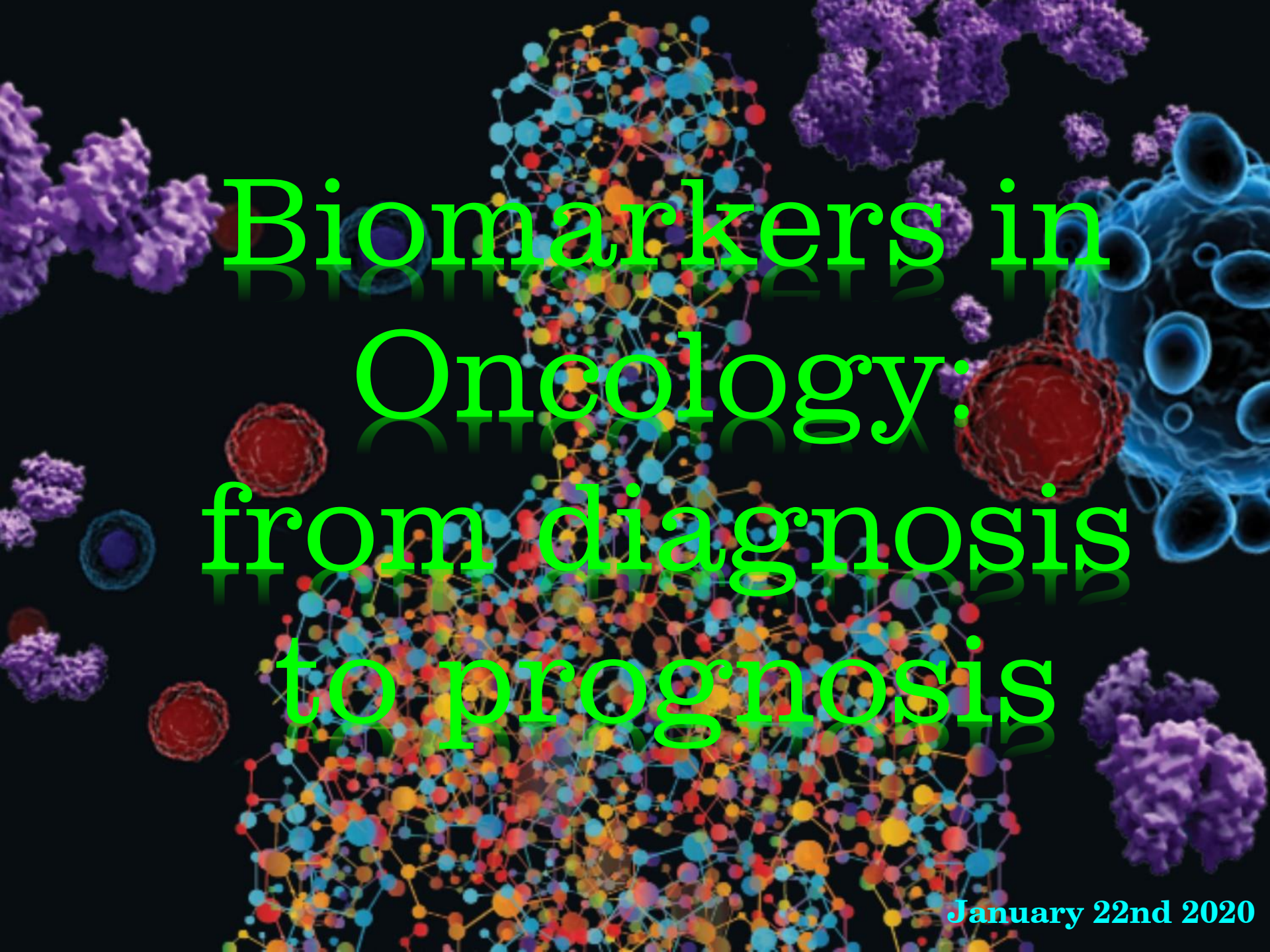

Biomarkers in Oncology: from diagnosis to prognosis
January 22nd 2020

OUTLINE OF THE TALK

- ✓ Definition of Biomarkers in oncology
- ✓ Diagnostic Tests
- ✓ Definition of Cancer Classification and Staging
- ✓ Histological Classification
- ✓ TNM Classification
- ✓ Grading
- ✓ Molecular Classification
- ✓ Examples: Breast Cancer
  Colorectal Cancer
- ✓ Treatment
- ✓ Conclusions

✓ Definition of Biomarkers in oncology

A cancer biomarker refers to a substance or process that is indicative of the presence of cancer in the body.

A biomarker may be a molecule secreted by a tumor or a specific response of the body to the presence of cancer.


BIOMARKERS & IMMUNO-ONCOLOGY
WORLD CONGRESS 2017
The Leading Annual Meeting Where Big Pharma and Biotech Drive Innovation and Collaboration in Biomarkers, Diagnostics and Immunotherapy


International Conference on Biomarkers
March 11-12, 2019
London, UK
Theme - Biomarkers: Heralding a Better Future
Biomarkers
Biomarkers in Oncology
Biomarkers research in Neuro-Oncology
Biomarkers research in Immuno-Oncology
Cardiovascular Biomarkers
Biomarkers in Genomics
Biomarkers in Proteomics
Molecular and Genetic Biomarkers
Biomarkers and Transcriptomics
Drug Discovery and Development
Biomarkers in Pharmacology
Therapeutic Biomarkers
Clinical Research and Clinical Trails
Digital Biomarkers
Imaging Biomarkers
Biomarkers for Disorders
Biomarkers in Personalized Medicine
Biomarkers and Next Generation Sequencing
Biomarkers Advancements
Applications of Biomarkers
http://biomarkers.alliedacademies.com/


2nd International Conference on
Biomarkers
and Clinical Reasearch
June 15-16, 2020 | Dubai, UAE
Biomarkers 2020
Theme: Awareness and Innovations of Biomarkers and Clinical Research


Radiology and Oncology 2019
COLORECTAL Ca
PROSTATE Ca
PANCREATIC Ca
LUNG Ca
ESOPHAGEAL Ca
BREAST Ca
GASTRIC Ca
Cancer Biomarkers and its targets

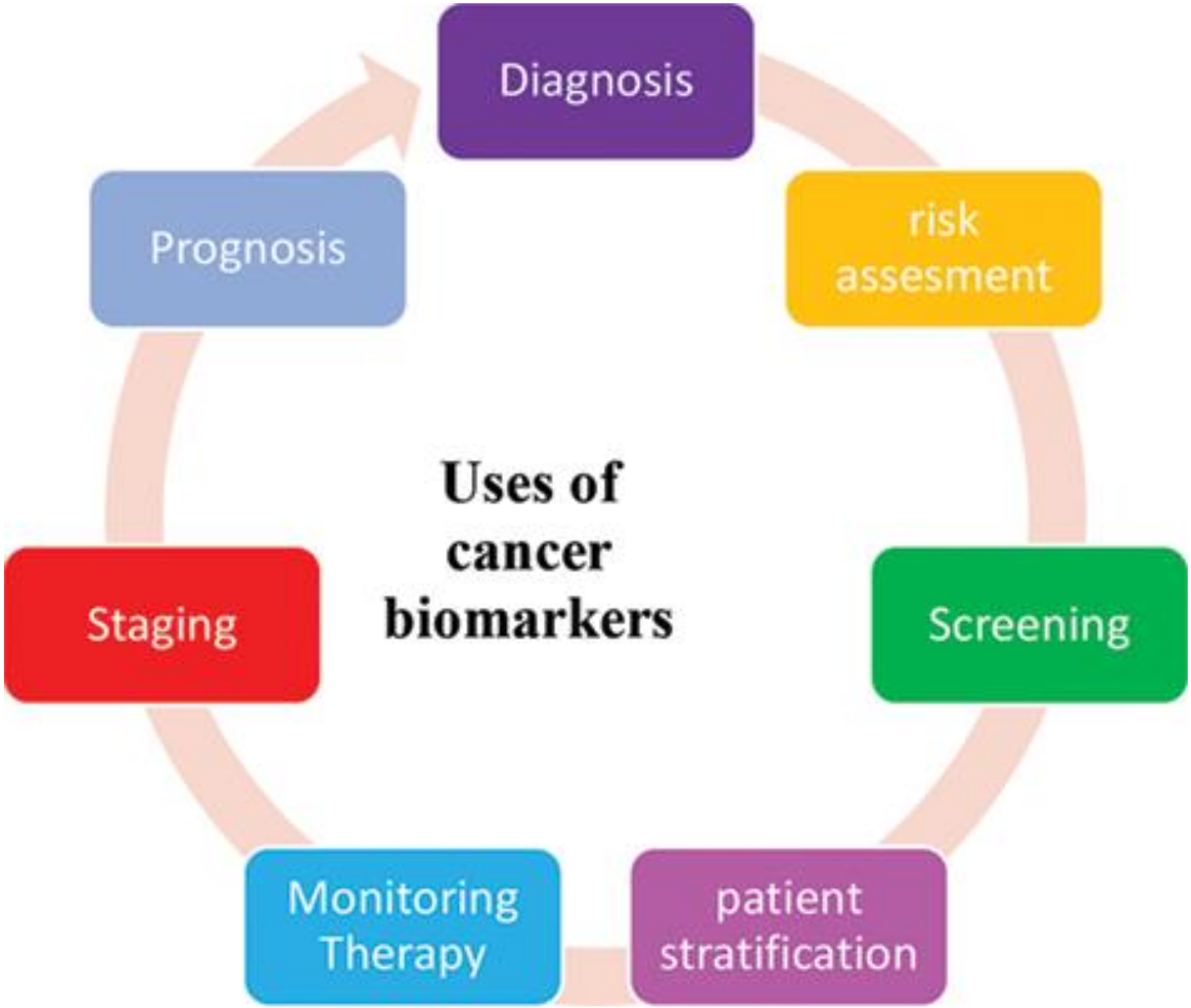

Cambridge Healthtech Institute's 3rd Annual
Immuno-Oncology Biomarkers
and Companion Dx
Predicting Response and Guiding IO Trials and Patient Care
March 2-4, 2020 San Francisco, CA ▲ MOSCONE SOUTH CONVENTION CENTER

BIOMARKERS & IMMUNO-ONCOLOGY
WORLD CONGRESS 2018
The Leading Annual Meeting Where Big Pharma and Biotech Drive Innovation and Collaboration in Biomarkers, Diagnostics and Immunotherapy


Biomarkers 2019
13th World Biomarkers and Clinical
Research Conference
August 22-23, 2019 | Vienna, Austria
Avail Special Discounts
on
Group Registrations
https://biomarkers.euroscicon.com/registration


INTERNATIONAL SOCIETY OF
ONCOLOGY AND BIOMARKERS
Hamburg 2018
Nov. 24 – 27
45th ISOBM Congress

Cambridge Healthtech Institute's Inaugural
Translational Biomarkers
in Immuno-Oncology
29-30 NOVEMBER 2018
SHERATON LISBOA HOTEL & SPA | LISBON, PORTUGAL
Part of WPC EUROPE 3rd Annual WORLD PRECLINICAL CONGRESS

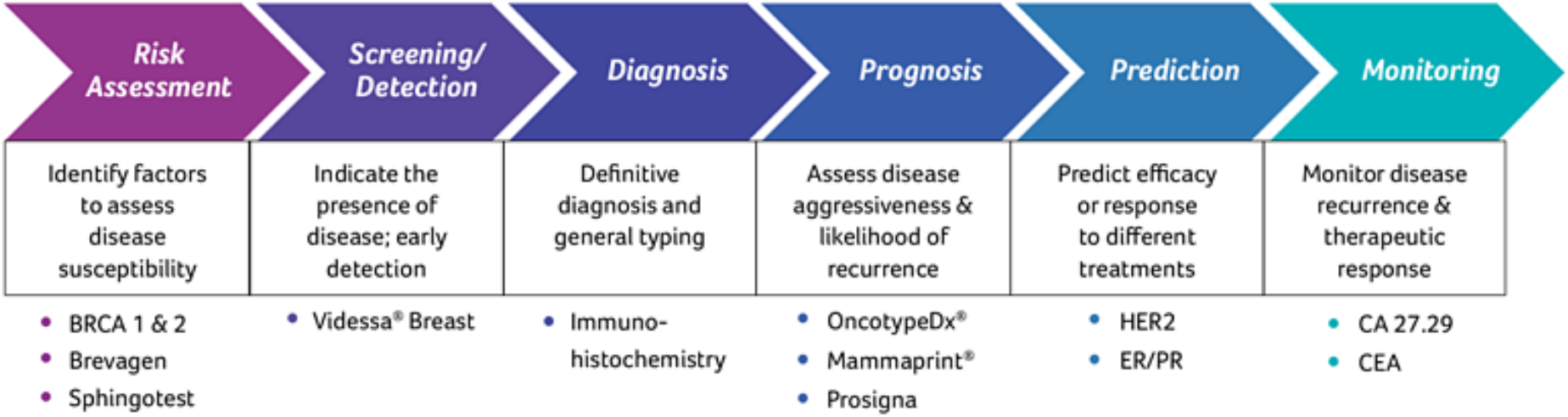

Diagnosis
risk assesment
Screening
patient stratification
Monitoring Therapy
Staging
Prognosis
Uses of cancer biomarkers

Biomarkers *allow physicians to classify patients by their probable disease risk, prognosis and/or response to treatment*

Insights into biomarkers analysis have resulted in scientists being able to understand **the diversity of lung cancer** better than ever before

References: Vargas AJ & Harris CC. Biomarker development in the precision medicine era: lung cancer as a case study. Nature Reviews Cancer. 2016;16:525-537 **Document ID: Z4-9122 Date of preparation: February 2018 Date of expiry: February 2020**

MedImmune AstraZeneca


Risk Assessment
Identify factors to assess disease susceptibility
BRCA 1 & 2
Brevagen
Sphingotest
Screening/ Detection
Indicate the presence of disease; early detection
Videssa® Breast
Diagnosis
Definitive diagnosis and general typing
Immuno-histochemistry
Prognosis
Assess disease aggressiveness & likelihood of recurrence
OncotypeDx®
Mammaprint®
Prosigna
Prediction
Predict efficacy or response to different treatments
HER2
ER/PR
Monitoring
Monitor disease recurrence & therapeutic response
CA 27.29
CEA

