Cancer and Tumor Markers

A Clinical Perspective

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Agenda

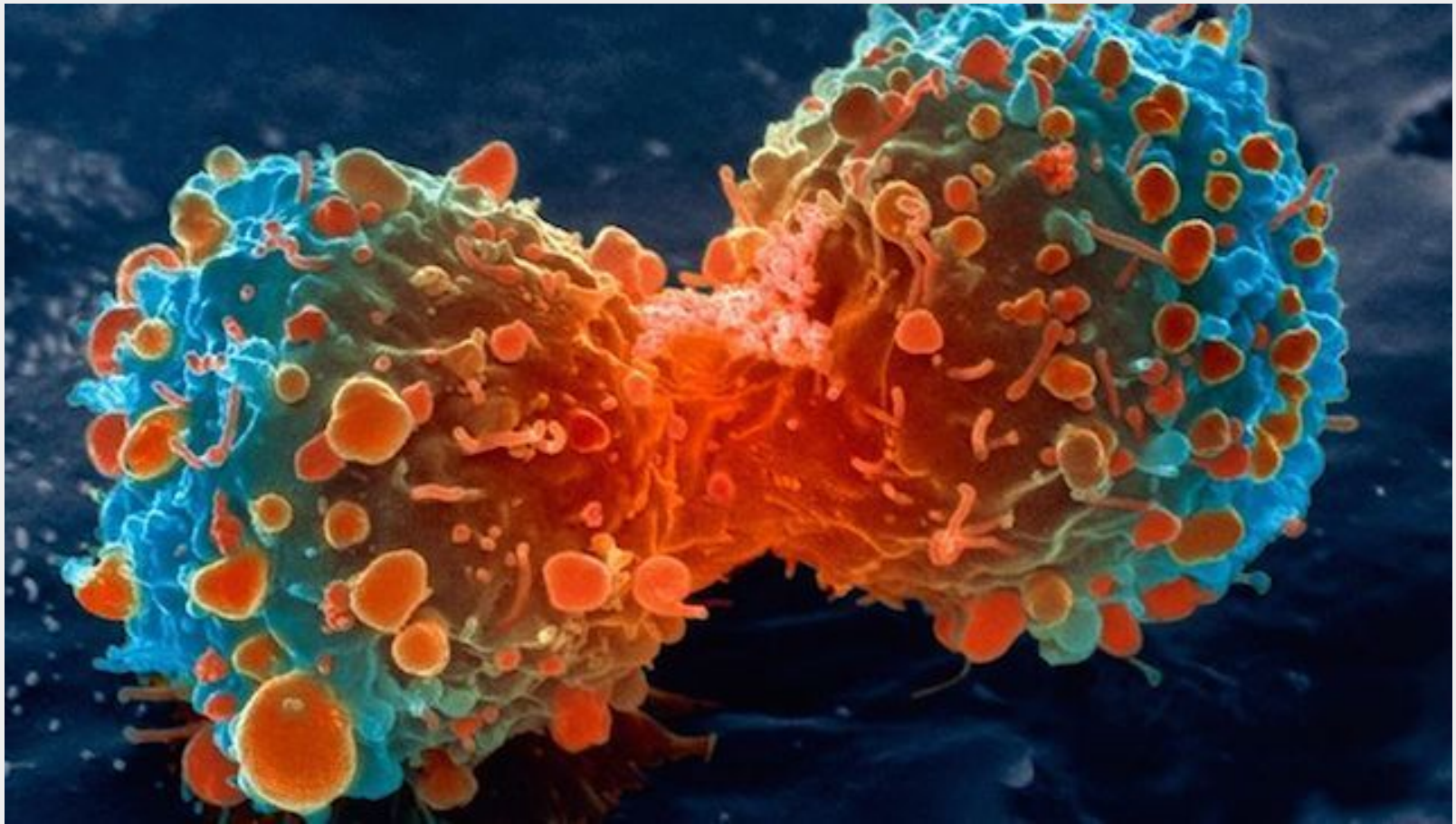
- Introduction to Cancer & Tumor Markers
- Clinical Applications of Tumor Markers
- Evaluating Clinical Utility of Tumor Markers
- Analytical Methods
- Types of Tumor Markers
- References

What is Cancer?

Tietz	• A relatively autonomous growth of tissue
NCI	• A term used for disease in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems
ASCO	• A group of more than 100 different diseases that can begin almost anywhere in the body, characterized by abnormal cell growth and the ability to invade nearby tissues
ACS	• a group of diseases which cause cells in the body to change and grow out of control
WHO	• Cancer is the uncontrolled growth and spread of cells

