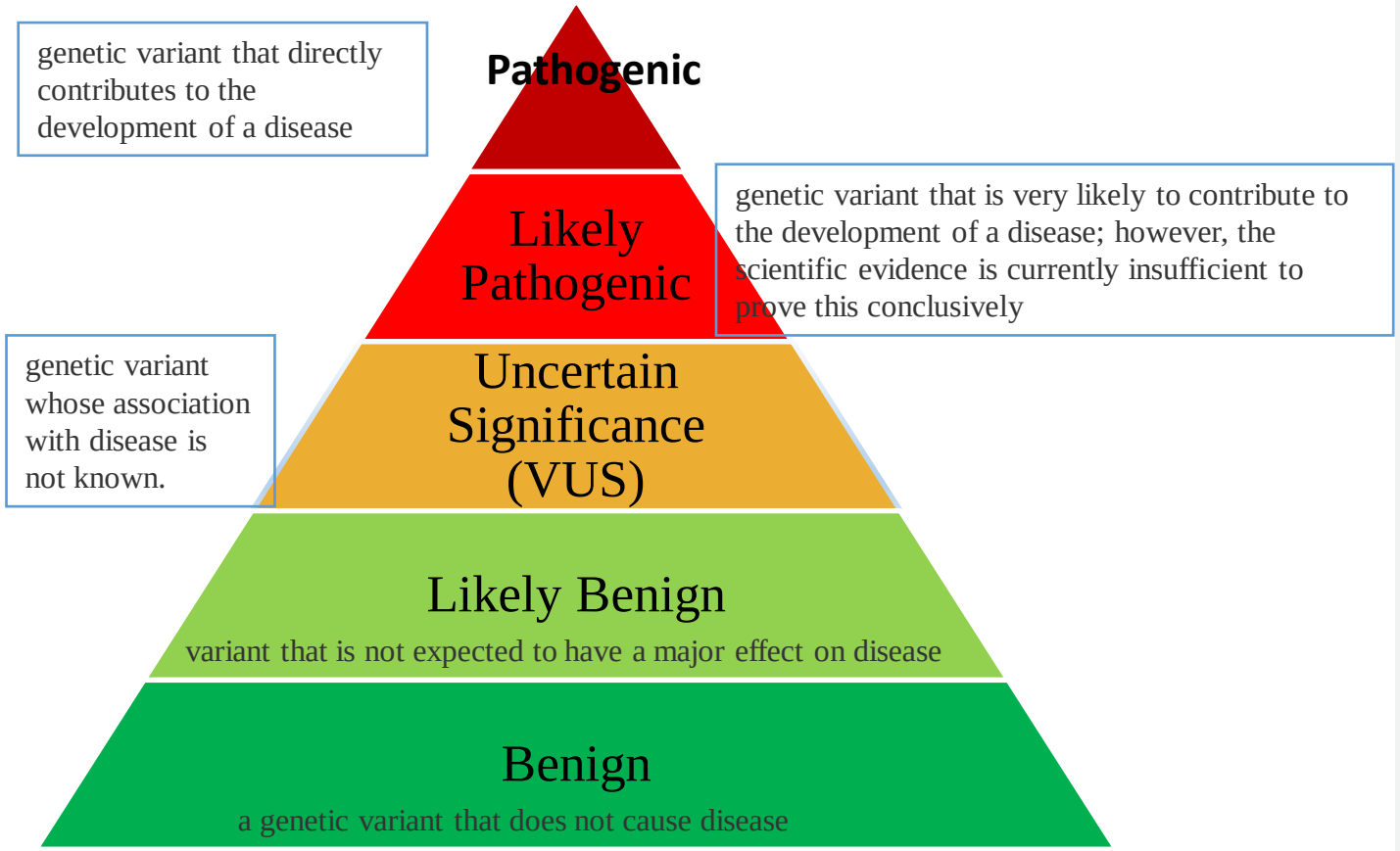


Target- Technique correlation: How to choose?