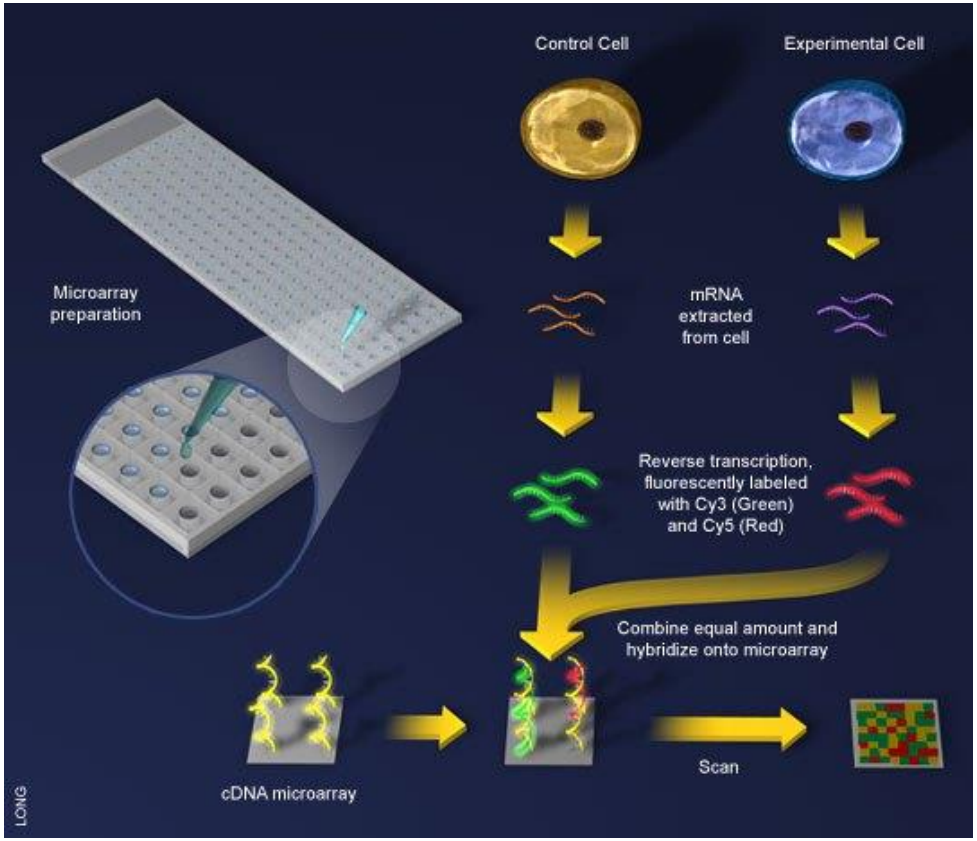
- ✓ Cancer is a genetic disease since it is due to alterations in patients' DNA.
- ✓ Deciphering the genetic changes is necessary to understand the disease.
- ✓ Unraveling the genetic bases of cancer allows us to design the best treatment protocols for each single patient.

✓ Diagnostic Tests

DIAGNOSTIC TESTS

- Identification of the presence/amount of a specific protein. It can be performed on blood samples (es. CEA, CA-125) and on tumour tissue (es. ER, HER2/Neu).

- Evaluation of the expression of a set of genes (microarray technology): diagnostic tests development, better classification, identification of new therapeutic targets, setting up of personalised treatments).



DIAGNOSTIC TESTS

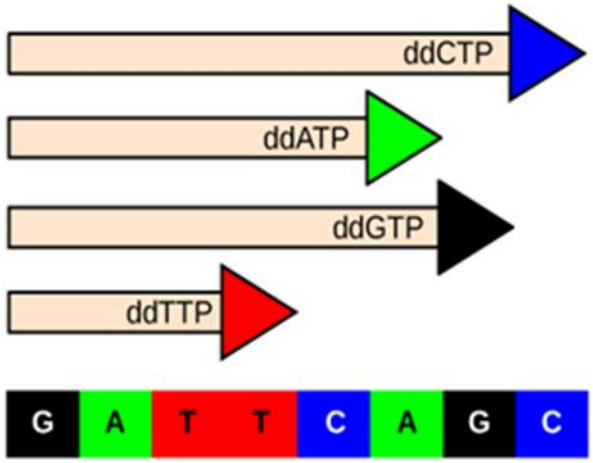
- Evaluation of mutations and epigenetic changes: gene sequencing (Sanger sequencing, Pyrosequencing, Next Generation Sequencing), Beaming.

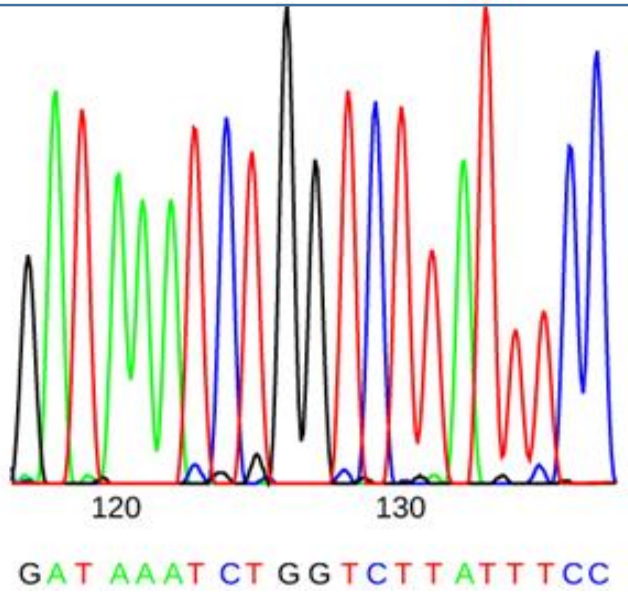
SANGER SEQUENCING

Evaluation of 200-300bp amplicons

Result= presence/absence

Variants determined by the operator





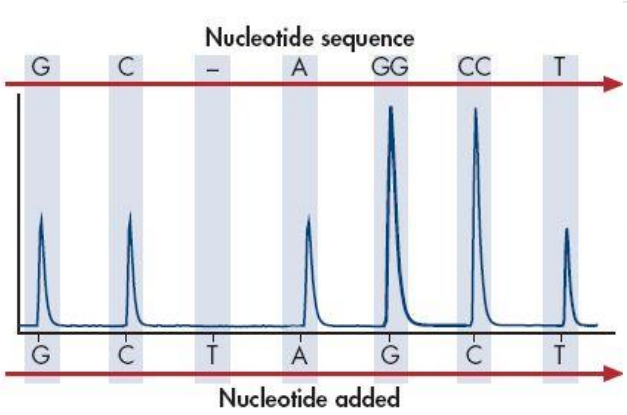
DIAGNOSTIC TESTS

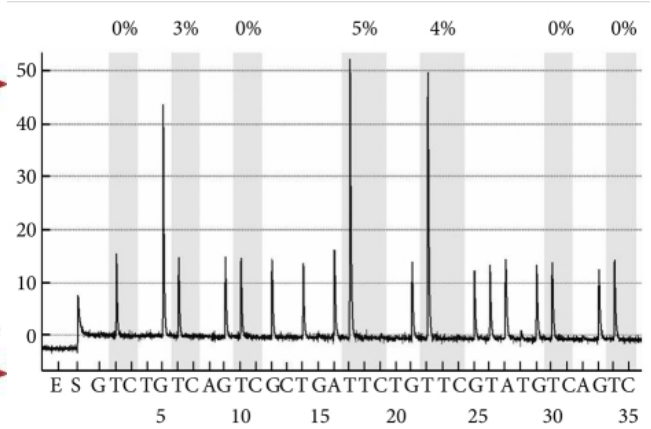
PYROSEQUENCING

Evaluation of 100-200bp amplicons

Result= percentage

Variants determined by the operator





DIAGNOSTIC TESTS

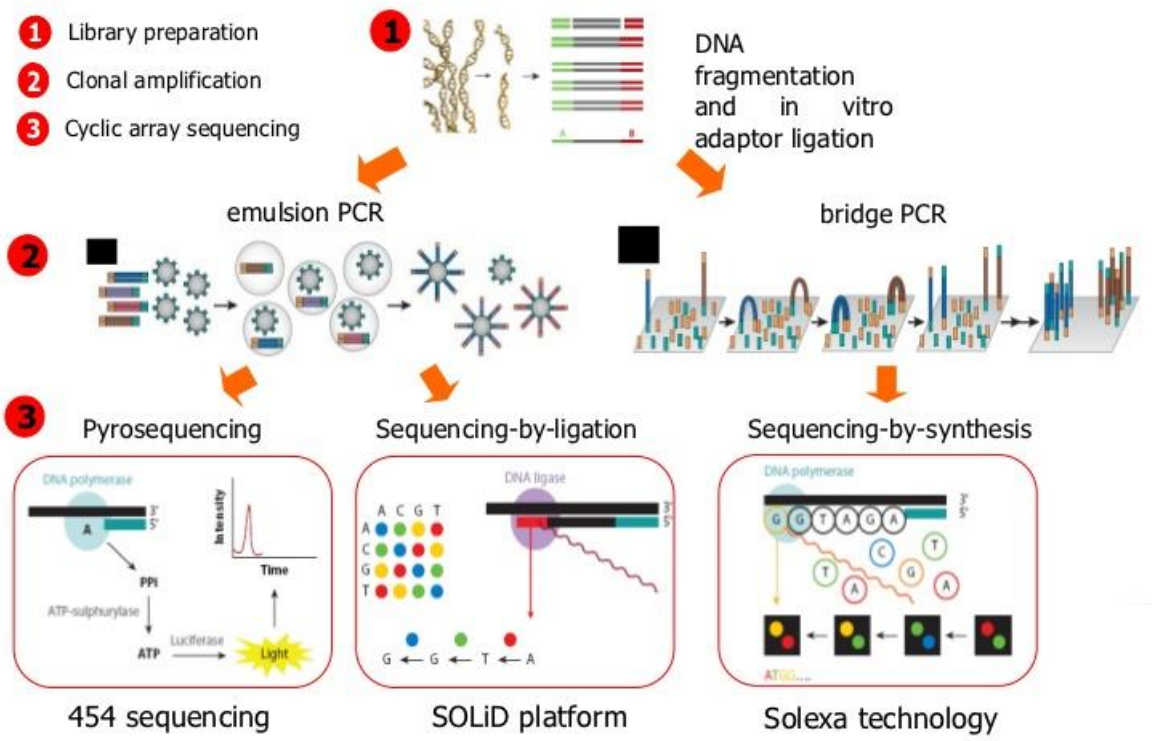
NGS

Evaluation of the whole genome or exome

Selection of tumour-specific genes

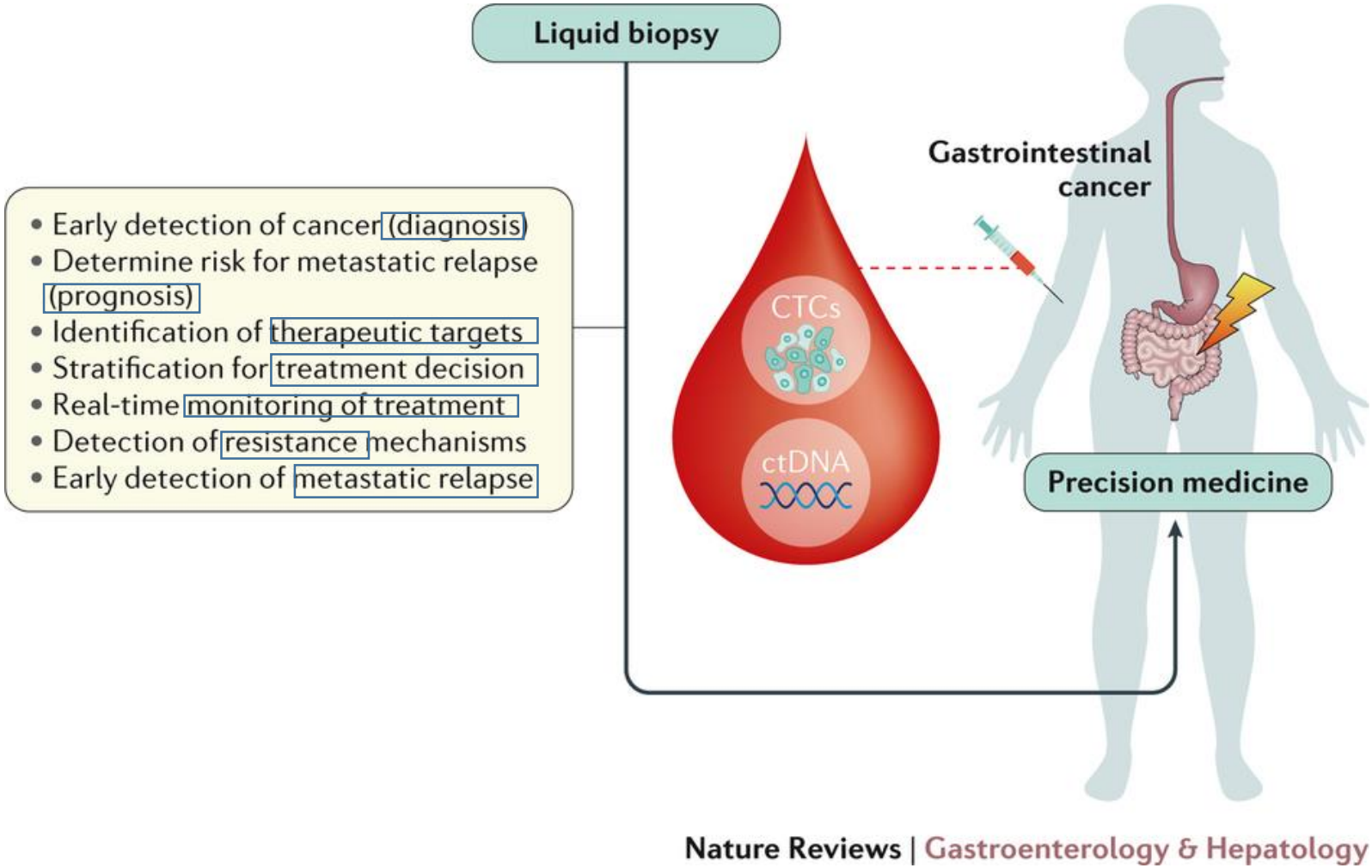
Result= percentage

Variants automatically determined in databases



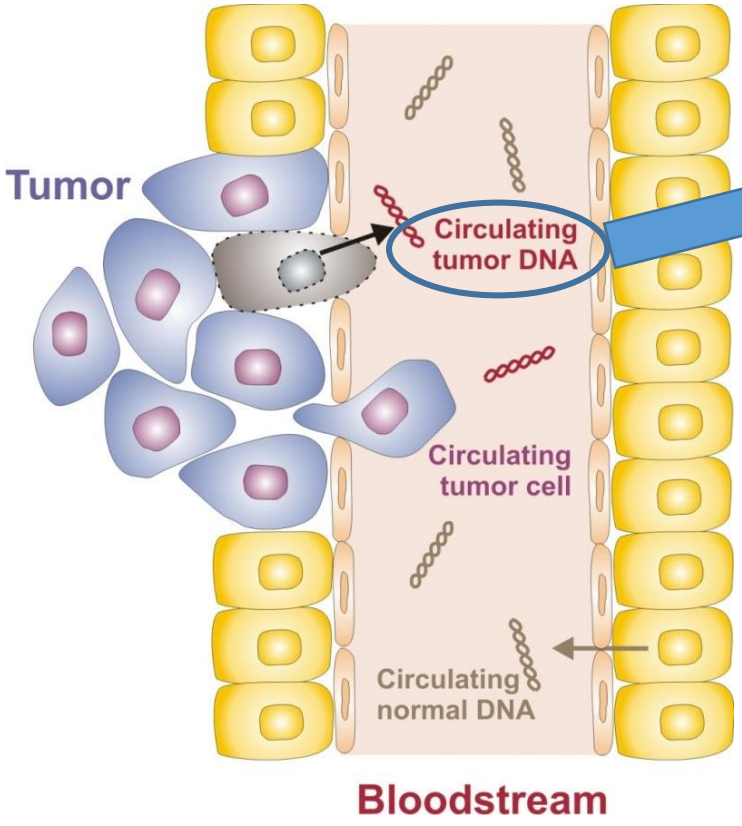
DIAGNOSTIC TESTS

BEAMing (performed on cell-free tumour DNA)