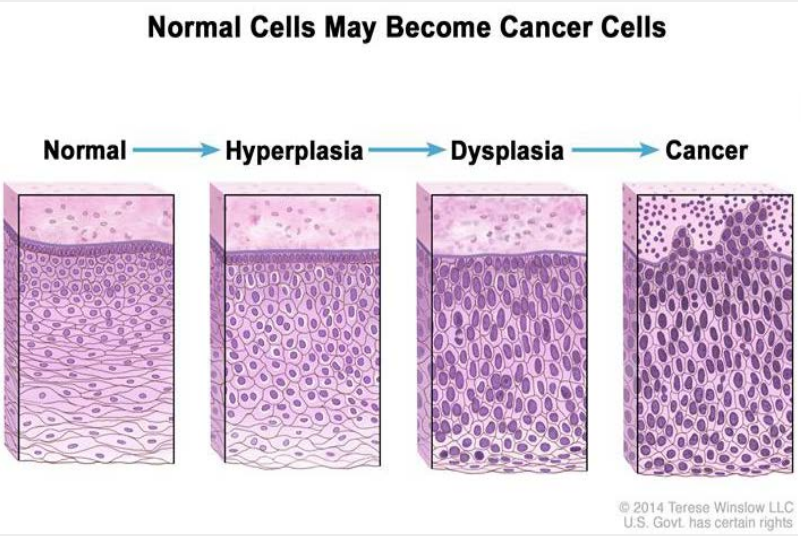
Common Concept in Different Definitions

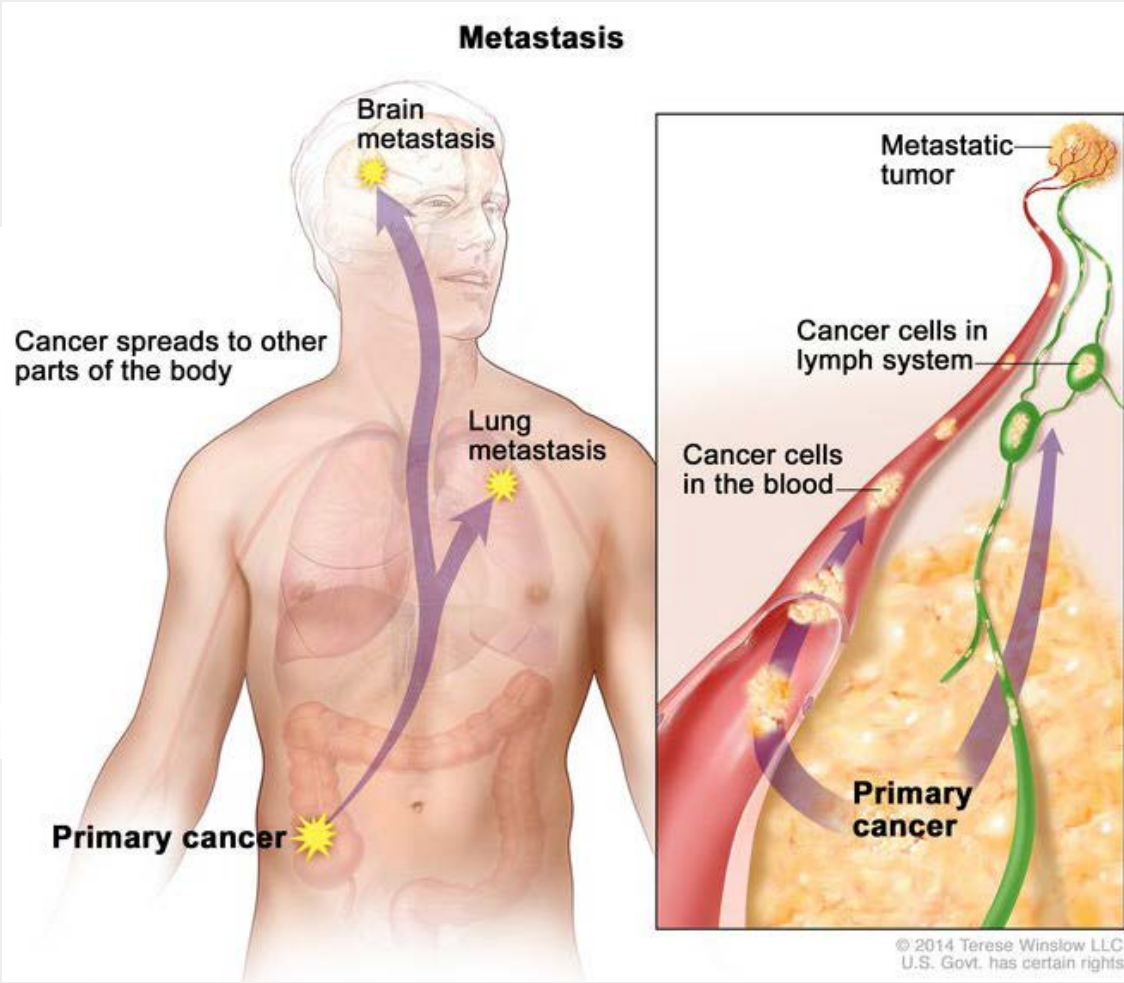
- ✓ Uncontrolled Proliferation
- ✓ Invasion