Reporting: Variant Categories

ACMG



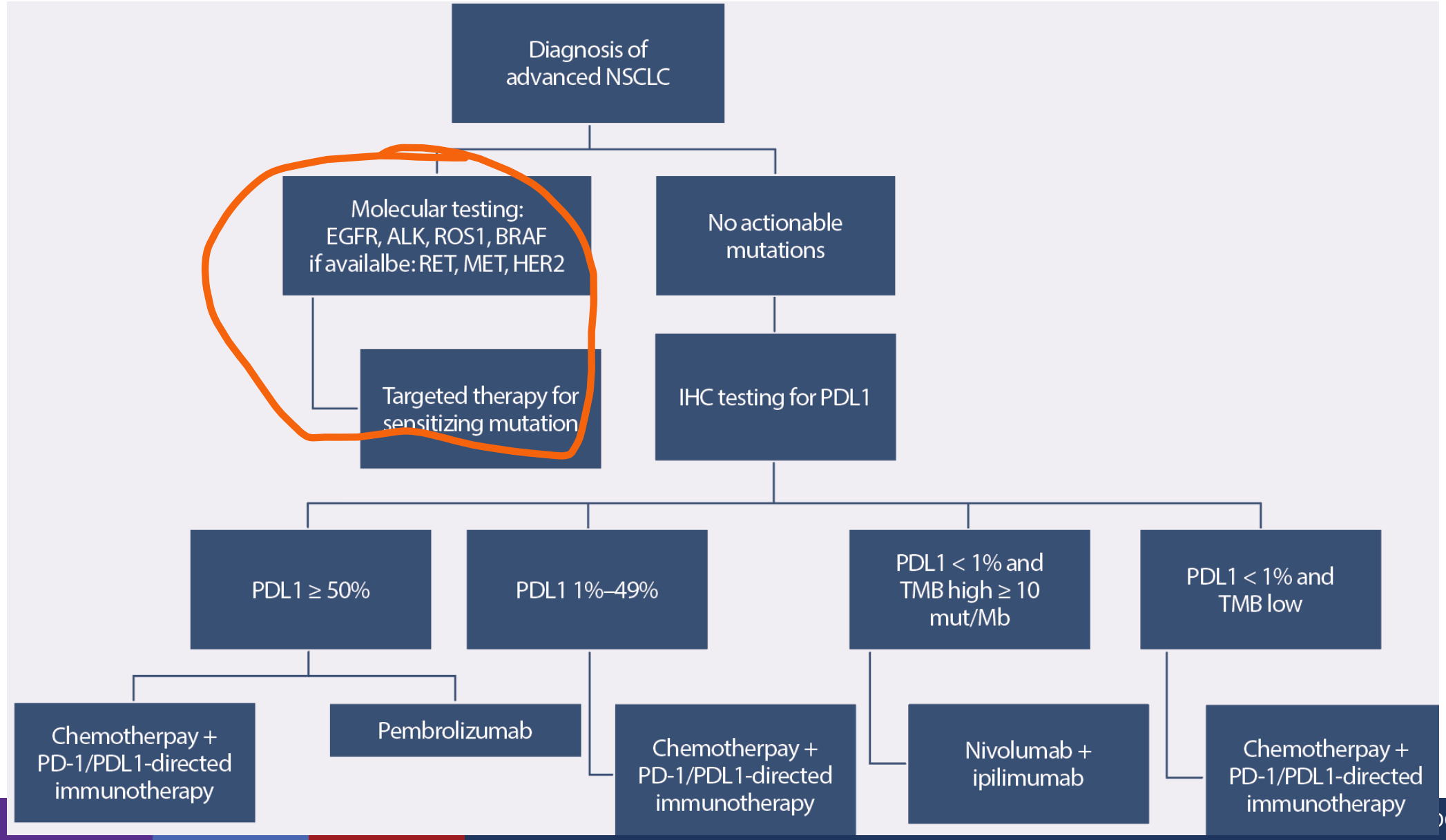
AMP

JCR Tier 1	**Strong clinical significance** A: FDA approved therapy / professional guidelines B: Well-powered studies with expert consensus
JCR Tier 2	**Potential clinical significance** C: FDA approval in different entity / inclusion in clinical trial / multiple small studies with some consensus D: Preclinical trials / case reports
JCR Tier 3	**Unknown clinical significance** No convincing evidence of cancer association
JCR Tier 4	**Benign variants** No existing evidence of cancer association

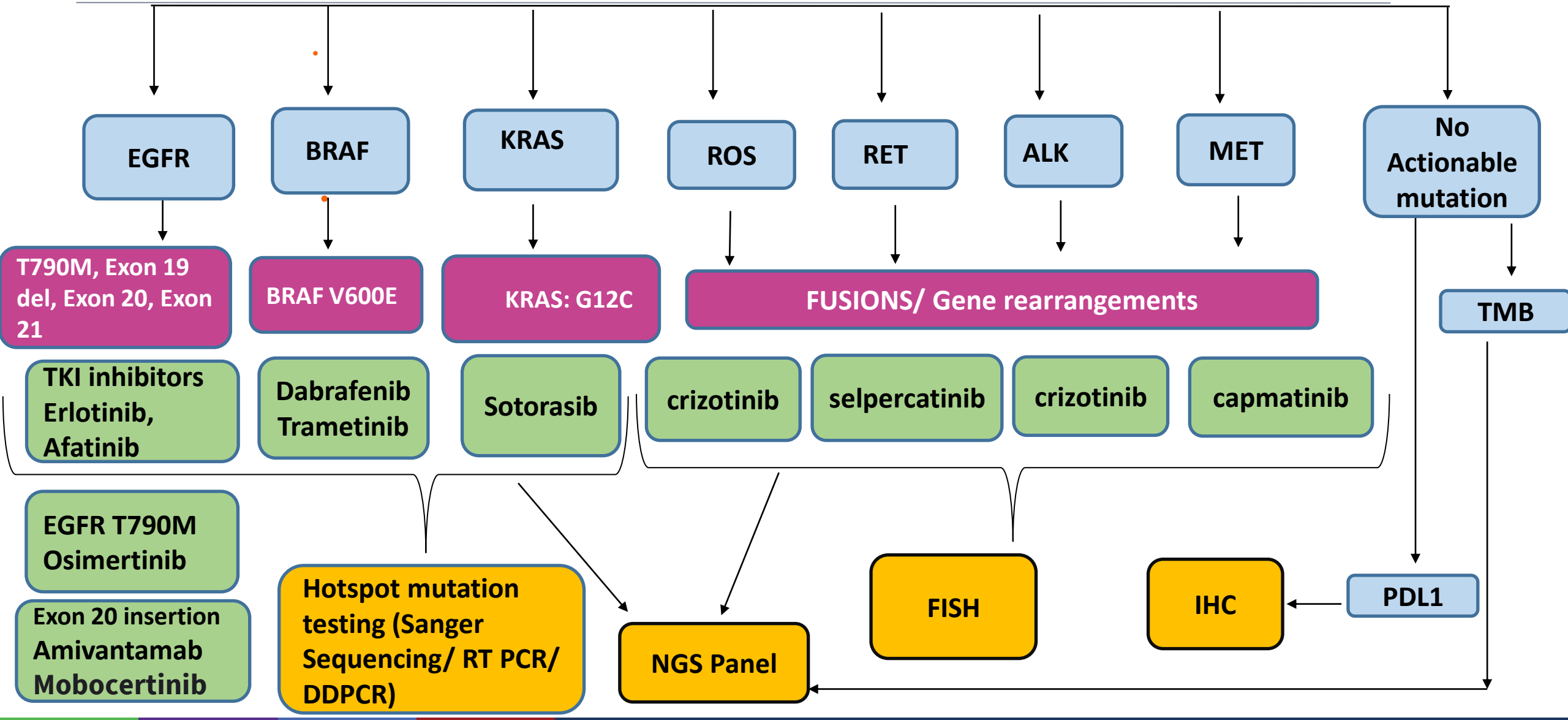
Applying Biomarker/ Target testing in Cancers