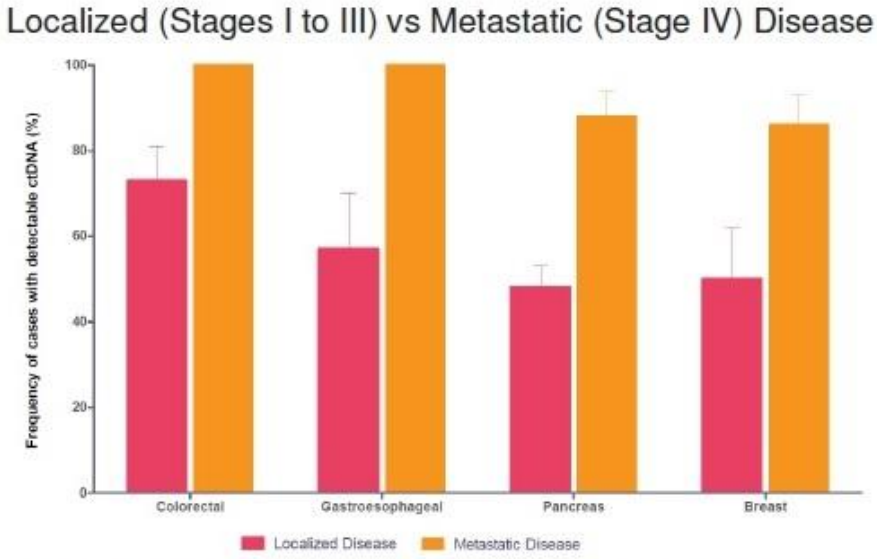


DIAGNOSTIC TESTS

BEAMing (performed on cell-free tumour DNA)



- Released from necrotic and apoptotic tumour cells into the bloodstream
- Short half-life after surgery
- Small DNA fragments (<120 bp)
- Low concentration (0.01% of total circulating DNA)
- More frequent in metastatic patients



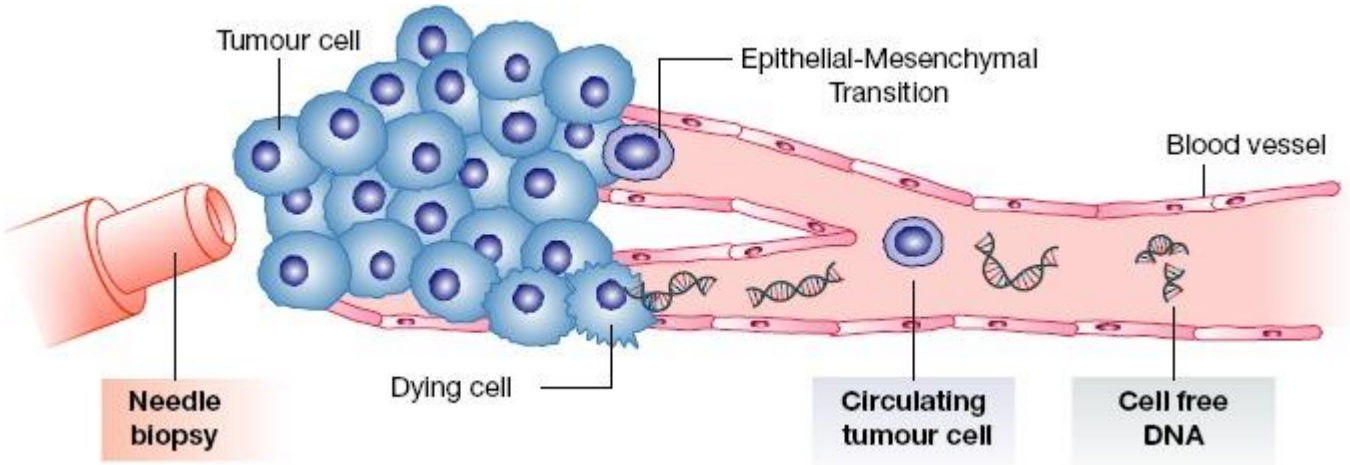
Detectable levels of ctDNA present in 49-78% of patients with localized tumors

Detectable levels of ctDNA present in 86-100% of patients with metastatic tumors

Bettegowda et al, Sci Tran Med Feb 2014

DIAGNOSTIC TESTS

BEAMing (performed on cell-free tumour DNA)

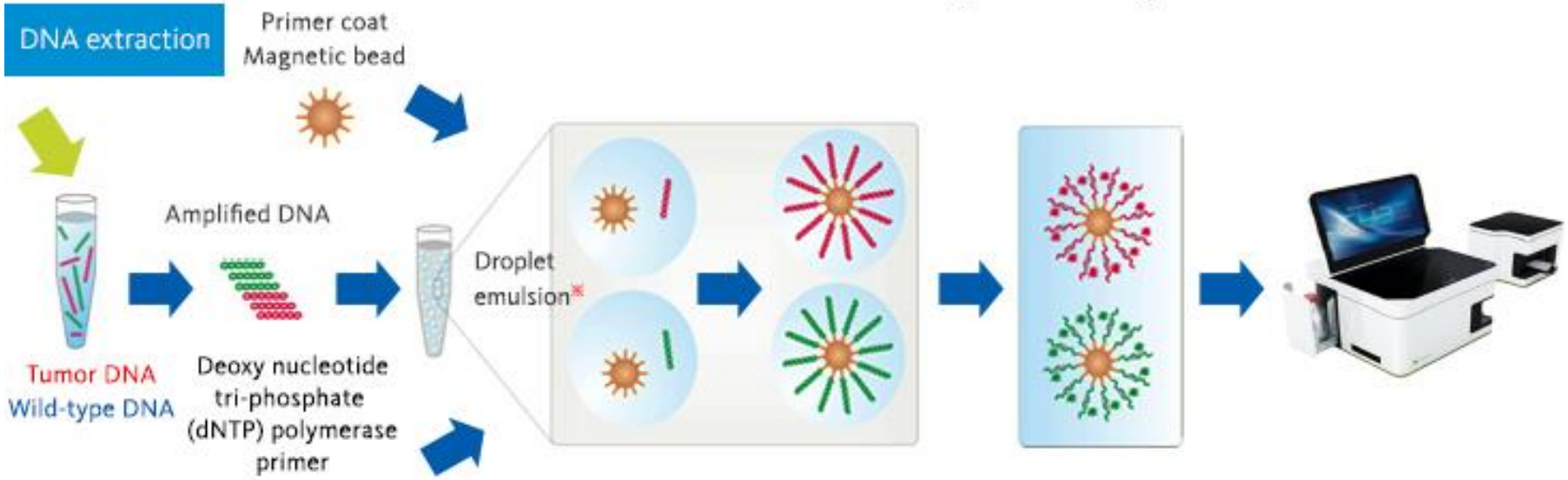


	Biopsy	CTC	cfDNA
Invasive	+	–	–
All patients eligible	–	+	+
Instrumentation required	+	+	–
WGA required	–	+	+/–
RNA profiling	+	+	–
Research applicability	+++	++	+
Biomarker applicability	–	++	+++

DIAGNOSTIC TESTS

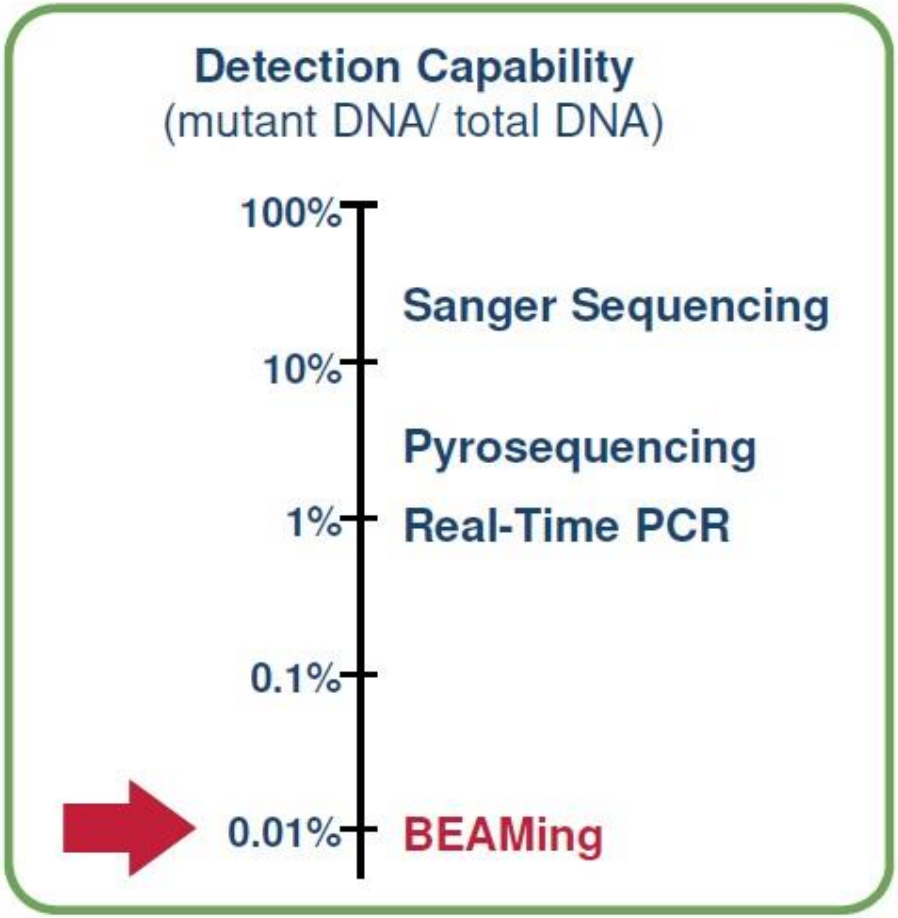
BEAMing (performed on cell-free tumour DNA)

1st gene amplification process	Emulsion PCR	Hybridization	Detection
Amplification of the target DNA area	Gene amplification within a droplet emulsion containing one DNA molecule and magnetic bead by PCR.	Forming of a complementary conjugate with fluorescent probe of a gene and a magnetic bead.	Detecting mutations of the cancer gene by FCM.



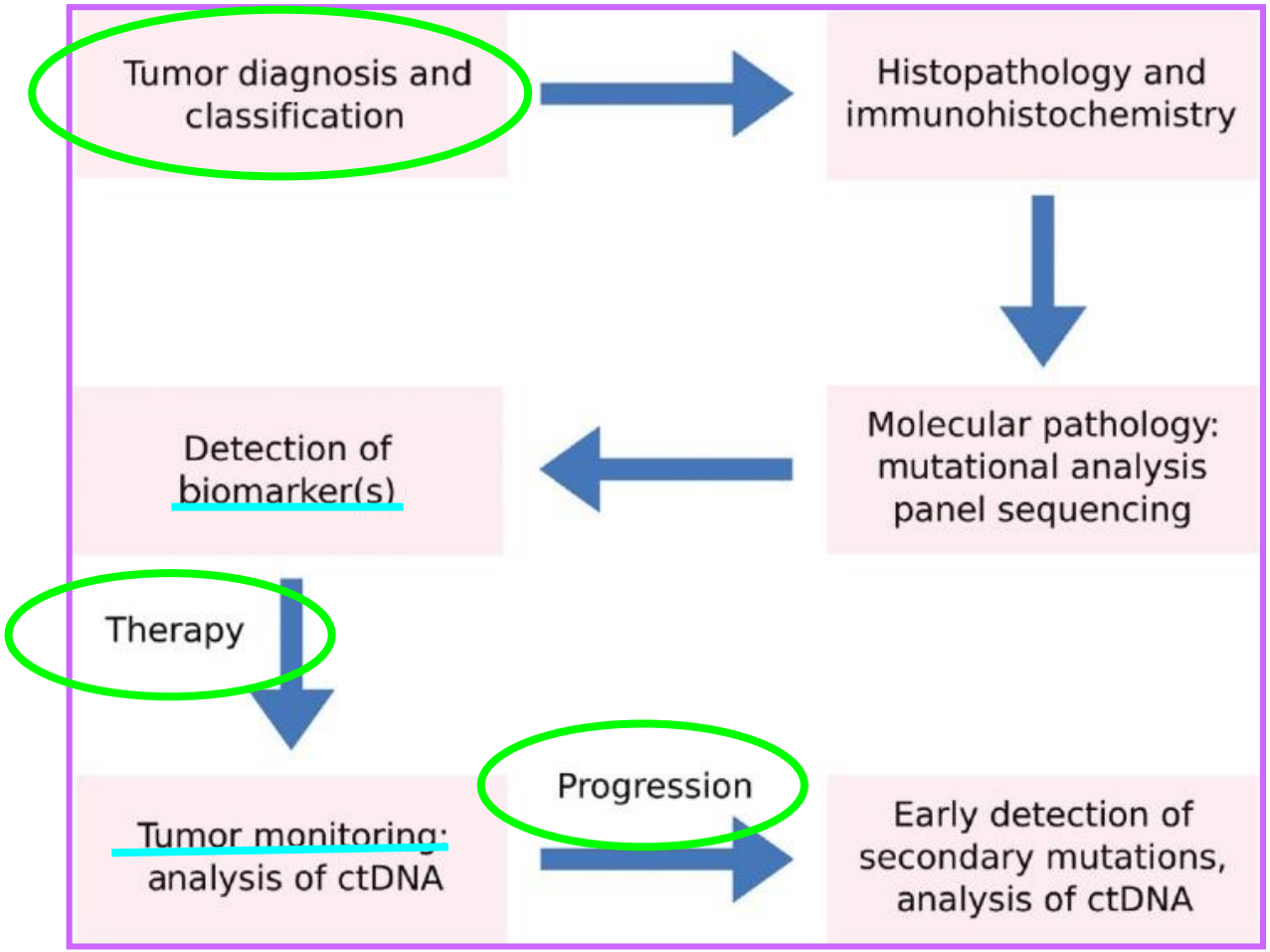
DIAGNOSTIC TESTS

BEAMing (performed on cell-free tumour DNA)



✓ Definition of Cancer Classification and Staging

DISEASE CLASSIFICATION is central to understand the bases of the diseases, make diagnosis and assign treatment.