Metastasis

The Spread of cancer from one part of the body to another



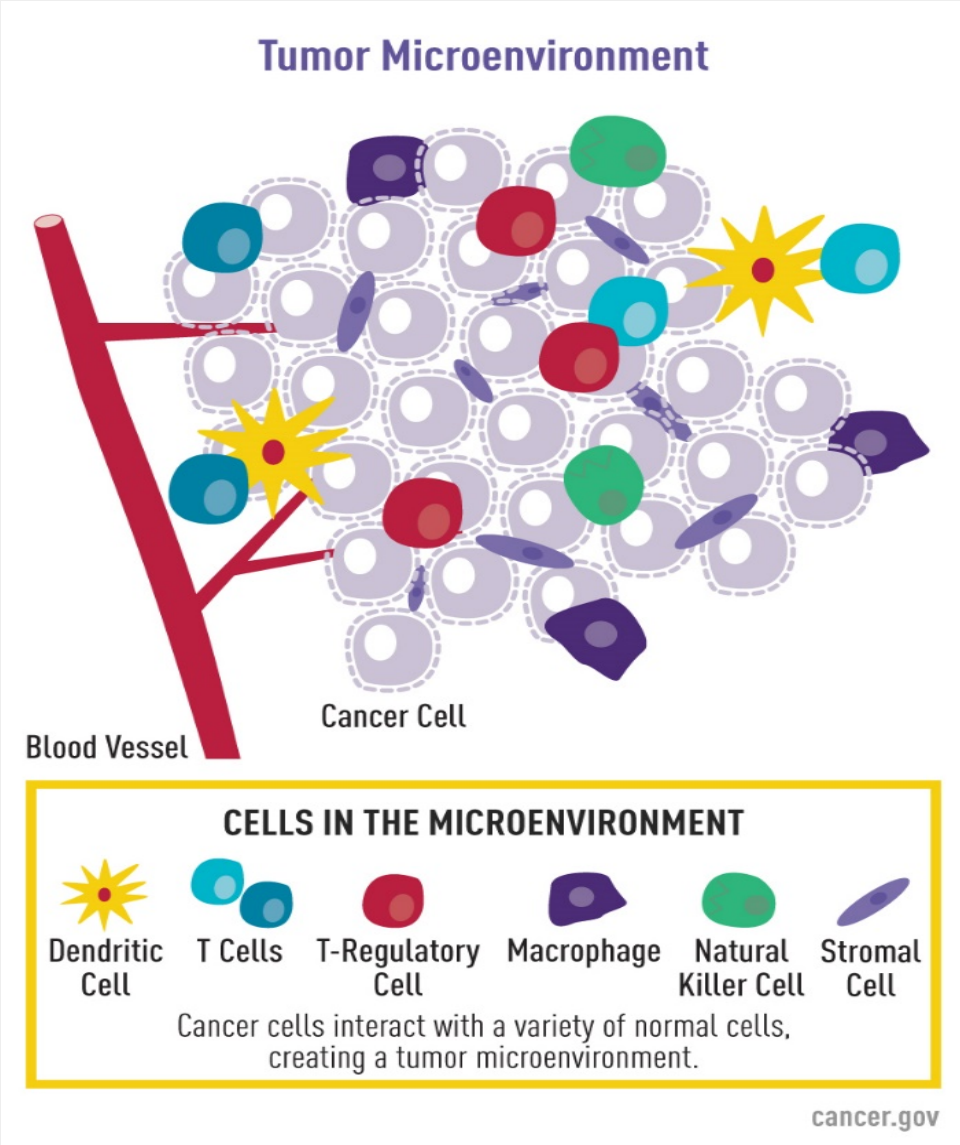


Steps of Metastasis

1) Growing into, or invading, nearby normal tissue
2) Moving through the walls of nearby lymph nodes or blood vessels
3) Traveling through the lymphatic system and bloodstream to other parts of the body
4) Stopping in small blood vessels at a distant location, invading the blood vessel walls, and moving into the surrounding tissue
5) Growing in this tissue until a tiny tumor forms
6) Causing new blood vessels to grow, which creates a blood supply that allows the tumor to continue growing

Angiogenesis

Blood vessel formation. Tumor angiogenesis is the growth of new blood vessels that tumors need to grow. This process is caused by the release of chemicals by the tumor and by host cells near the tumor.



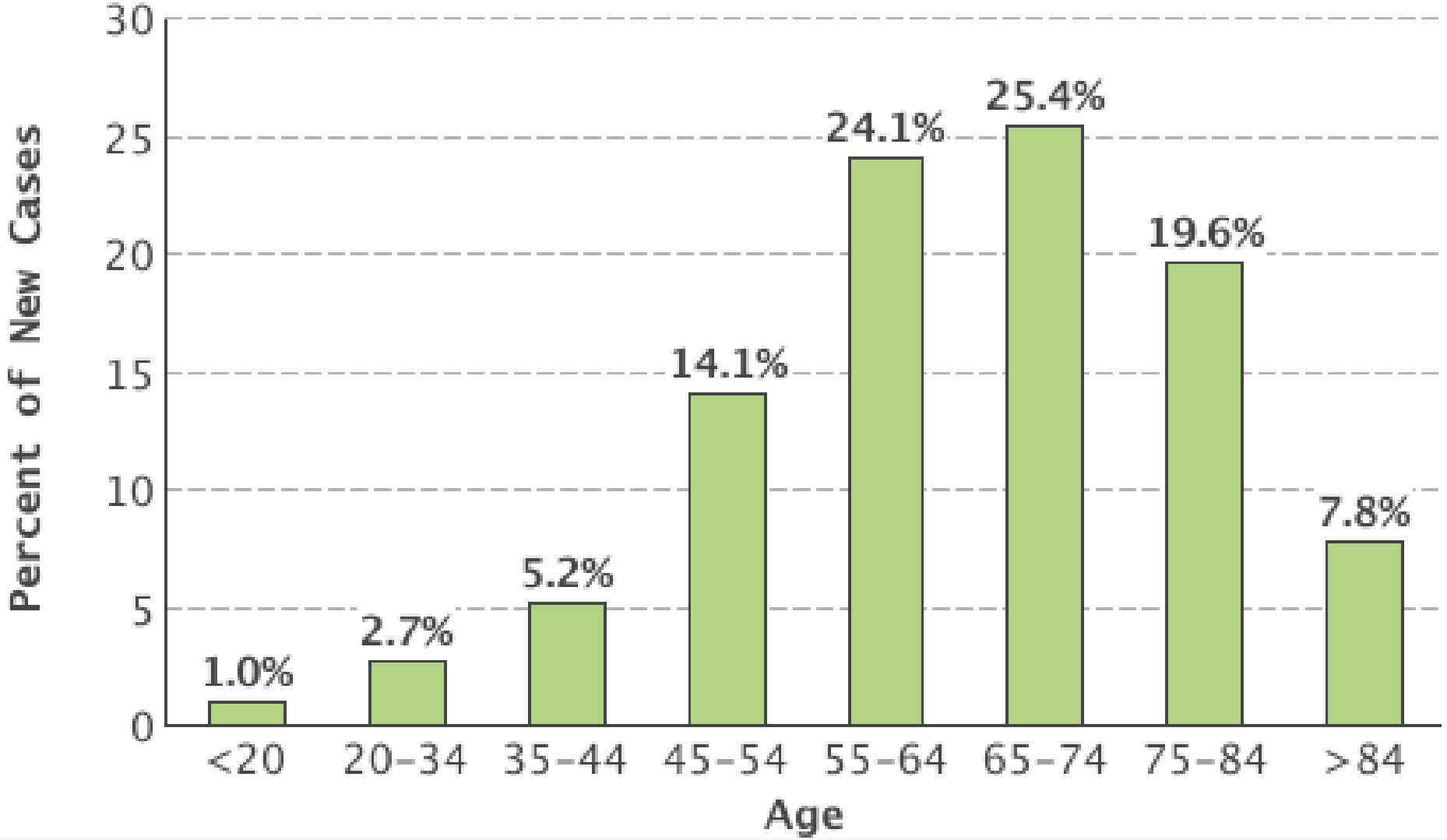
Common Sites of Metastasis

Cancer Type	Main Sites of Metastasis
Breast	Bone, brain, liver, lung
Colon	Liver, lung, peritoneum
Lung	Adrenal gland, bone, brain, liver, other lung
Prostate	Adrenal gland, bone, liver, lung
Ovary	Liver, lung, peritoneum
Thyroid	Bone, liver, lung