- Lung Cancer
- Breast Cancer
- Colorectal Cancer

Treatment Algorithm for Non-Small Cell Lung Cancer



Treatment algorithm for patients with advanced/metastatic NSCLC



ASCO Guidelines

BIOMARKERS FOR SYSTEMIC THERAPY IN METASTATIC BREAST CANCER

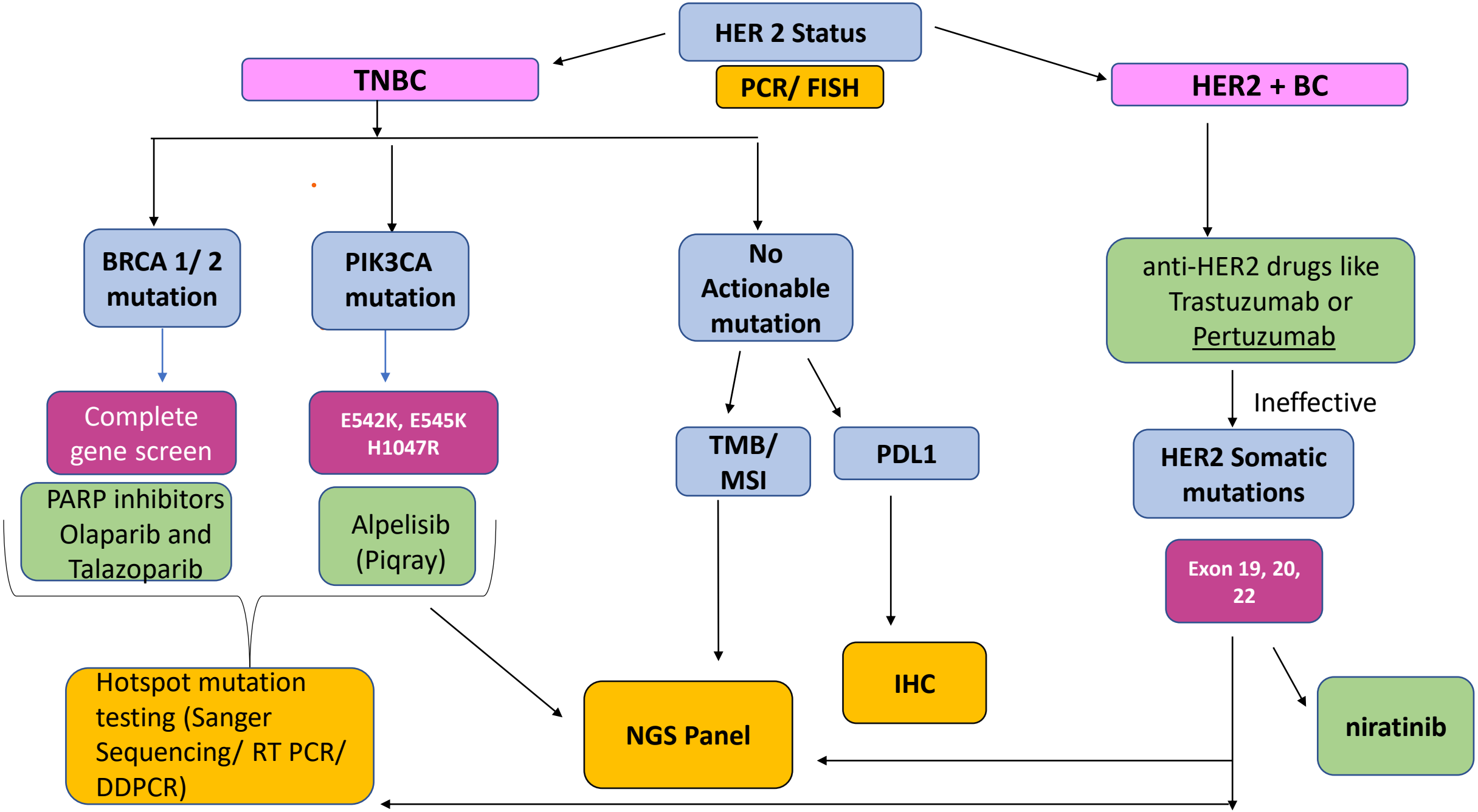
GUIDELINE UPDATE AT-A-GLANCE RECOMMENDATIONS

Test	Type of Recommendation	Quality of Evidence	Strength of Recommendation
Biomarker Tests Recommended by the ASCO Expert Panel			
• *PIK3CA*	• Evidence-based	• High	• Strong
• Germline *BRCA1* and *BRCA2*	• Evidence-based	• High	• Strong
• PD-L1	• Evidence-based	• Intermediate	• Strong