Cancer nomenclature is based on:

1. Localization (breast cancer, lung cancer.....)

1. Within each organ-specific major type several subgroups are defined, taking into account cell type, histological grades and MOLECULAR MARKERS

✓ Histological Classification

Neoplasia

Neoplasms Nomenclature:

Oma - Tumour
Carcin-oma – Hard Tumour
Sarc-oma - Soft Tumour

Cell of Origin	Benign	Malignant
• Gland. Epithelium	• Adenoma -	Adencarcinoma
• Lining. Epithelium	• Papilloma -	Squamous cell ca.
• Fibroblast	• Fibroma -	Fibrosarcoma
• Osteoblast	• Osteoma -	Osteosarcoma
• Chondrocyte	• Chondroma	Chondrosarcoma
• Lipocyte	• Lipoma	Liposarcoma
• Smooth muscle	• Leiomyoma	Leiomyosarcoma
• Skeletal muscle	• Rhabdomyoma	Rhabdomyosarcoma

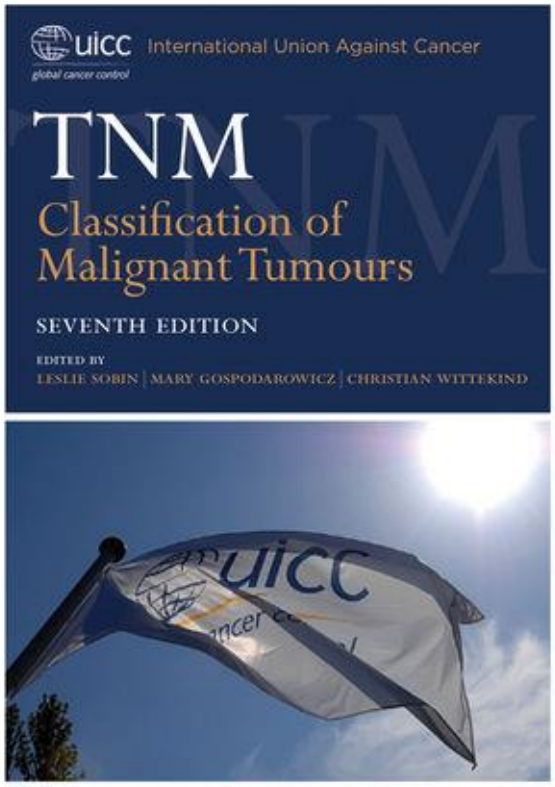
Neoplasia

Nomenclature: exceptions

- Teratoma – Tumour of Germ cell – multiple tissues. Benign (mature) or malignant (immature)
- Melanoma (Melano-carcinoma) – Malignancy of melanocytes.
- Seminoma (Seminal carcinoma) –carcinoma of Testes.
- Leukemia – white blood – Ca. of Haemopoietic stem cells.
- Lymphoma (Lymphosarcoma)– Malignancy of lymphocytes.
- Mixed Tumours: Both epithelial & connective tissue components. Pleomorphic adenoma (Salivary gland) & Carcinosarcoma (breast/uterus)

What is a Granuloma, Hamartoma & Choristoma?

✓ TNM Classification



1. To aid the clinician in the planning of treatment
2. To give some indication of prognosis
3. To assist in evaluation of the results of treatment
4. To facilitate the exchange of information between treatment centres
5. To contribute to the continuing investigation of human cancer
6. To support cancer control activities

The General Rules of the TNM System

The TNM system for describing the anatomical extent of disease is based on the assessment of three components:

T – The extent of the primary tumour
N – The absence or presence and extent of regional lymph node metastasis
M – The absence or presence of distant metastasis

The addition of numbers to these three components indicates the extent of the malignant disease, thus:

T0, T1, T2, T3, T4 N0, N1, N2, N3 M0, M1

cTNM (CLINICAL)

Essential to select and evaluate therapeutic options
Defined before treatment
Based on evidences aquired by clinical examination, imaging, endoscopy, biopsy....

pTNM (PATHOLOGICAL)

Assessed after surgery
Essential to guide adjuvant therapy
Provides data useful for prognosis estimation

G (HISTOPATHOLOGICAL GRADING)

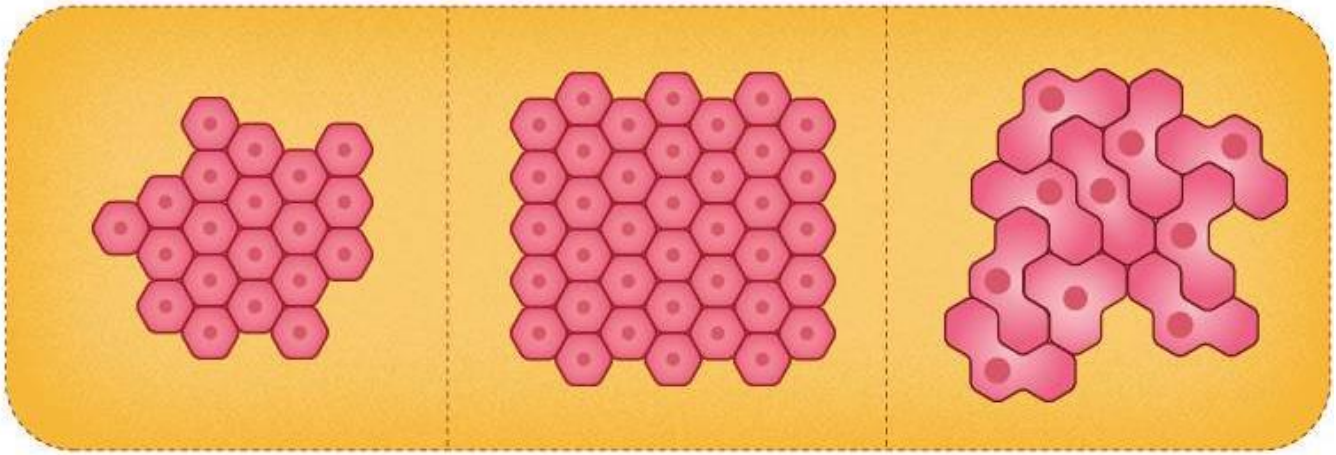
TNM STAGING

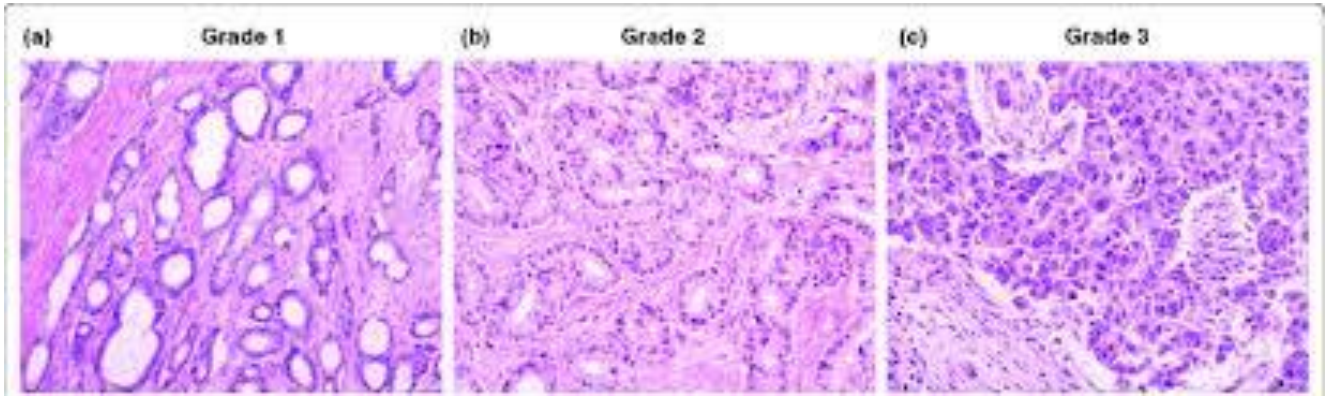
Tumor grade: description of a tumor based on how abnormal the tumor cells and the tumor tissue look under a microscope.
It is an indicator of how quickly a tumor is likely to grow and spread.

If a grading system for a tumor type is not specified, the following system is generally used:

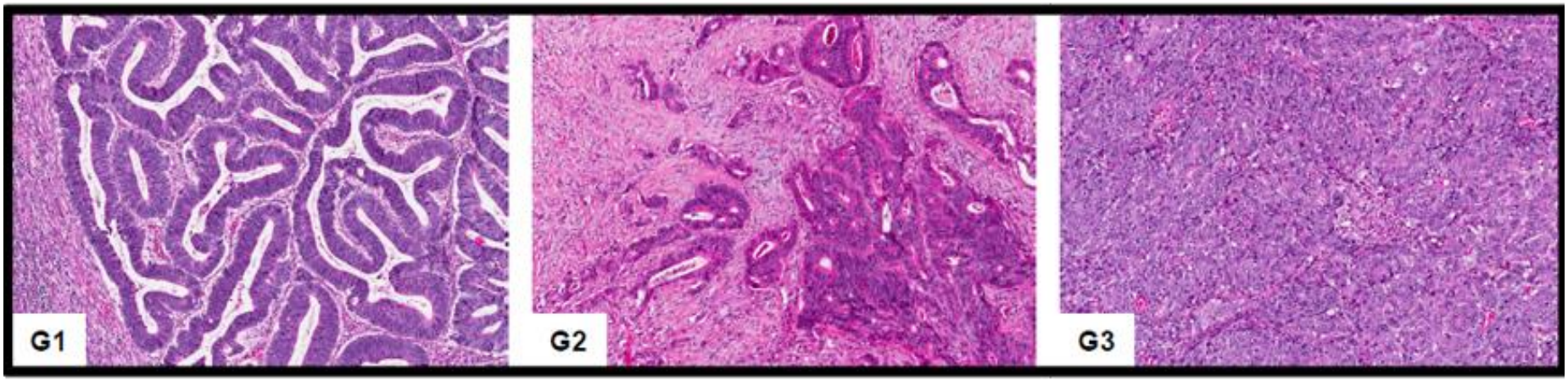
GX: Grade cannot be assessed (undetermined grade)
G1: Well differentiated (low grade)
G2: Moderately differentiated (intermediate grade)
G3: Poorly differentiated (high grade)
G4: Undifferentiated (high grade)

Example: breast cancer





Example: colorectal cancer



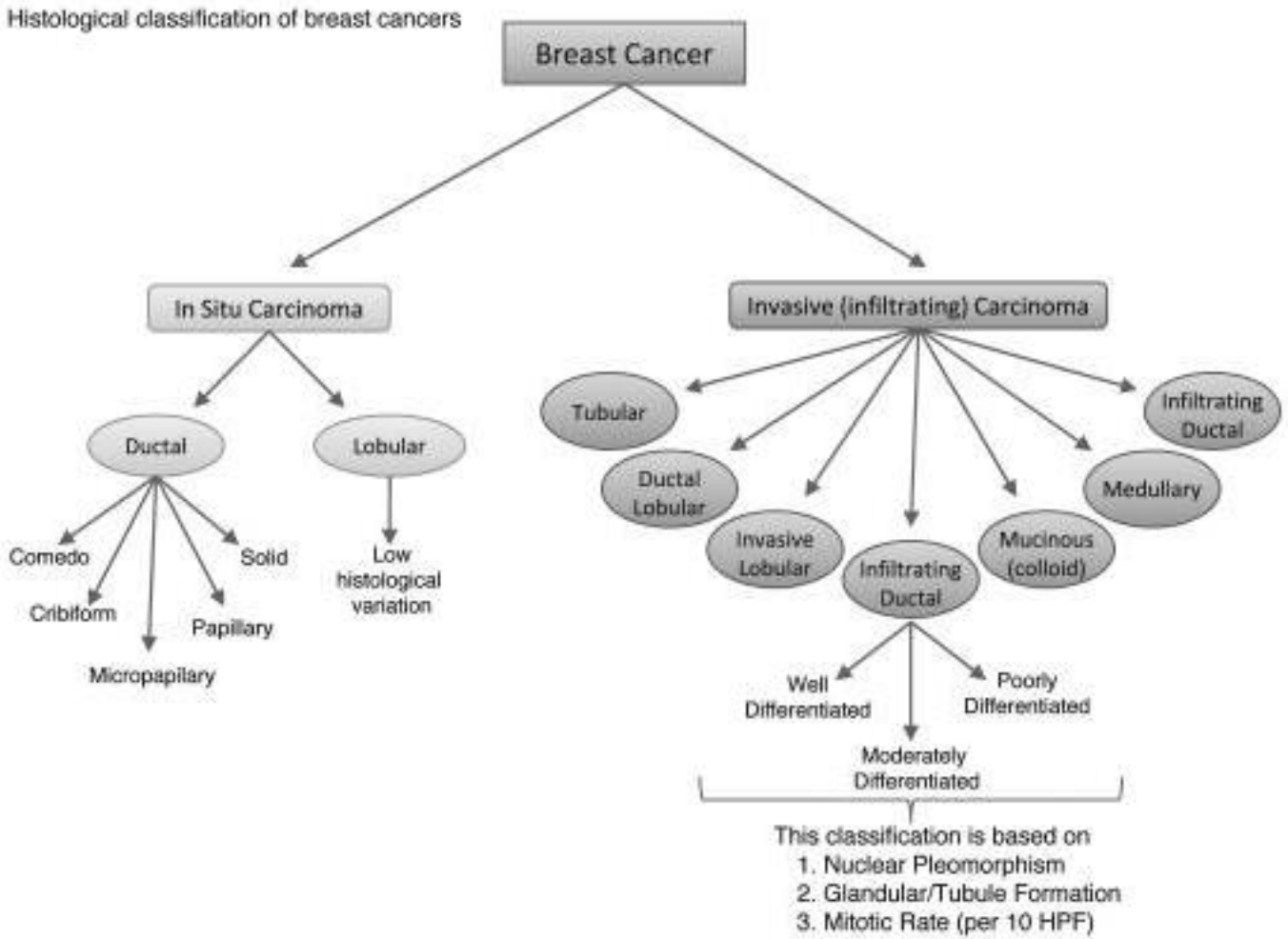
✓ Molecular Classification

BIOMOLECULAR STAGING

- Identification of tumour markers involved in different processes that lead to tumour progression.
- Better patients' stratification into TNM staging-defined risk groups.
- Potentially applicable to: primary tumour, lymphnodes, bone marrow, serum.
- Useful for: early diagnosis, prognosis estimation, occulte metastases identification, predictive markers for chemotherapy resistence or response.
- Panels of biomarkers depending on the tumour type.