Risk Factors for Cancer

- Age
- Alcohol
- Cancer-Causing Substances
- Chronic Inflammation
- Diet
- Hormones
- Immunosuppression
- Infectious Agents
- Obesity
- Radiation
- Sunlight
- Tobacco

Risk Factors for Cancer: Age



Risk Factors for Cancer: Alcohol

- Alcohol use has been linked with cancers of the:
  - ✓ Mouth
  - ✓ Throat (pharynx)
  - ✓ Voice box (larynx)
  - ✓ Esophagus
  - ✓ Liver
  - ✓ Colon and rectum
  - ✓ Breast

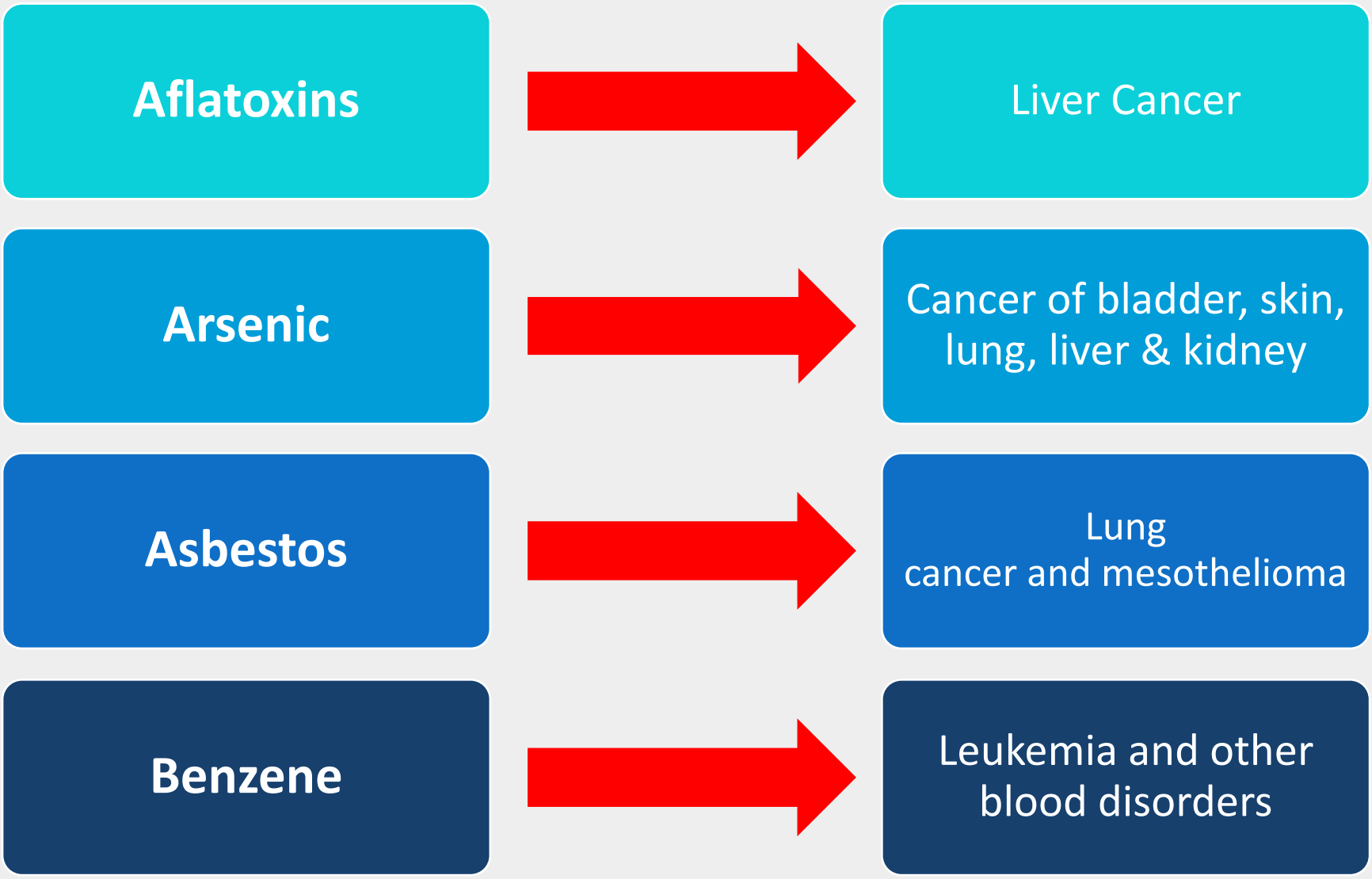
- Alcohol may also increase the risk of cancers of the pancreas and stomach.

Risk Factors for Cancer: Cancer-Causing Substances

Most Likely Carcinogens:

- Aflatoxins
- Arsenic
- Asbestos
- Benzene
- Benzidine
- Cadmium
- Coal Tar and Coal-Tar Pitch
- Coke-Oven Emissions
- Crystalline Silica (respirable size)
- Formaldehyde
- Nickel Compounds
- Secondhand Tobacco Smoke
- Wood Dust

Risk Factors for Cancer: Infectious Agents



Risk Factors for Cancer: Infectious Agents

- Epstein-Barr Virus (EBV)
- Hepatitis B Virus and Hepatitis C Virus (HBV and HCV)
- Human Immunodeficiency Virus (HIV)
- Human Papillomaviruses (HPVs)
- Human T-Cell Leukemia/Lymphoma Virus Type 1 (HTLV-1)
- Kaposi Sarcoma-Associated Herpesvirus (KSHV)
- Merkel Cell Polyomavirus (MCPyV)
- *Helicobacter pylori (H. pylori)*
- *Opisthorchis viverrini*
- *Schistosoma hematobium*