• dMMR/MSI-H	• Informal consensus-based	• Low	• Moderate
• TMB	• Informal consensus-based	• Low	• Moderate
• *NTRK* Fusions	• Informal consensus-based	• Low	• Moderate
Biomarker Tests Not Recommended by the ASCO Expert Panel			
• *ESR1*	• Evidence-based	• Insufficient	• Moderate
• *PALB2*	• Evidence-based	• Low	• Moderate
• HRD	• Informal consensus-based	• Low	• Moderate
• TROP2 expression	• Informal consensus-based	• Low	• Moderate
• ctDNA	• Informal consensus-based	• Low	• Moderate
• CTCs	• Informal consensus-based	• Low	• Moderate

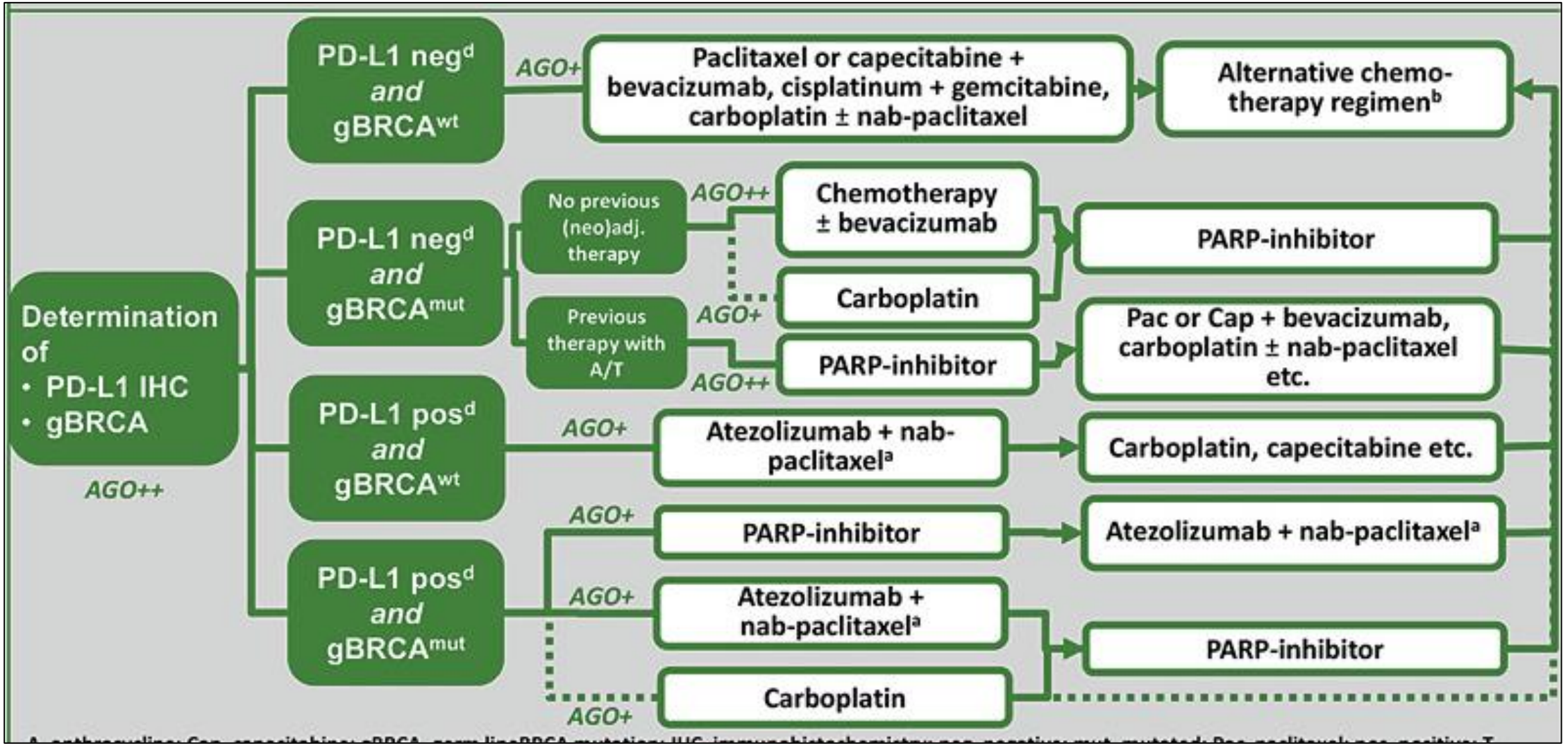
Henry et al *J Clin Oncol* **2022**
asco.org/breast-cancer-guidelines