Breast Cancer

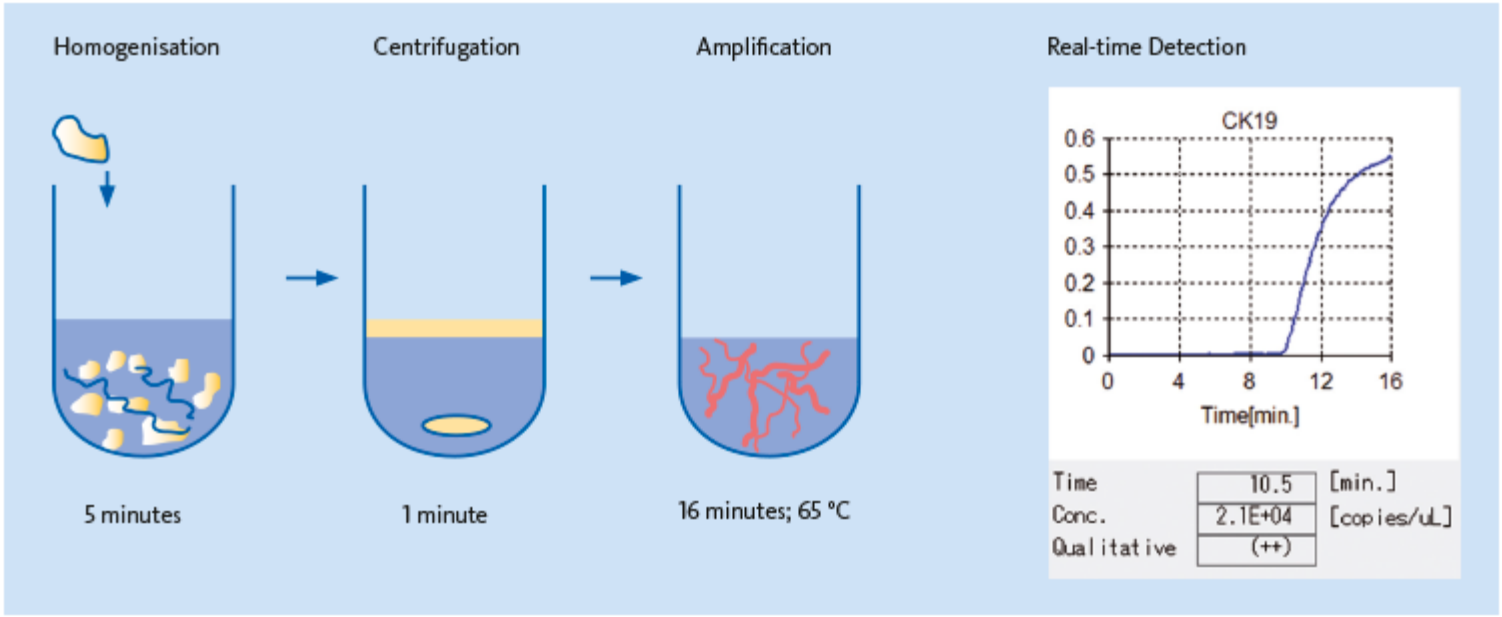
HISTOLOGICAL CLASSIFICATION



TNM CLASSIFICATION

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

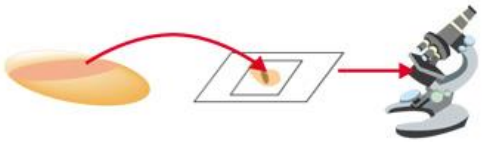
The One-Step Nucleic acid Amplification (OSNA) assay is a molecular procedure that can identify deposits of breast cancer cells in the sentinel lymph node.



sysmex

Conventional method of pathological diagnosis

Diagnosis of lymph node metastasis: Qualitative analysis by pathologists



Only analyze a part of tissue

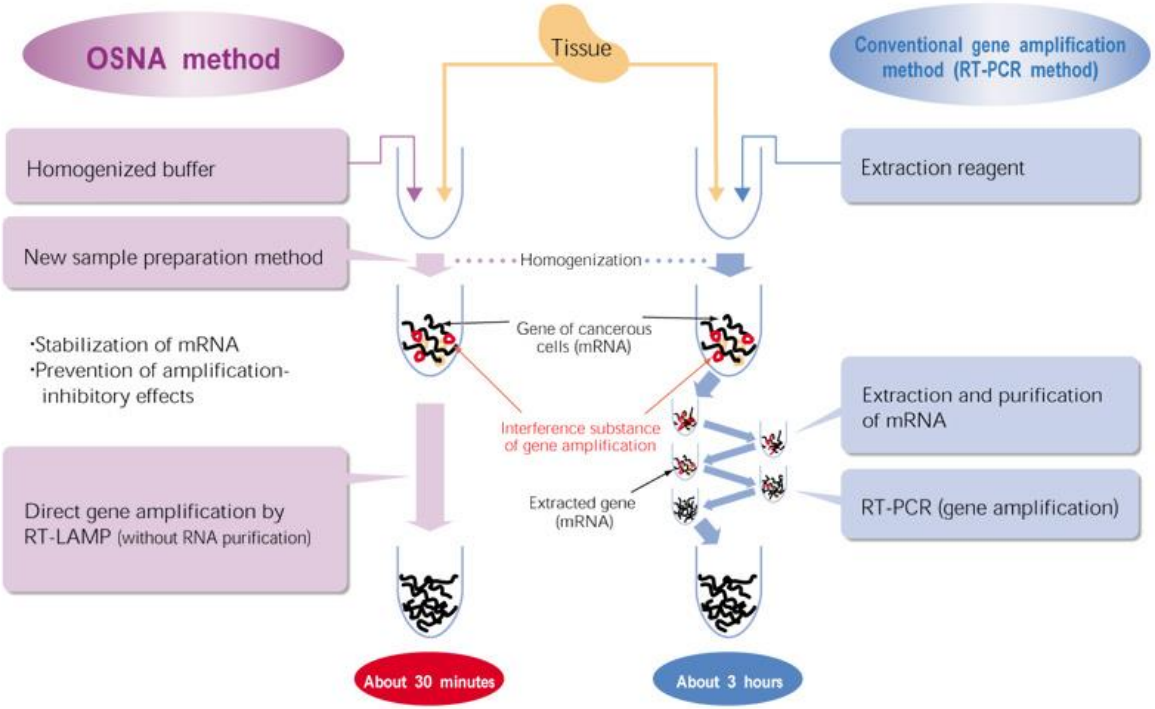
However, from now on. . .

Molecular pathological diagnosis by the OSNA method

Gene amplification analyzer

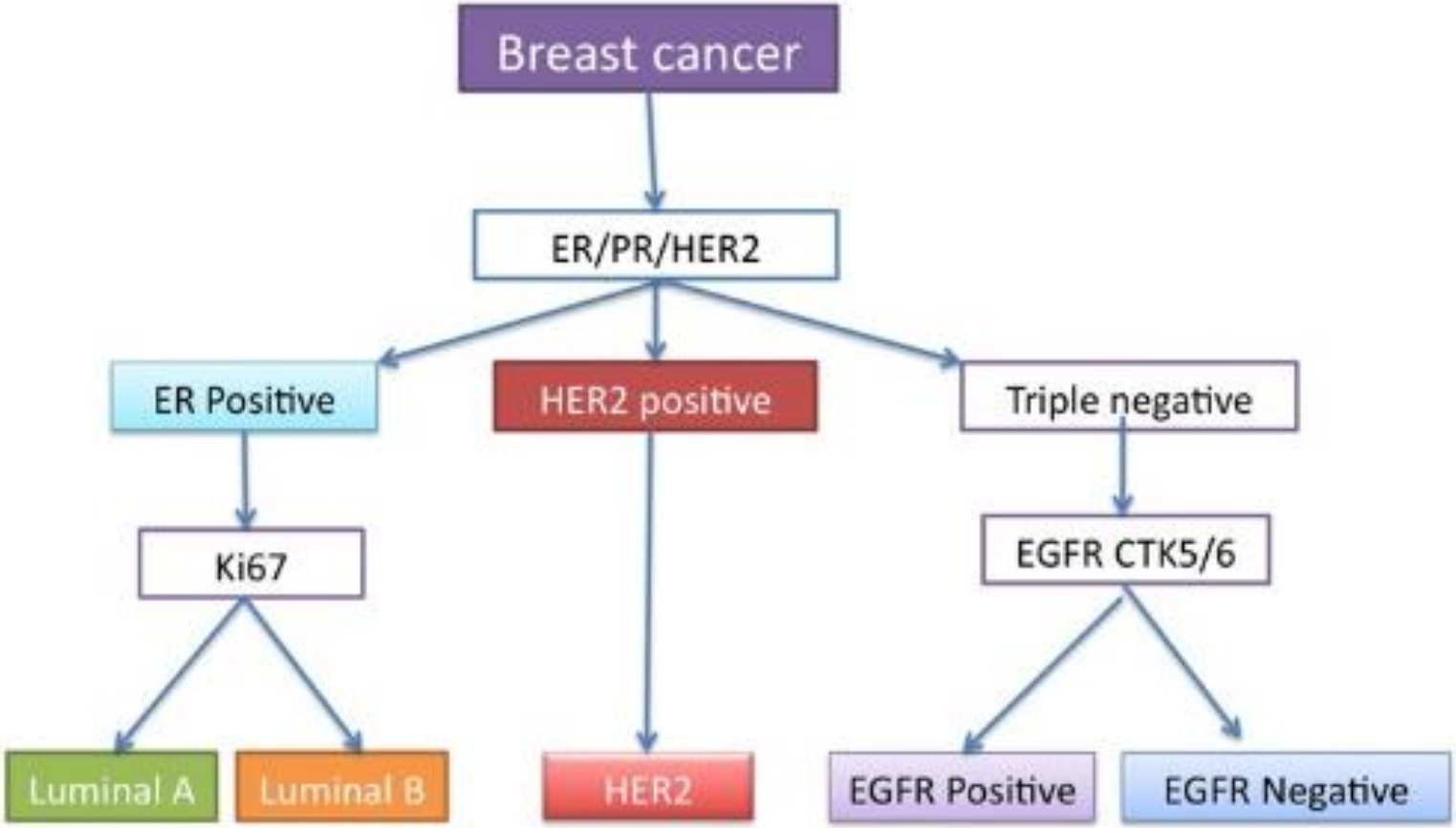
- Analyze whole part of tissue
- Analyze lymph node metastasis within 30 minutes