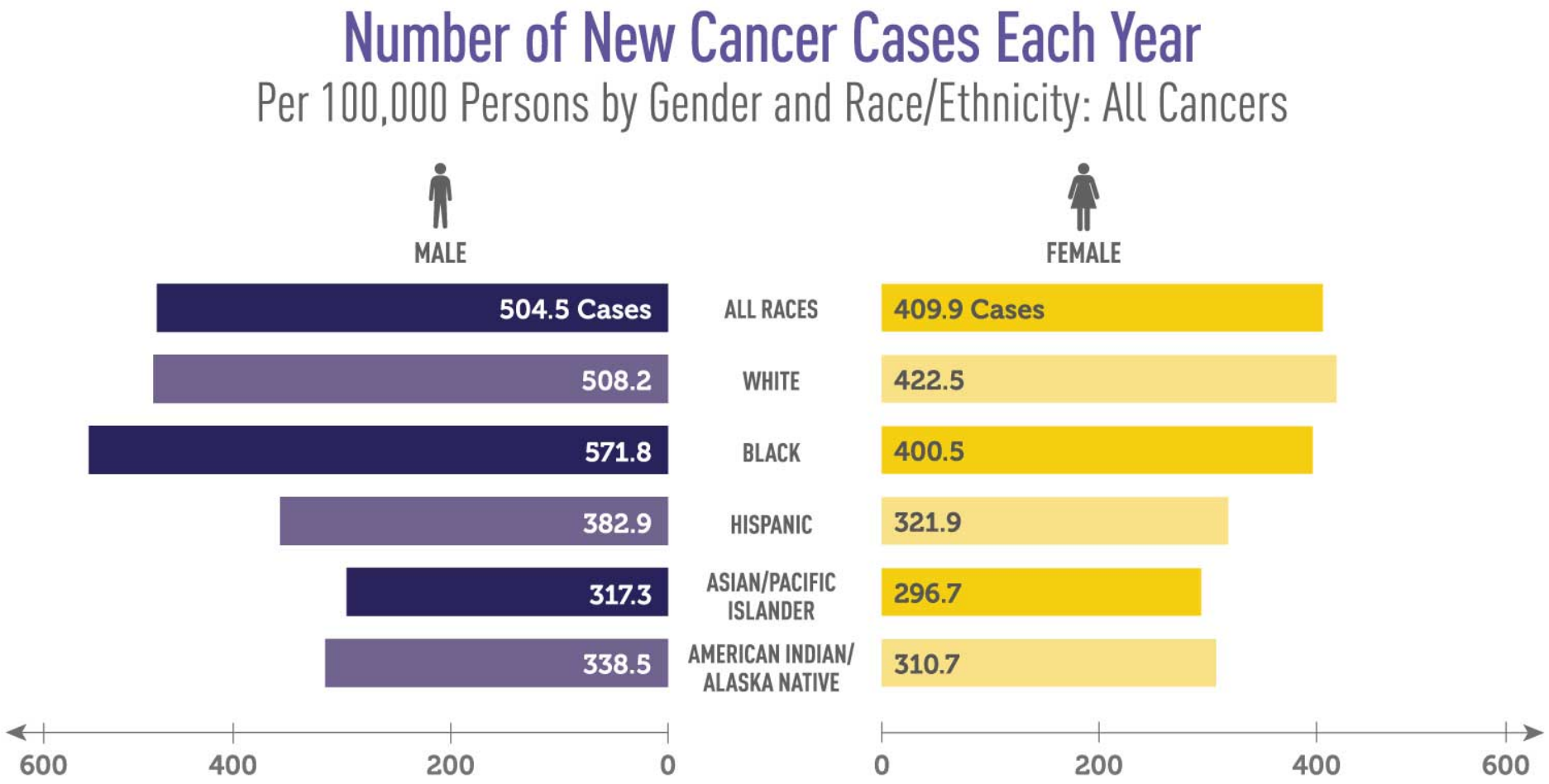
Risk Factors for Cancer: Infectious Agents

Epstein-Barr Virus (EBV)	→	Certain types of lymphoma & cancers of the nose and throat
Hepatitis B Virus and Hepatitis C Virus (HBV and HCV)	→	Liver Cancer
Human Papillomaviruses (HPVs)	→	Most anal cancers and many oropharyngeal, vaginal, vulvar , and penile cancers
Human T-Cell Leukemia/Lymphoma Virus Type 1 (HTLV-1)	→	Adult T-cell leukemia/lymphoma (ATLL)

Risk Factors for Cancer: Chronic Inflammation

- Inflammation is a normal physiological response that causes injured tissue to heal.
- chronic inflammation can cause **DNA damage** and lead to cancer.
- people with **chronic inflammatory bowel diseases**, such as ulcerative colitis and Crohn disease, have an increased risk of colon cancer.