Abbreviations. CTCs, circulating tumor cells; ctDNA, circulating tumor DNA; dMMR, deficient mismatch repair; HRD, homologous recombination deficiency; MSI-H, microsatellite instability-high; NTRK, neutotrophic tyrosine receptor kinase; PD-L1, programmed cell death ligand-1; TMB, tumor mutational burden; TROP2, trophoblast cell-surface antigen 2

Treatment algorithm for patients with advanced/metastatic Breast cancer



Treatment Algorithm for Triple Negative Breast Cancer



https://www.karger.com/Article/Fulltext/511925

BRCA: Who Should get Tested?

PREDISPOSITION TEST

- A history of Breast/ Ovarian cancer in family
- A history of breast cancer at a young age in two or more blood relatives, such as your parents, siblings or children
- A close male relative with breast cancer
- A relative with a known BRCA1 or BRCA2 mutation

PATIENT TEST

- A personal history of Breast / Ovarian cancer diagnosed before age 45
- A personal history of triple negative breast cancer diagnosed at age 60 or younger
- A personal history of two or more types of cancer
- A personal history of breast cancer and one or more relatives with breast cancer diagnosed before age 50

ESMO consensus guidelines CRC patient Management

Recommendation 4: RAS testing

- *RAS* mutational status is a negative predictive biomarker for therapeutic choices involving EGFR antibody therapies in the metastatic disease setting [I, A]
  - *RAS* testing should be carried out on all patients at the time of diagnosis of mCRC [I, A]
- *RAS* testing is mandatory before treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab [I, A]
- A network of arrangements should be established to ensure the rapid and robust transit of tissue samples from referral centres to testing laboratories, to minimise the turnaround time and avoid delays in having this information available for all patients with mCRC
- Primary or metastatic colorectal tumour tissue can be used for *RAS* testing (see also *Recommendation 3*)
- *RAS* analysis should include at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117)

Recommendation 5: BRAF testing

- Tumour *BRAF* mutation status should be assessed alongside the assessment of tumour *RAS* mutational status for prognostic assessment (and/or potential selection for clinical trials) [I, B]

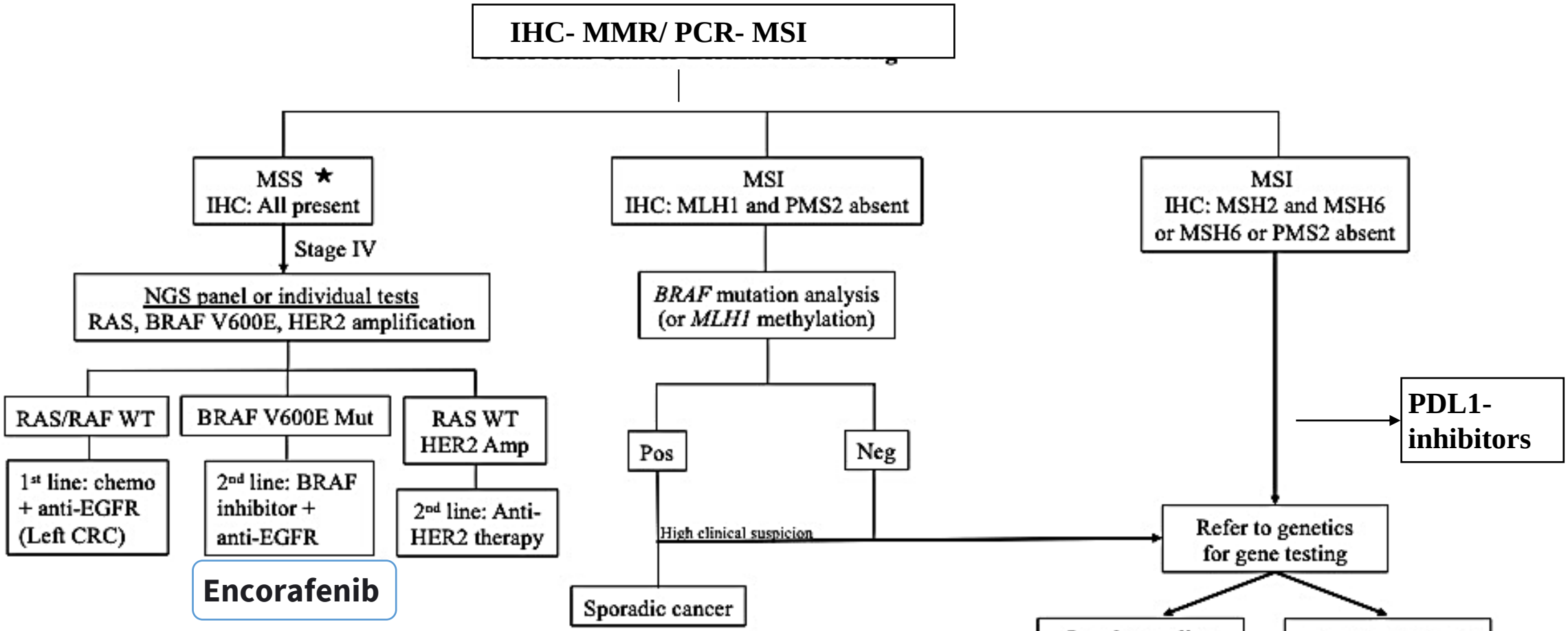
Recommendation 6: Microsatellite instability testing