OSNA method

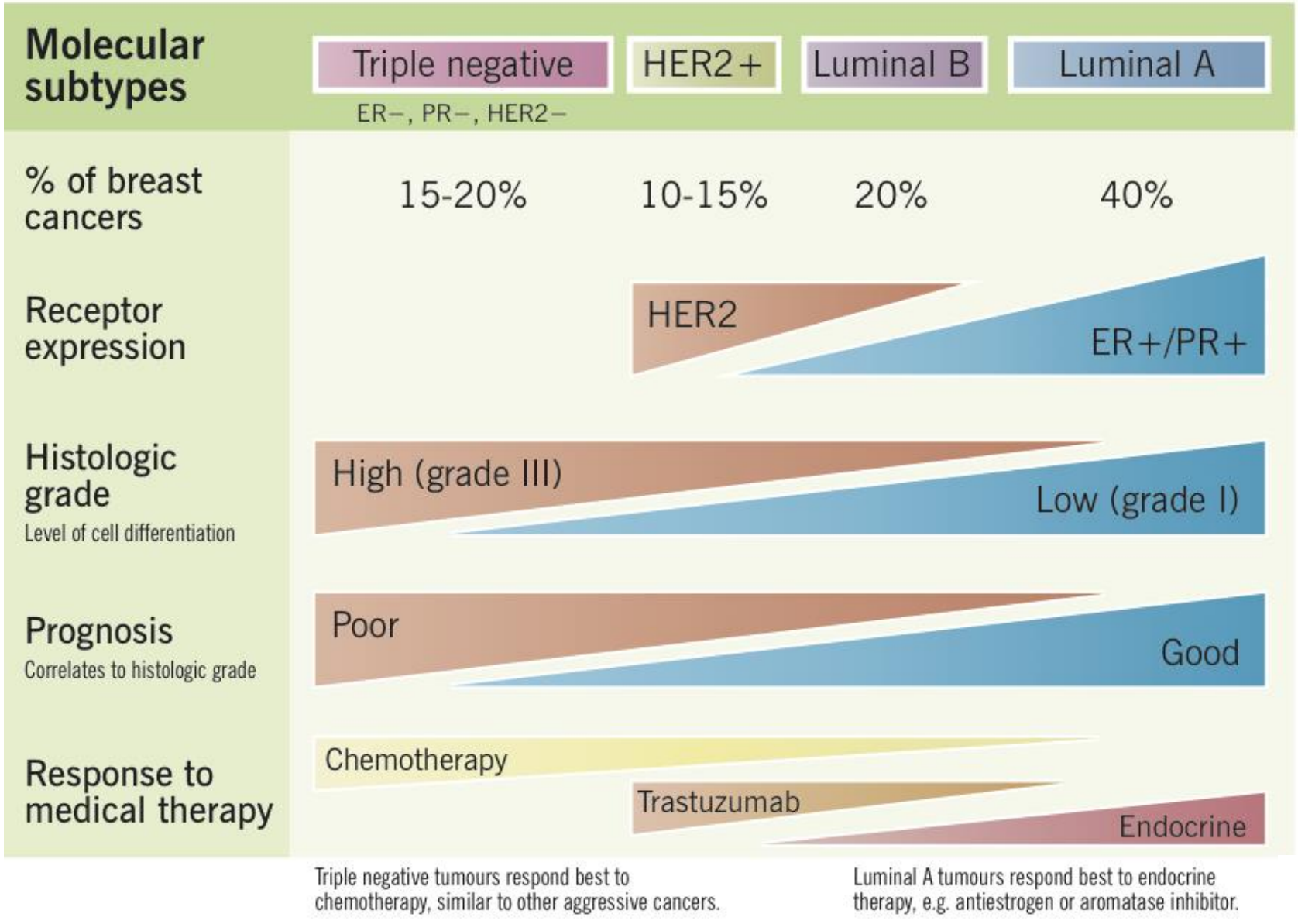


sysmex

MOLECULAR CLASSIFICATION



MOLECULAR CLASSIFICATION

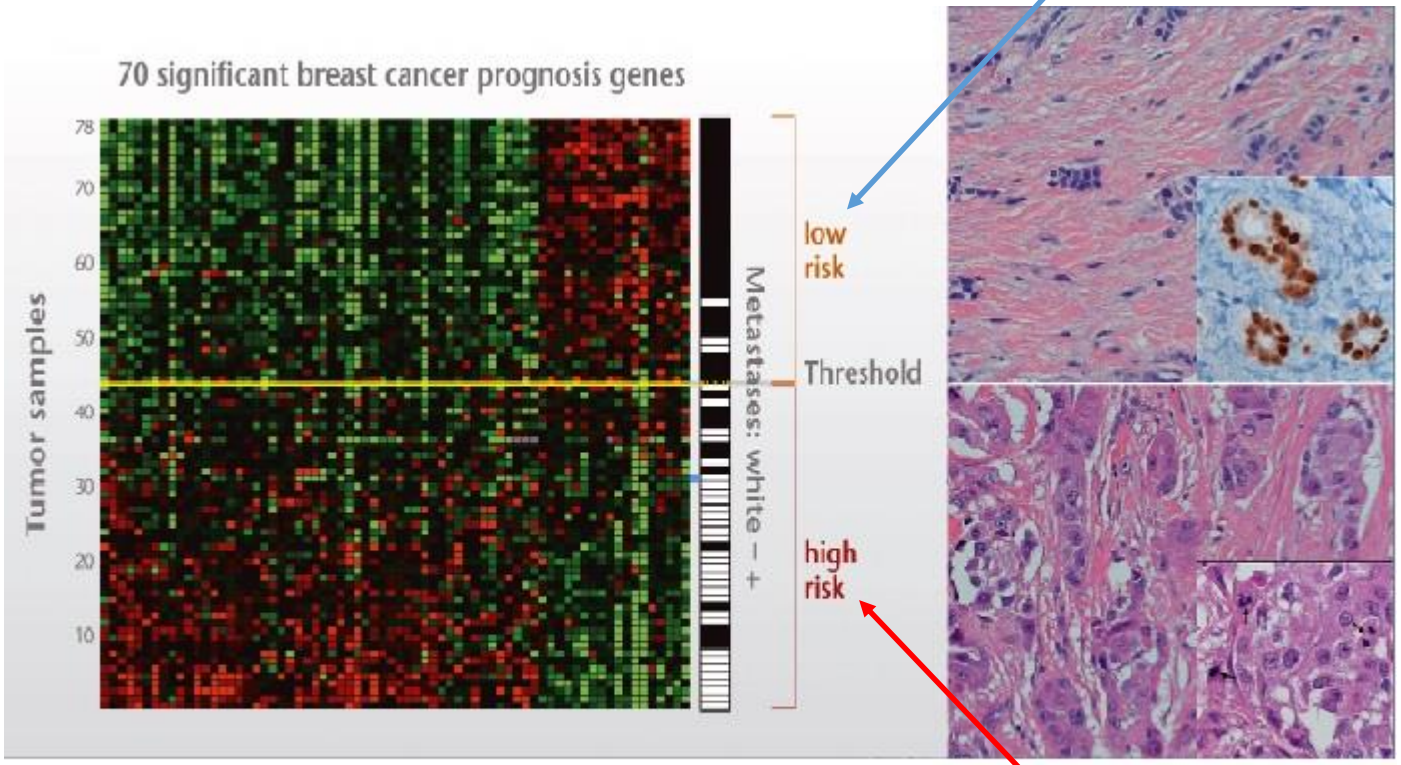


MOLECULAR DIAGNOSTICS TESTS

MAMMAPRINT®

Stage 1 and 2 Breast Cancer, node negative

10% chance of recurrence within 10 years with no treatment

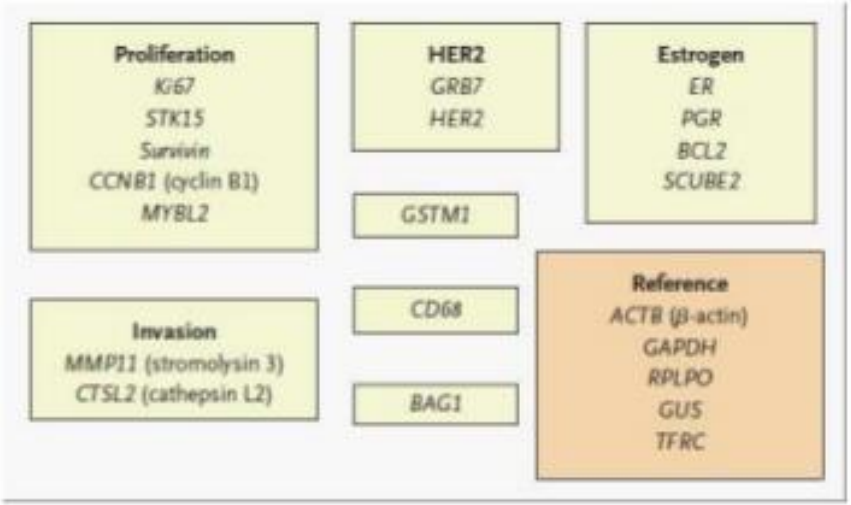


29% chance of recurrence within 10 years with no treatment

MOLECULAR DIAGNOSTICS TESTS

ONCOTYPE DX®

Stage 1 and 2 Breast Cancer, node negative, ER+; expression of 21 genes (16 genes known to be related with breast cancer and 5 reference genes)



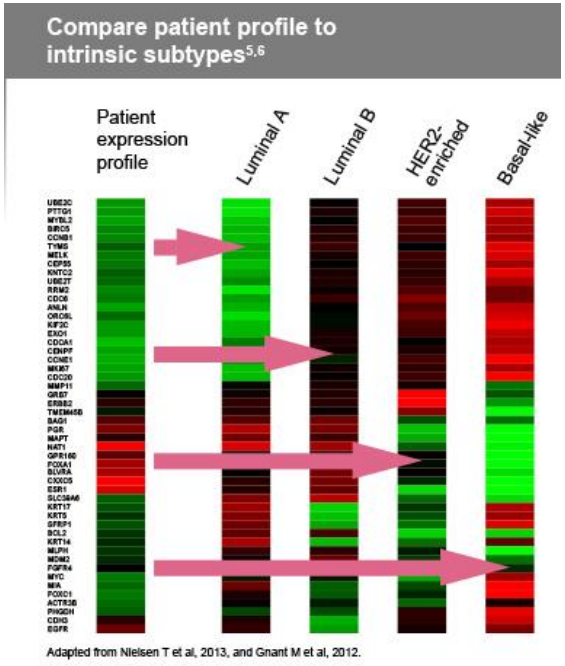
- Quantifies the standard pathologic characterization
- Complex algorithm that adds the HER2, proliferation, and invasion scores, and subtracts the estrogen score in a weighted fashion

- Reported as a Recurrence Score (RS)
- RS < 18 = low risk
- 18 ≤ RS < 31 = intermediate risk
- RS ≥ 31 = high risk

Paik et al. *NEJM*, 2004

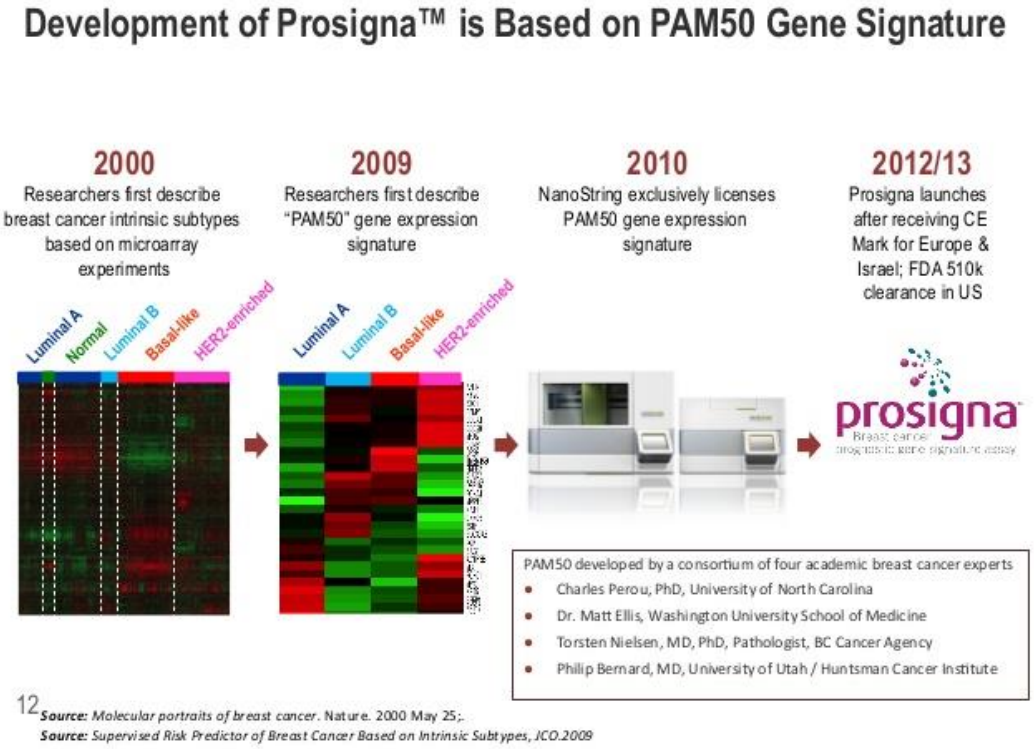
MOLECULAR DIAGNOSTICS TESTS

PROSIGNA®



The end result is the Risk of Recurrence (ROR, 0-100) estimating the risk of relapse within 10 years.

ROR is calculated taking into account the PAM50 gene signature, intrinsic subtype, tumour size, nodal status, and proliferation score.

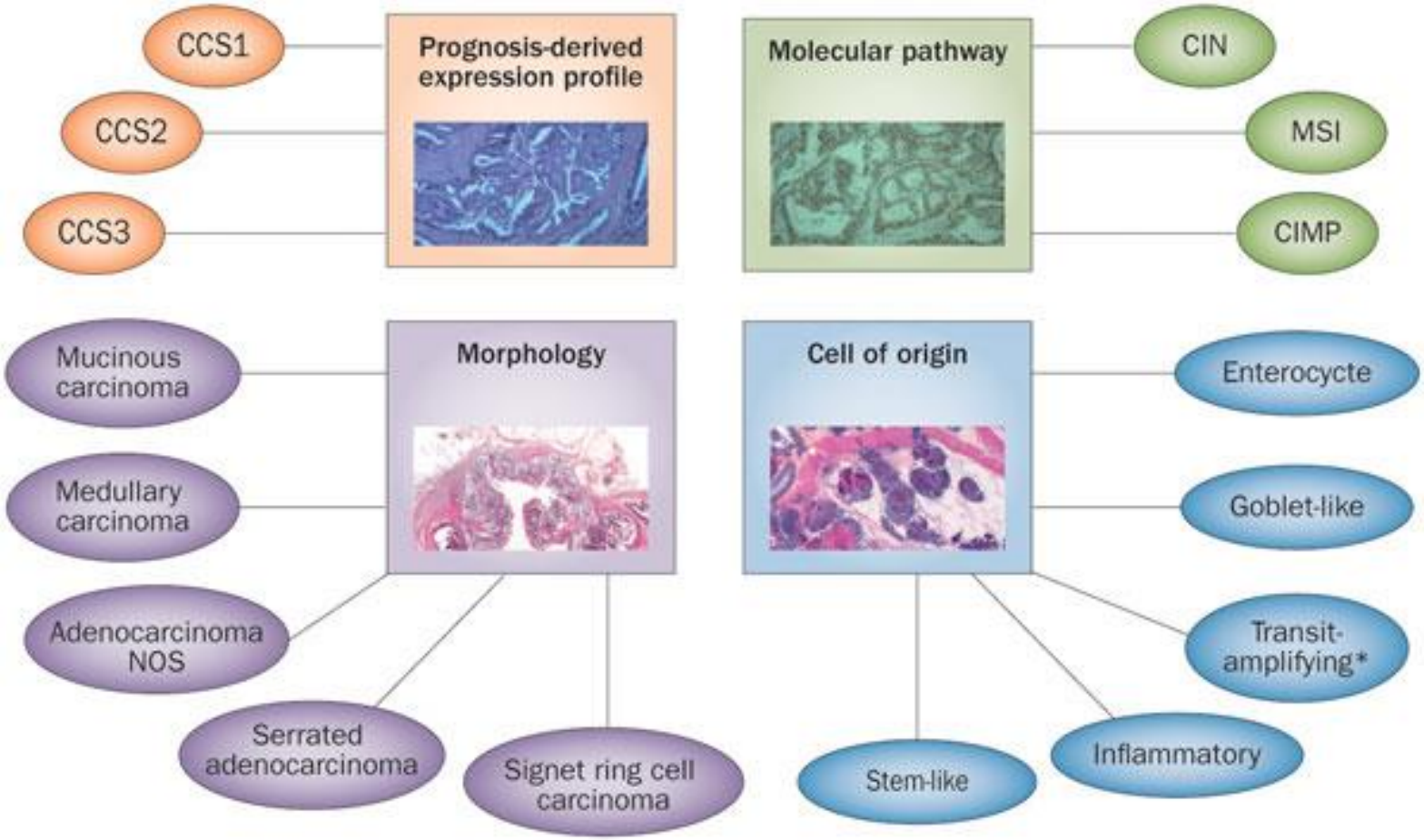


Colorectal Cancer

HISTOLOGICAL CLASSIFICATION

- **Adenocarcinoma (85%)**
- **Mucinous adenocarcinoma (10%)**
- **Signet-ring cell carcinoma**
- **Medullary carcinoma**
- **Undifferentiated carcinoma**
- **Small cell carcinoma**
- **Adenosquamous carcinoma**
- **Squamous carcinoma**