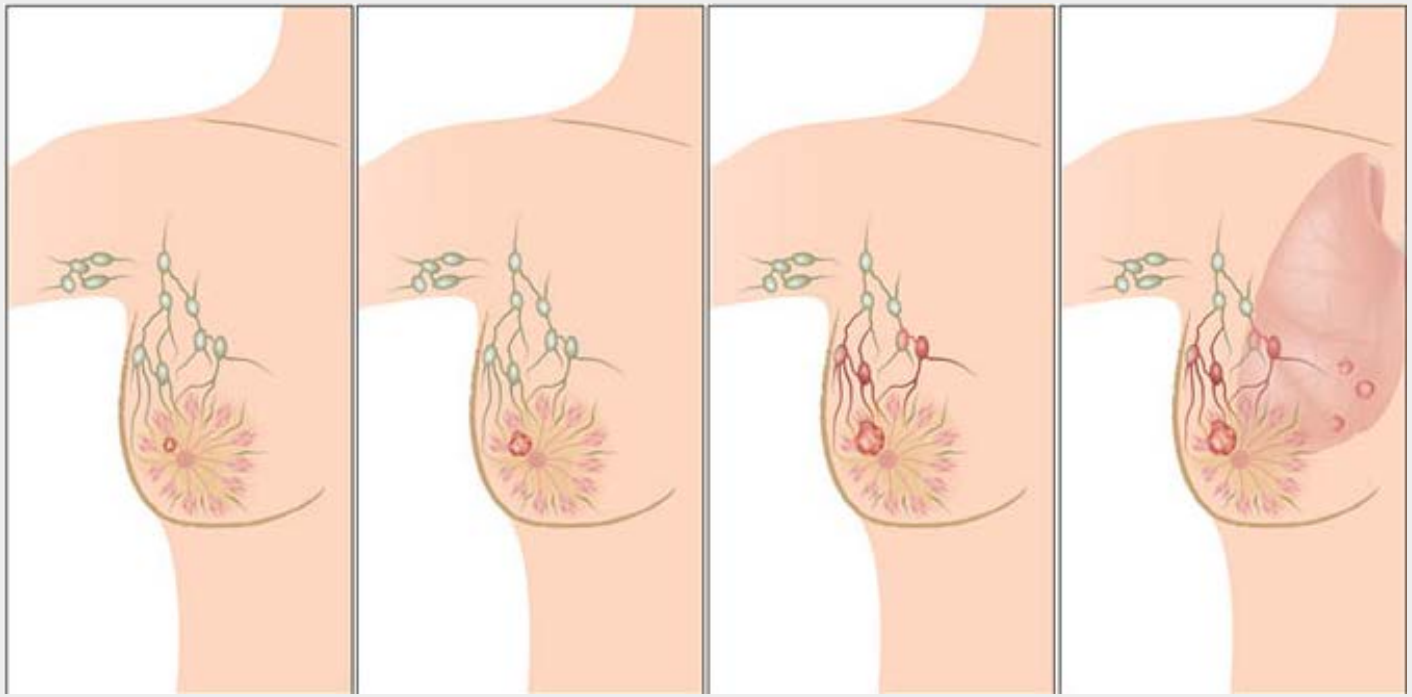
Racial/Ethnic & Cancer



Cancer Staging

Stage refers to the extent of the cancer, such as how large the tumor is, and if it has spread. Knowing the stage of the cancer helps doctor:

1) Understand how serious the cancer is and the chance of survival
2) Plan the best treatment
3) Identify clinical trials that may be treatment options



https://www.ausmed.com/articles/cancer-staging/

Cancer Staging Methods

Stage Determining:

1) Biopsy
   a) With a needle
   b) With an endoscope
   c) With surgery
2) Imaging Procedures
   a) CT Scan
   b) Nuclear Scan
   c) Ultrasound
   d) MRI
   e) PET Scan
   f) X-ray
3) Lab Tests

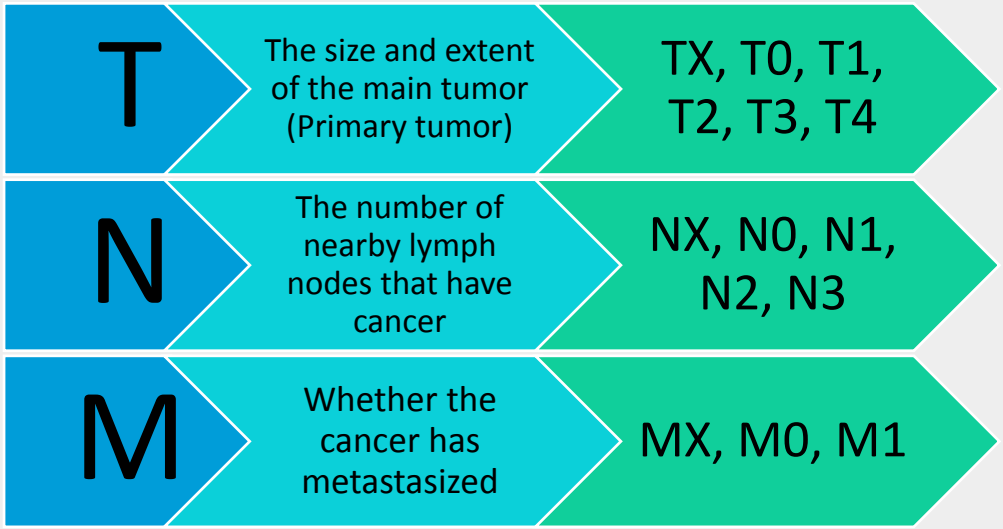
Cancer Staging Systems

There are many staging systems. Some, such as the **TNM staging system**, are used for many types of cancer. Others are specific to a particular type of cancer

Most staging systems include information about:

- Where the tumor is located in the body
- The cell type (such as, adenocarcinoma or squamous cell carcinoma)
- The size of the tumor
- Whether the cancer has spread to nearby lymph nodes
- Whether the cancer has spread to a different part of the body
- Tumor grade, which refers to how abnormal the cancer cells look and how likely the tumor is to grow and spread

TNM Staging System



Stage	Meaning
Stage 0	Abnormal cells are present but have not spread to nearby tissue. Also called carcinoma in situ, or CIS. CIS is not cancer, but it may become cancer.
Stage *I*, *II*, *III*	Cancer is present. The higher the number, the larger the cancer tumor and the more it has spread into nearby tissues.
Stage *IV*	The cancer has spread to distant parts of the body.

Definition of Tumor Marker

- A **tumor marker** is a substance produced by a tumor or by the host in response to a tumor.
- Tumor marker may be found in **blood**, **body fluids** or **tissue** and it is used to:
    1) Determine the presence of tumor or differentiate a tumor from normal tissue
    2) Predict the size of tumor
    3) Monitor tumor response to therapy
- Some tumor markers are associated with only one type of cancer; others are seen in several cancer types and also in noncancerous conditions.
- Cancer tissue is more resemble to **fetal tissue** than adult differentiated tissue. Some tumor markers represent re-expression of substances produced normally by embryonic related tissue.