- MSI testing in the metastatic disease setting can assist clinicians in genetic counselling [II, B]
- MSI testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC [II, B]

Recommendation 7: Biomarkers of chemotherapy sensitivity and toxicity

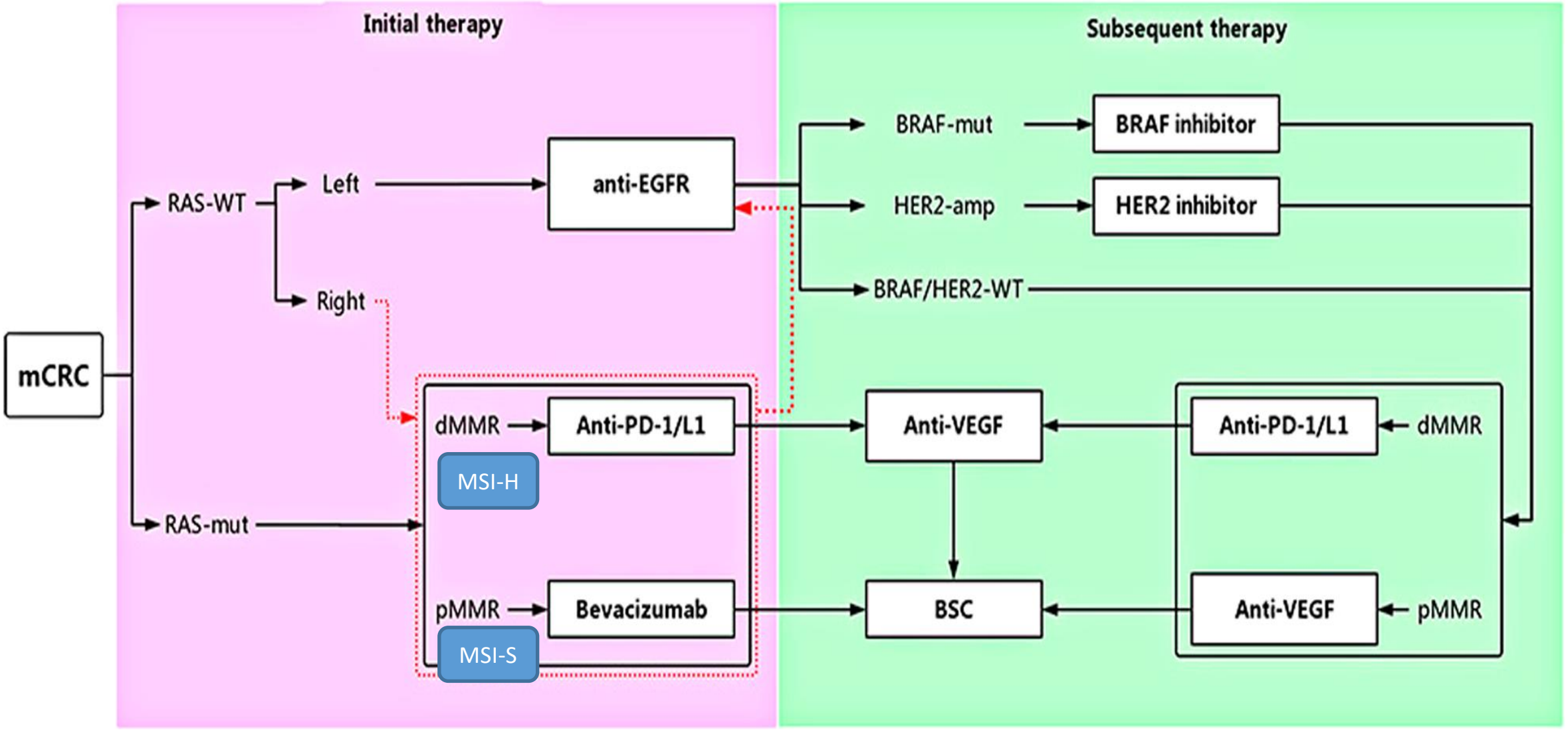
- DPD testing before 5-FU administration remains an option but is not routinely recommended [II, D]
- UGT1A1 phenotyping remains an option and should be carried out in patients with a suspicion of UGT1A1 deficiency as reflected by low conjugated bilirubin and in patients where an irinotecan dose of >180 mg/m^2 per administration is planned [95] [III, C]