CLASSIFICATION



TNM CLASSIFICATION

Colorectal Cancer

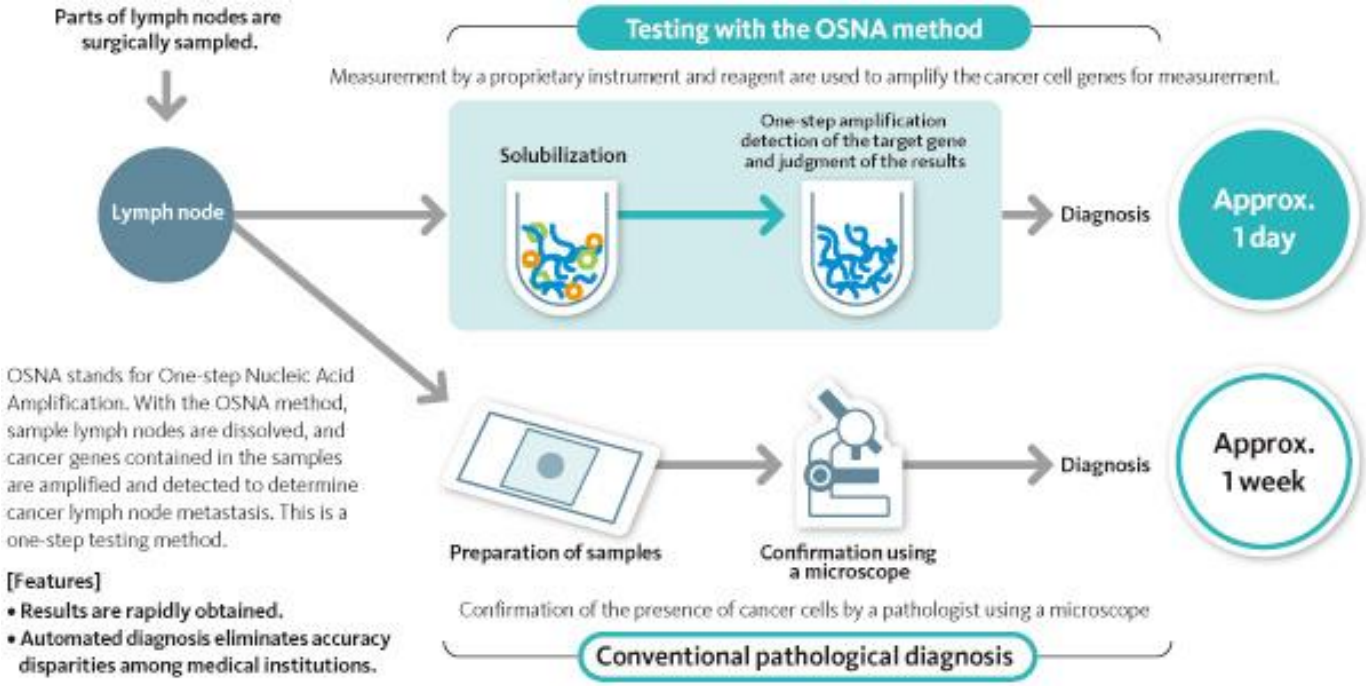
ANATOMIC STAGE/PROGNOSTIC GROUPS					
Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

NOTE: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (for example, ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).
* Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

Up to 30% of all patients classified in stage II suffer from local recurrence or distant metastases within 5 years of undergoing surgery, leading to significantly poorer survival rates.
These patients are classified in a lower lymph node status (false-negative rates up to 24%), which impacts on the decisions made concerning their further therapy options.

OSNA® allows the investigation of the entire lymph node and its results are comparable with ultra-staging (IHC). Studies have shown that a lymph node analysis of pN0 patients with OSNA® yielded an upstaging rate of approximately 26%, compared with the standard histological test method. These patients' therapies could thus be adjusted accordingly.

Colorectal Cancer



sysmex

Colon Cancer

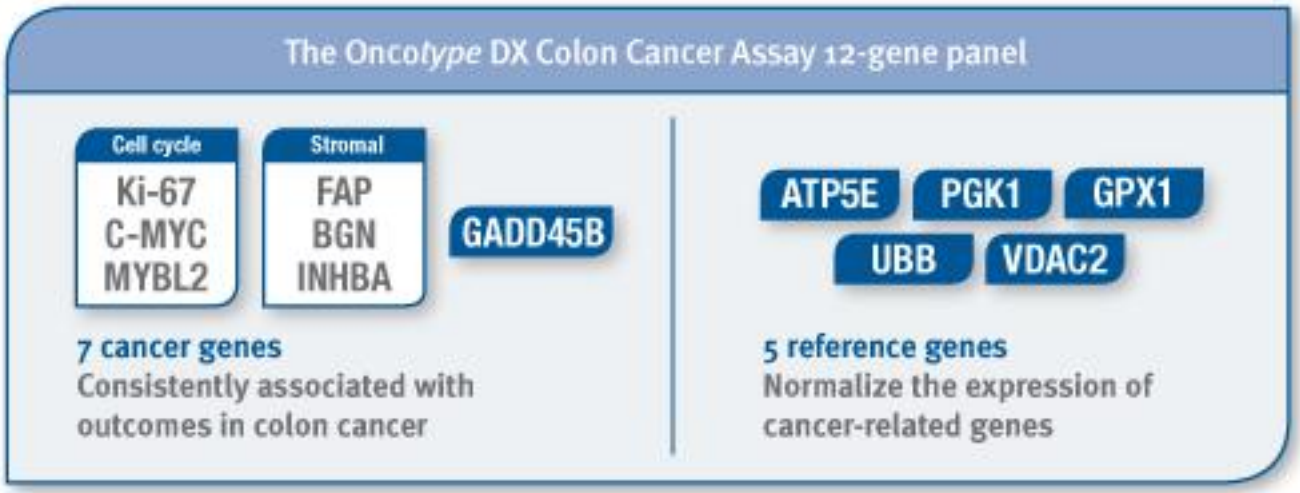
MOLECULAR CLASSIFICATION

- *k-ras* mutations
- *P53* mutations
- LOH 17p (p53)
- LOH 18q (dcc)
- Microsatellite instability (MMR)
- DNA methylation
- Altered expression of TGFb
- *Apc* mutation/loss

MOLECULAR DIAGNOSTICS TESTS

ONCOTYPE DX COLON®

Stage 2 Colon Cancer; expression of 12 genes
(7 genes known to be related with colon cancer and 5 reference genes)



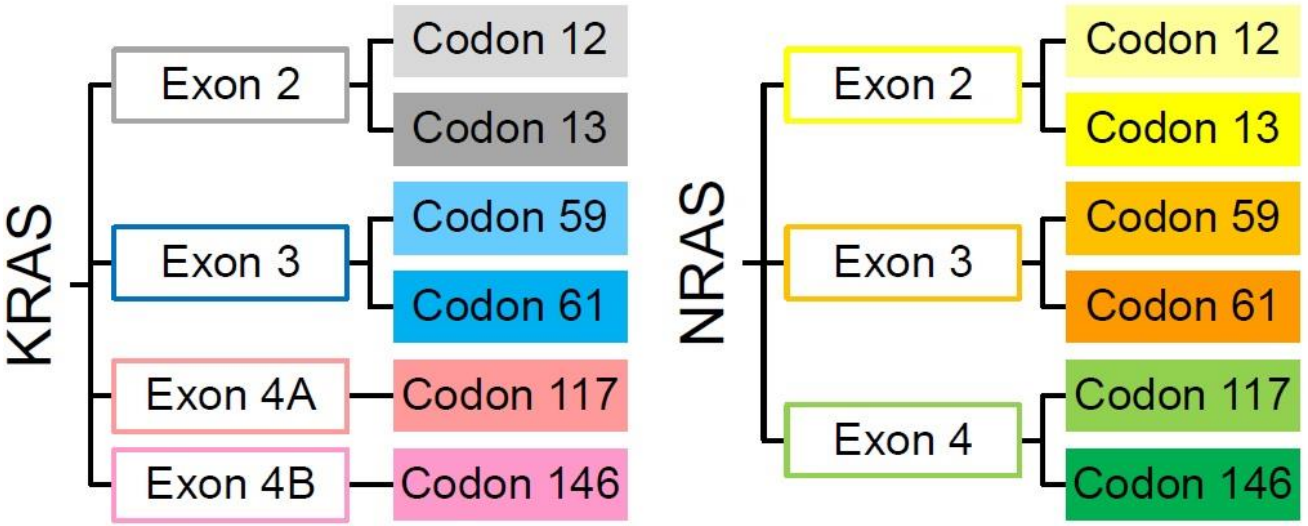
The end result of the testing is a Recurrence Score (0-100) indicating the risk of recurrence in the three years after surgery.

The test has been validated but it's not currently included in standard clinical practice.

MOLECULAR DIAGNOSTICS TESTS

ONCOBEAM™ RAS CRC ASSAY

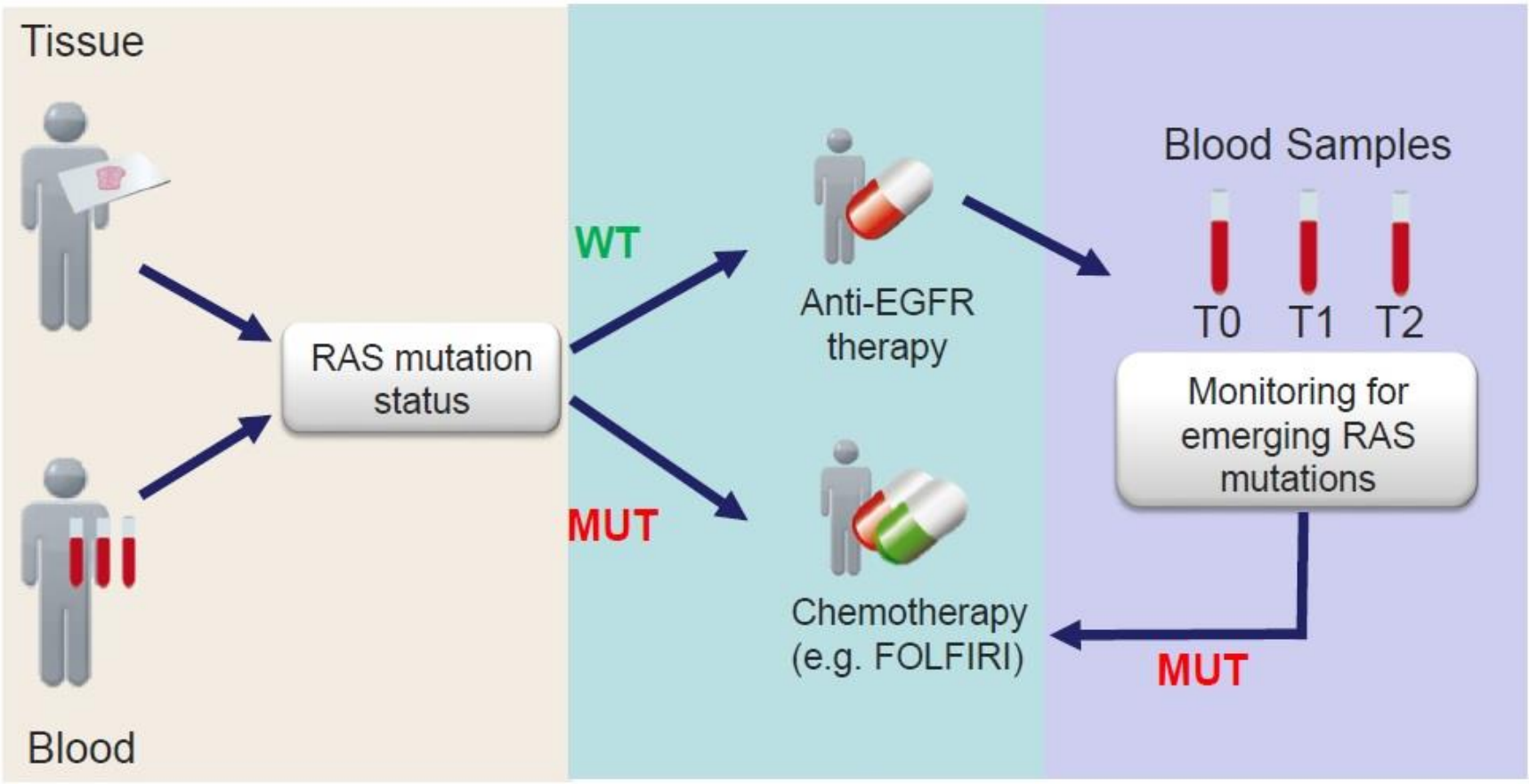
Stage 4 Colon Cancer; evaluation of *K*- and *N-RAS* mutations in specific codons



The end result of the testing is the mutational status of *K*- and *N-RAS* in plasma (ctDNA).

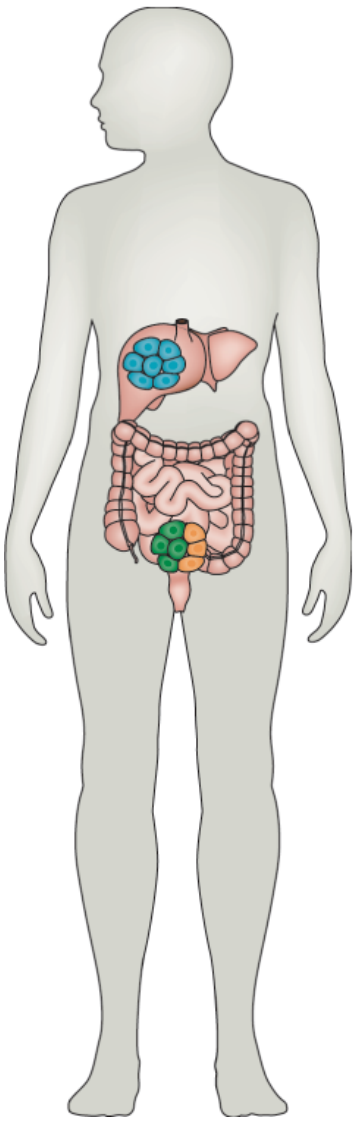
The test has been validated but it's not included in standard clinical practice yet.