Clinical Applications of Tumor Markers

Specificity & Sensitivity of Tumor Marker:

- ✓ An ideal tumor marker should be both **specific** for a particular type of cancer and **sensitive** enough to detect small tumors for early diagnosis.
- ✓ Ideal tumor marker should not be present in healthy people or in benign conditions.
- ✓ Most of tumor markers are found with different tumors of the same tissue type, also in normal and benign conditions.

Current Applications of Tumor Markers

1. Screening for cancer
2. Diagnosis cancer
3. Evaluating cancer prognosis
4. Predicting therapeutic response
5. Performing tumor staging
6. Detecting tumor recurrence or remission
7. Localizing tumor and directing radiotherapeutic agents
8. Monitoring the effectiveness of cancer therapy

Evaluating Clinical Utility of Tumor Markers

- Reference Intervals
- Predictive Value Models
- Distribution of Markers
- Disease Management

Evaluating Clinical Utility of Tumor Markers

Reference Intervals

Reference intervals are obtained from healthy population of the same age and sex as those with cancer of interest.

For using tumor marker in the diagnosis and management of cancer, a decision cut point may be more appropriate that upper limit of reference interval.

Using patients with benign disease as noncancerous group is more suitable than a healthy population.

Predictive Value Models

Predictive value model includes the clinical sensitivity and specificity and the predictive value of a test.

Predictive value of a positive test is the proportion of subjects with a positive test who have the disease.

Predictive value of a negative test is the proportion of subjects with a negative test who do not have the disease.

Evaluating Clinical Utility of Tumor Markers

Distribution of Markers

The distribution of tumor marker concentrations is usually shown as the percentage of patient with elevated concentrations as determined by using various cutoffs

For example. In breast cancer, normal woman are used as the healthy group for comparison. Nonmalignant or benign groups are selected to include people with the most likely causes of marker elevation.

Benign liver disease, breast disease, pregnancy. Non breast metastatic cancer groups are selected to show the specificity of marker

Disease Management

Tumor markers may be used to determine the success of initial treatment and detect the recurrence of cancer.

When effectiveness of therapy is monitored marker concentration should increase with progression of cancer, decrease with regression of cancer, and remain constant in the presence of stable disease.

Progressive of disease is defined by an increase in the marker concentration of at least 25%. A decrease in marker concentration of at least 50% is indicative of partial remission.

Analytical Methods

Tumor markers are measured qualitatively and quantitatively by a variety of analytical methods including:

- Enzyme assay
- Immunoassay
- Receptor assay
- Chromatography
- Electrophoresis
- Mass spectrometry
- Microarrays

Types of Tumor Markers

Enzymes

- Alkaline Phosphatase
- Lactate Dehydrogenase
- Neuron-Specific Enolase
- Prostatic Acid Phosphatase
- Prostate Specific Antigen
- The Urokinase-Plasminogen Activator System
- Cathepsins

Hormones

- ACTH
- Calcitonin
- HCG

Oncofetal Antigens

- α-Fetoprotein
- Carcinoembryonic Antigen

Cytokeratins

- Tissue Polypeptide Antigen
- Tissue Polypeptide-Specific Antigen
- CYFRA 21-1
- Squamous Cell Carcinoma Antigen

Carbohydrate Markers (Mucins)

- CA 15-3
- CA 27.29
- CA 125
- HE4
- OVA1

Blood Group Antigens

- CA 19-9
- CA 19-5
- CA 50
- CA 72-4
- CA 242

Types of Tumor Markers

Proteins

- Immunoglobulin
- Urinary Bladder Tumor Markers
- Nuclear Matrix Protein
- Bladder Tumor Associated Analytes
- Soluble Mesothelin-Related Peptides
- Des-γ-Carboxy Prothrombin
- S-100 Proteins
- Thyroglobulin & Antibodies
- Chromogranins

Receptors

- Estrogen & Progesterone Receptors
- Epidermal Growth Factor Receptors

Circulating Tumor Cells

- CTCs

Genetic & Molecular Markers

- RAS Genes
- HER2
- BRC-ABL
- RB
- APC
- BRCA1
- BRCA2

Other Molecular Tests

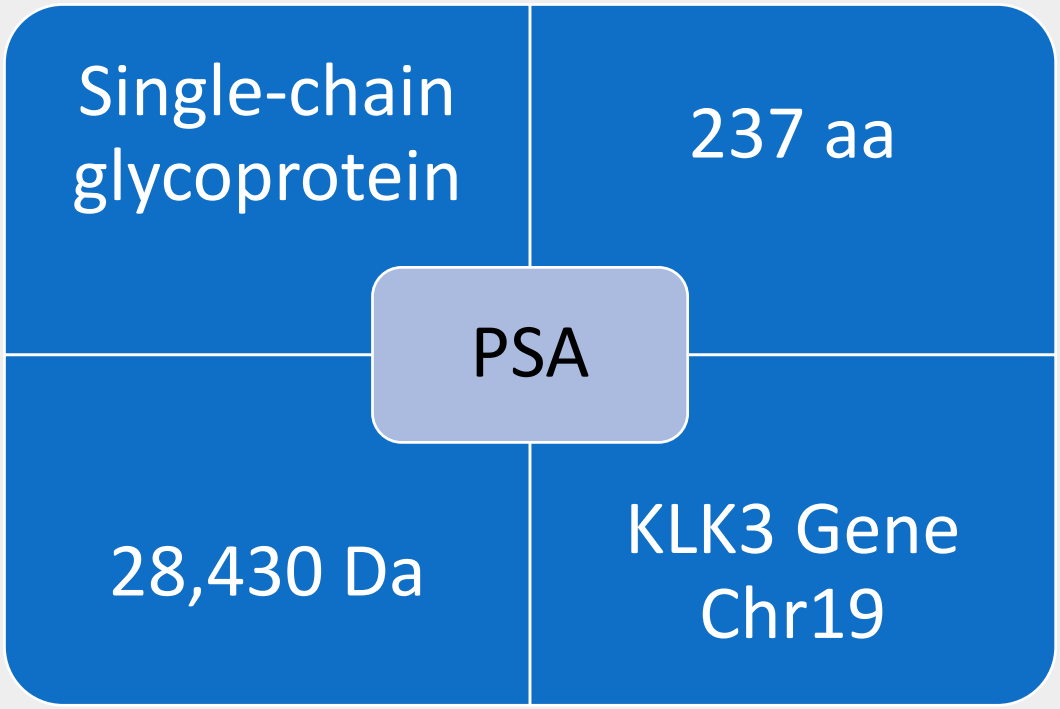
- Prostate Cancer Gene or Antigen
- SNPs
- Cell-Free Nucleic Acids