Treatment Algorithm in m-CRC



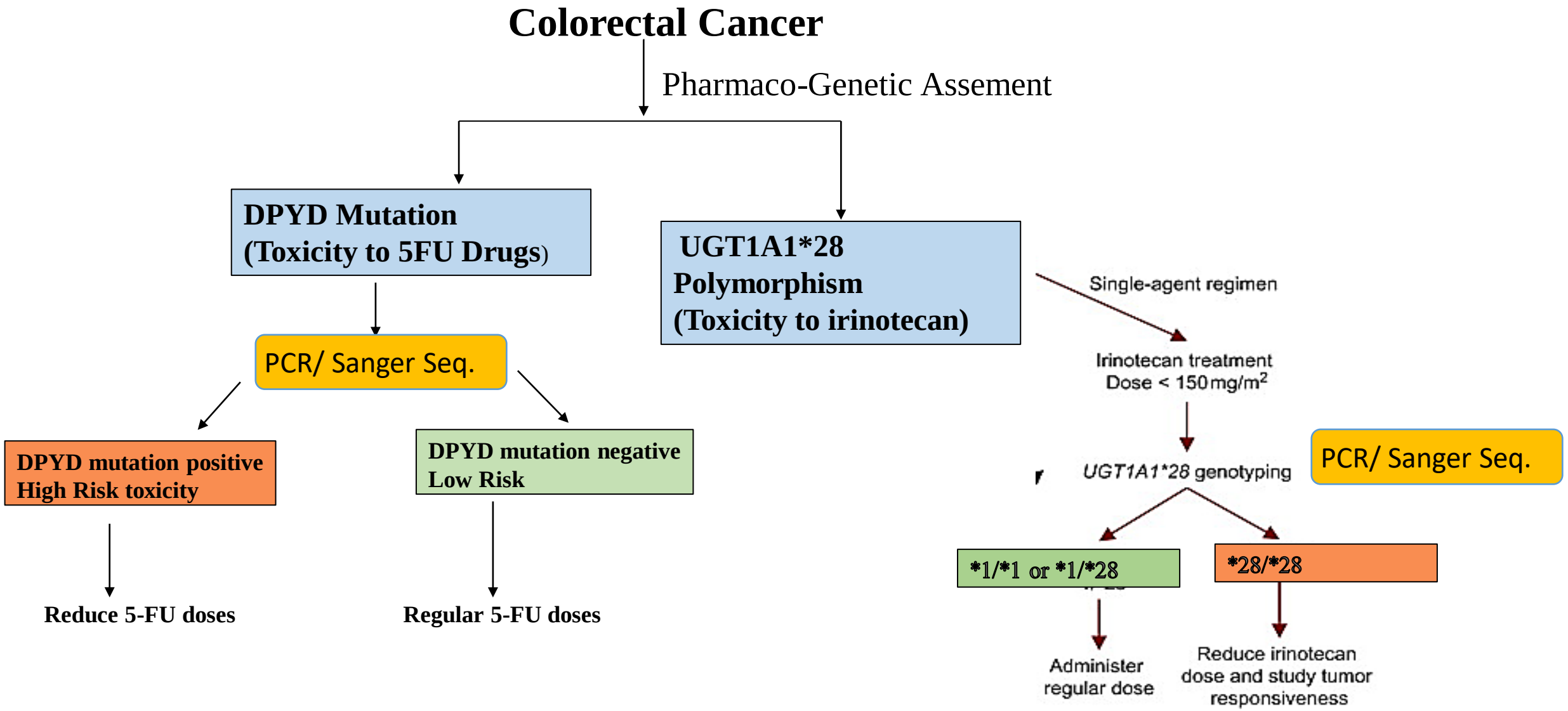
★ May stop Lynch syndrome workup, unless if <50 years old, strong family history, ≥10 adenomatous polyps or has