✓ Treatment



Example: Blood-based RAS testing for colorectal cancer

Treatment



RAS_{WT}

Alterations in *BRAF*, *ERBB2*, *MET*, *PIK3CA*, *MAP2K1*

Improved initial response rates to anti-EGFR antibodies

Targeted combination therapies with or without anti-EGFR antibodies

MSI-H

$BRAF^{V600E}$

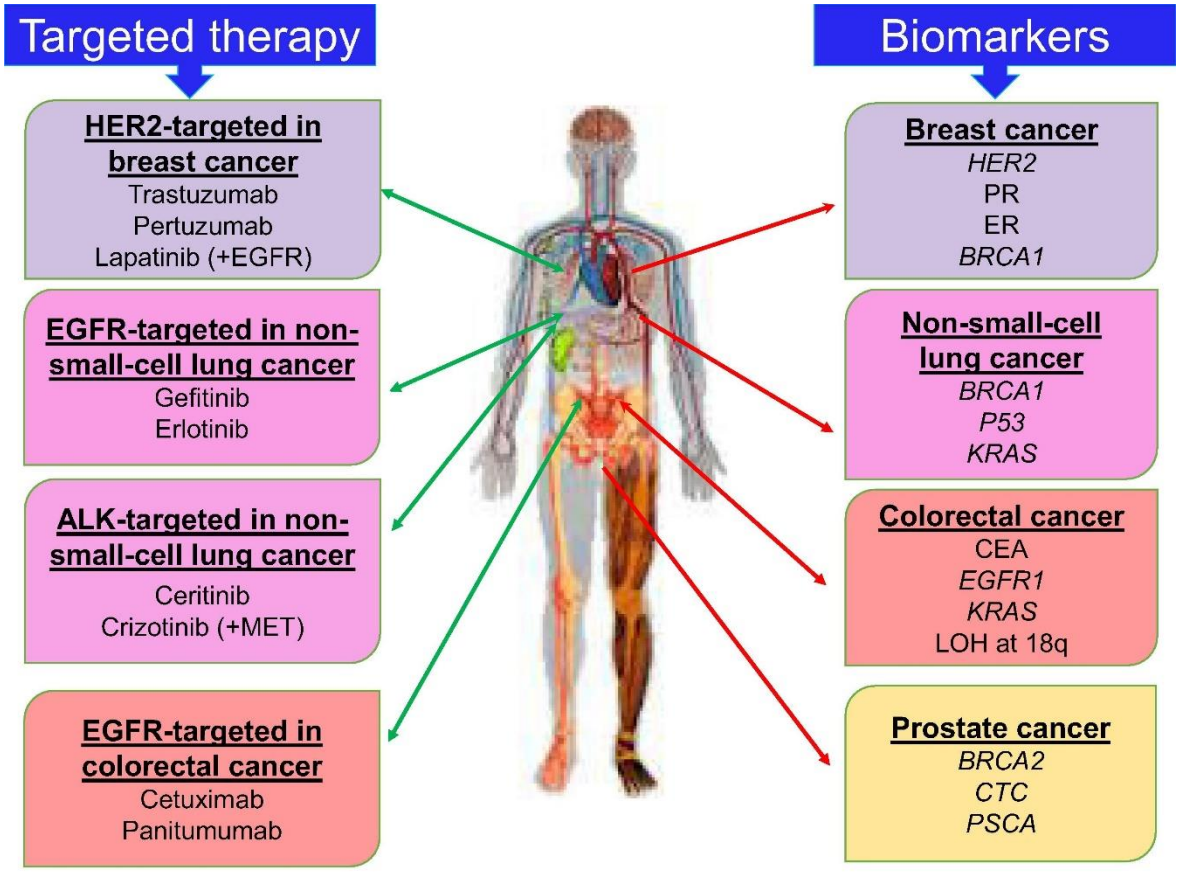
$ERBB2^{amp}$

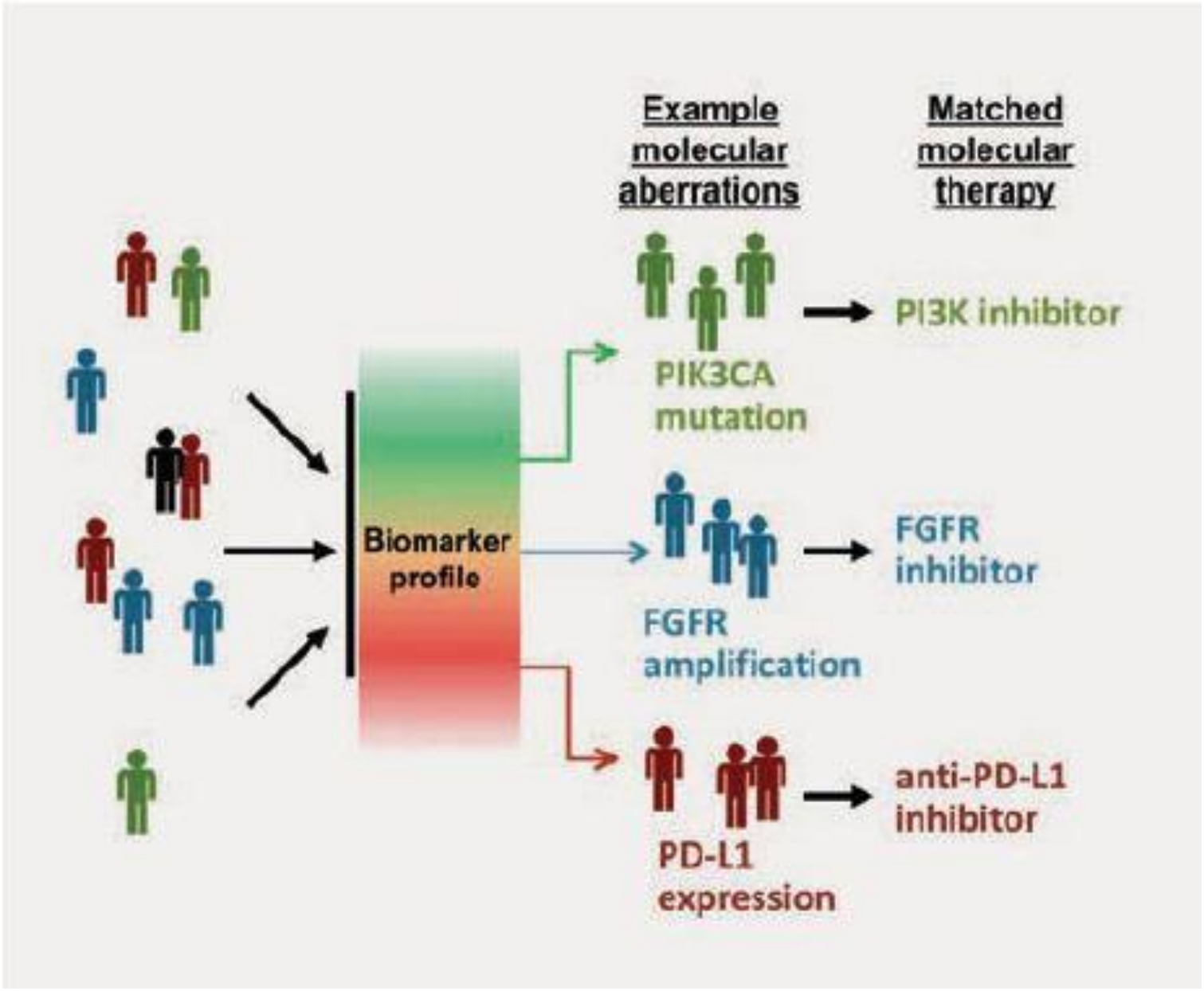
Fusion positive

Targeted therapies available to additional patients

Co-occurrence of >1 targetable alteration

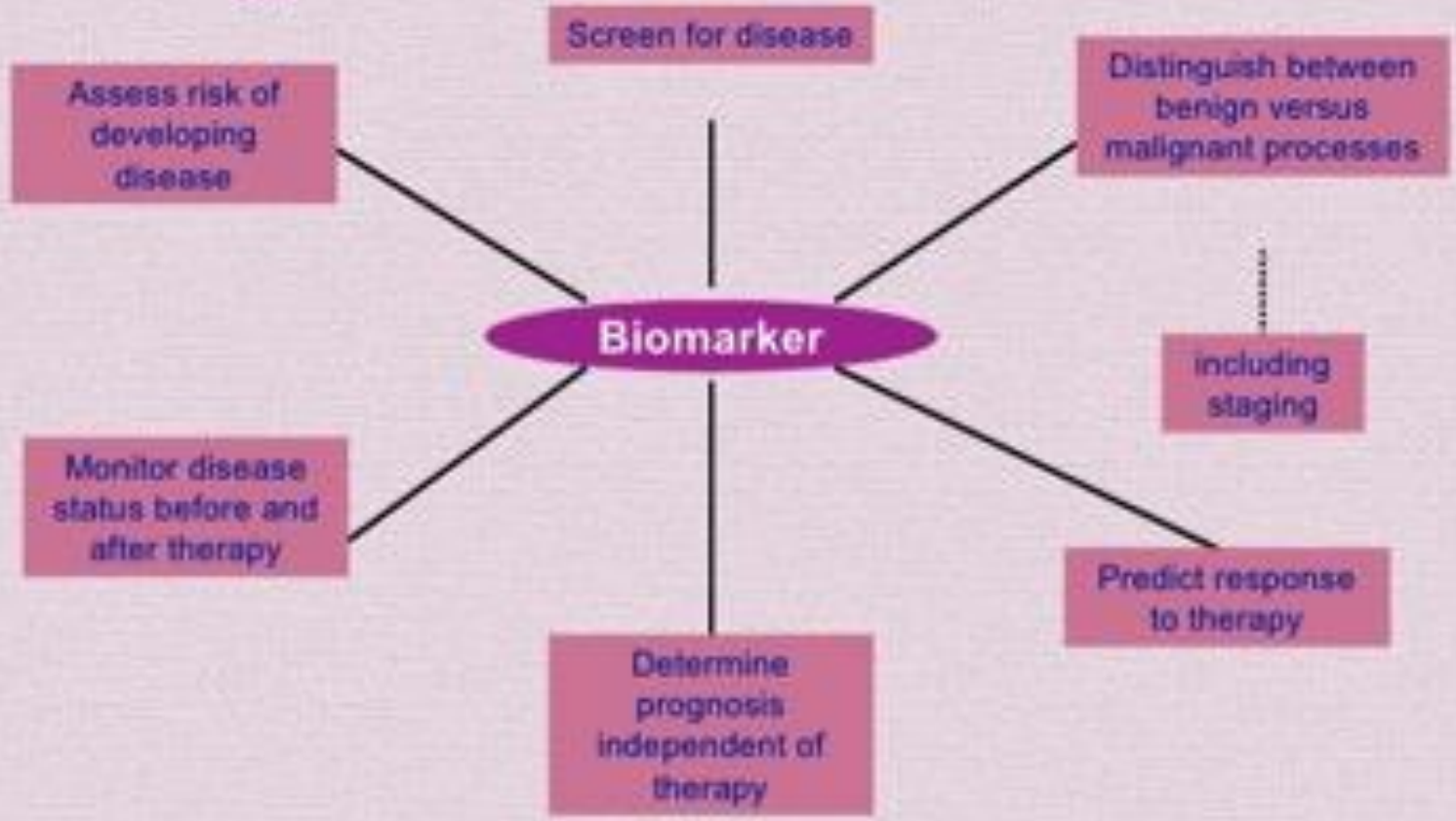
Novel options for second-line therapy

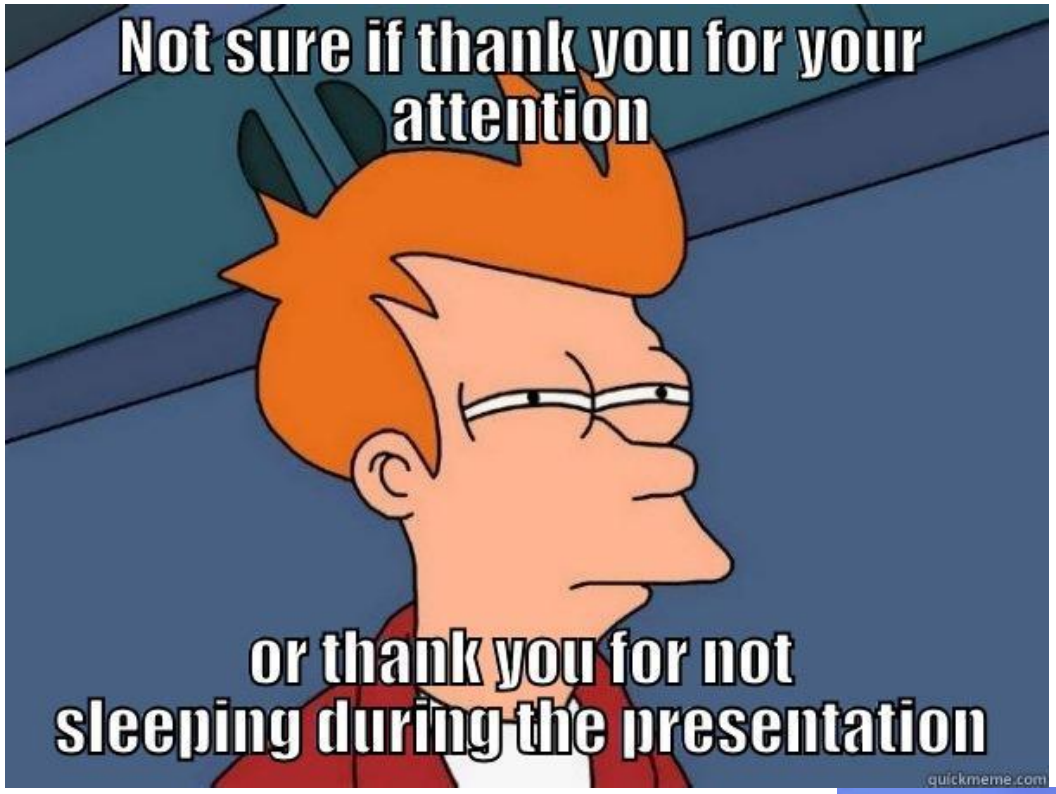

Targeted therapy
HER2-targeted in breast cancer
Trastuzumab
Pertuzumab
Lapatinib (+EGFR)
EGFR-targeted in non-small-cell lung cancer
Gefitinib
Erlotinib
ALK-targeted in non-small-cell lung cancer
Ceritinib
Crizotinib (+MET)
EGFR-targeted in colorectal cancer
Cetuximab
Panitumumab
Biomarkers
Breast cancer
HER2
PR
ER
BRCA1
Non-small-cell lung cancer
BRCA1
P53
KRAS
Colorectal cancer
CEA
EGFR1
KRAS
LOH at 18q
Prostate cancer
BRCA2
CTC
PSCA


Example molecular aberrations
Matched molecular therapy
Biomarker profile
PIK3CA mutation
PI3K inhibitor
FGFR amplification
FGFR inhibitor
PD-L1 expression
anti-PD-L1 inhibitor

✓ Conclusions

Potential uses for biomarkers in oncology




Not sure if thank you for your attention
or thank you for not sleeping during the presentation
quickmeme.com


THANK YOU FOR YOUR ATTENTION
PLEASE DONT ASK TOUGH QUESTIONS