NCCN-recommended strategy for m-Colorectal cancer targeted therapy



https://www.nature.com/articles/s41392-020-0116-z/figures/4

Biomarkers for CT sensitivity/ Toxicity- CRC



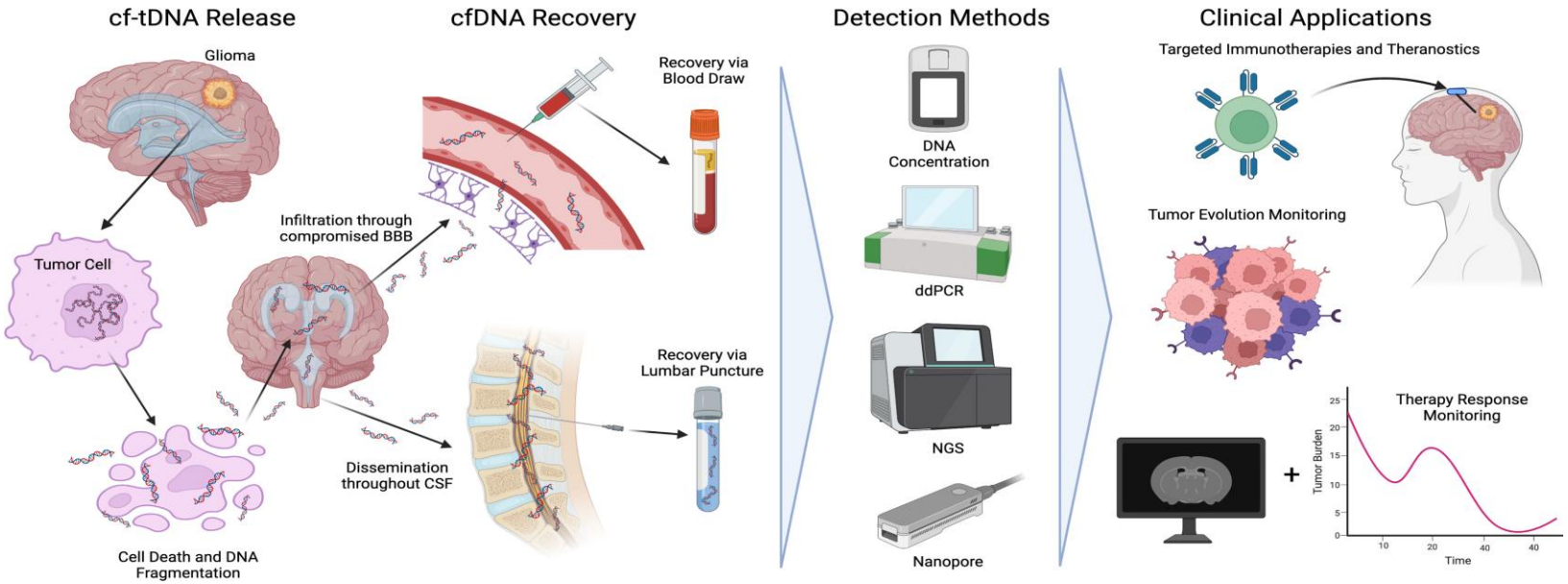
Bioserve: Biomarker Testing

Marker	Cancer	Technique
EGFR, KRAS,NRAS, BRAF	LUNG, CRC, MELANOMA	Sanger sequencing, RT-PCR
Met Exon 14 skipping	Lung	PCR
RET/ ROS/ ALK/NTRK FUSIONS	LUNG, CRC	FISH, NGS
BRCA 1/ 2 MUTATIONS	BREAST	NGS
PIK3CA MUTAIONS	BREAST	Sanger Sequencing
IDH1/ 2 MUTATIONS	GIOMA, AML	Sanger Sequencing
KIT MUTATIONS	GIST	Sanger Sequencing
BCR/ABL TRANSCRIPT/FUSION	CML	FISH, RT-PCR
JAK2 MUTAIONS	MPN	Sanger Sequencing
HRR GENE MUTATIONS	BREAST, PROSTATE	NGS
TUMOUR MUTATION BURDEN	**SOLID TUMORS**	**NGS**
MSI	**CRC, LUNG, BREAST**	**PCR+ Fragment Analysis**

Marker	Cancer	Technique
PAN-CANCER LIQUID BIOPSY PANEL	PAN CANCER	NGS
CEBPA, NPM1, FLT3 mutations	AML	Sanger sequencing, RT-PCR
TERT mutation	Melanoma	Sanger Sequencing
HER 2 MUTATIONS	BREAST	Sanger Sequencing
IMANITIB RESISTANCE	CML	Sanger Sequencing
HER 2 AMPLIFICATION	BREAST, CRC	FISH, RT-PCR
MGMT METHYLATION ASSAY	GLIOMA	RT-PCR
CALR, MPL MUTATIONS	MPN	Sanger Sequencing
Comprehensive genomic profiling	Solid tumors	NGS

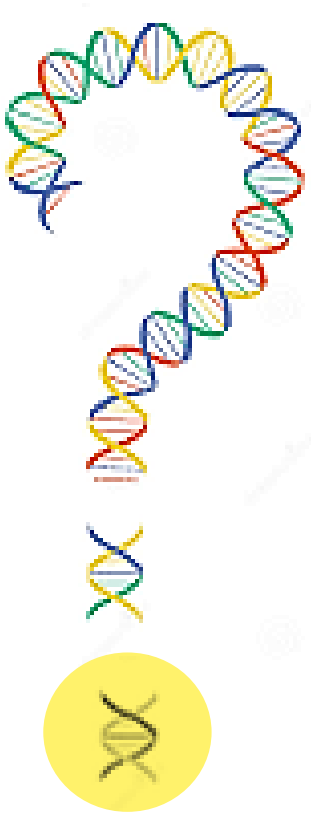
Future Directions

- **Liquid Biopsy for Biomarker Detection and residual Disease monitoring**



- **Gut microbiome- predict immune therapy response**
  - gut microbiota influences anti-tumor immunity
  - thereby impacting the clinical responses and outcomes of the patients receiving cancer immunotherapy
  - FMT in combination with checkpoint inhibitors are able to reprogram the tumor microenvironment and activate host immunity with favorable changes in immune cell infiltrates in patients with prostate cancer, melanoma, gastrointestinal and prostate cancer.
  - NCT04758507, NCT03353402, NCT04130763, NCT05094167

Thank You!



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