Microarray-Based Markers

- Roche Amplichip P450
- Oncotype Dx
- MammaPrint

Enzymes: Prostate Specific Antigen

Prostate Specific Antigen (PSA) is a protein that is produced by prostate gland. It is a serine protease of the kallikrein family. PSA has been widely used to screen men for prostate cancer. It is also used to monitor for recurrence after initial treatment and response to therapy.



Prostate Specific Antigen

Molecular Forms of PSA:

1) Complex with α_1-antichymotrypsin (ACT)
2) Complex with α_2-macroglobulin (AMG)
3) Free PSA

Physiological Properties:

The metabolic clearance rate of PSA follows a two-compartment model, with initial half-lives of 1.2 hours for free PSA and 0.75 hour for total PSA, and subsequent half-lives of 22 to 33 hours.

Prostate Specific Antigen

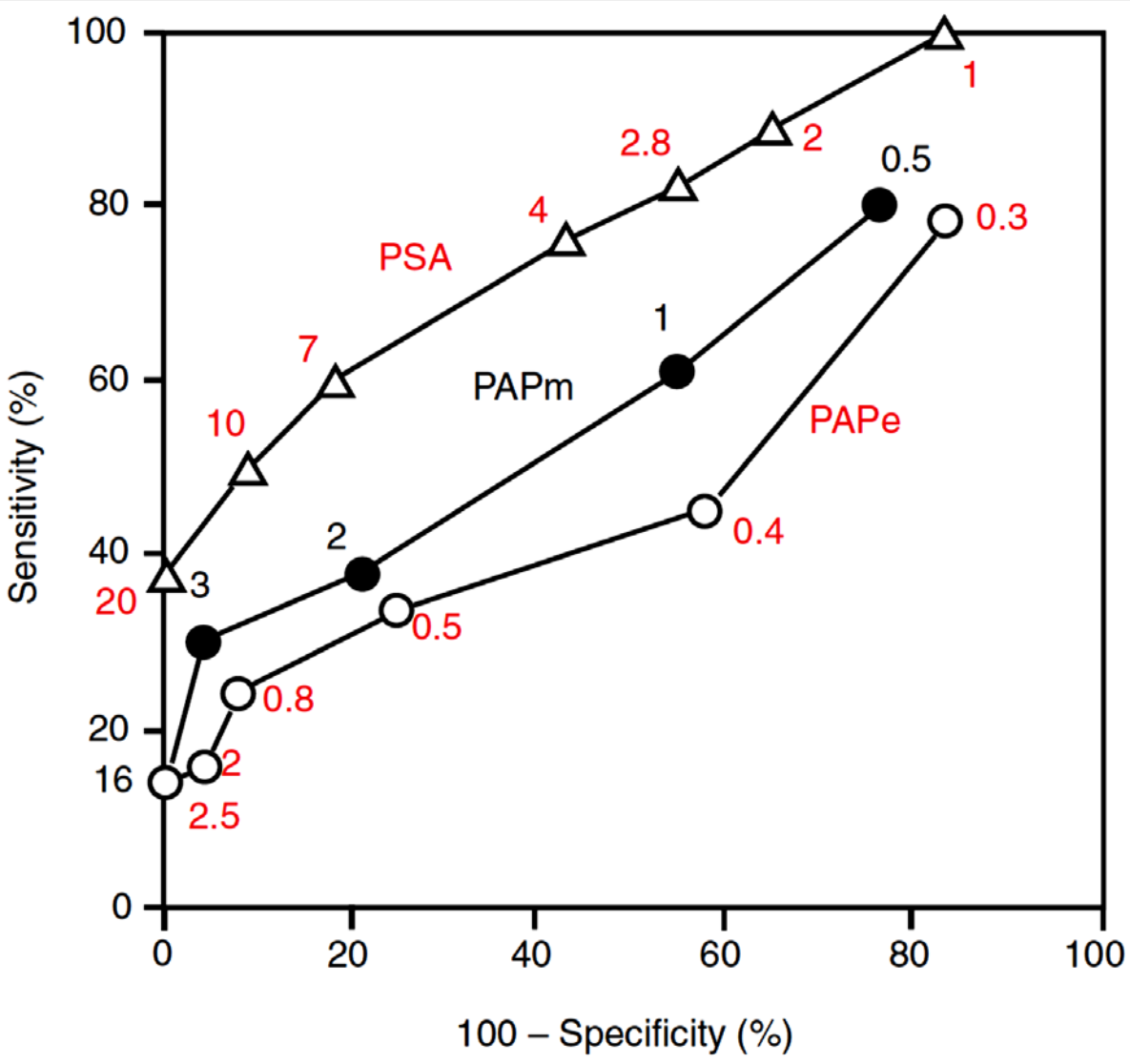
Clinical Applications of PSA:

1) Screening and early detection of prostate cancer
2) Staging of prostate cancer
3) Monitoring treatment

- ✓ PSA is specific for prostate tissue but not for prostate cancer. Thus serum PSA in increased not only by prostate cancer but also by BPH (benign prostatic hyperplasia) and prostatitis.
- ✓ The clinical sensitivity of PSA is 78% at the cutoff of 4.0 μg/L.

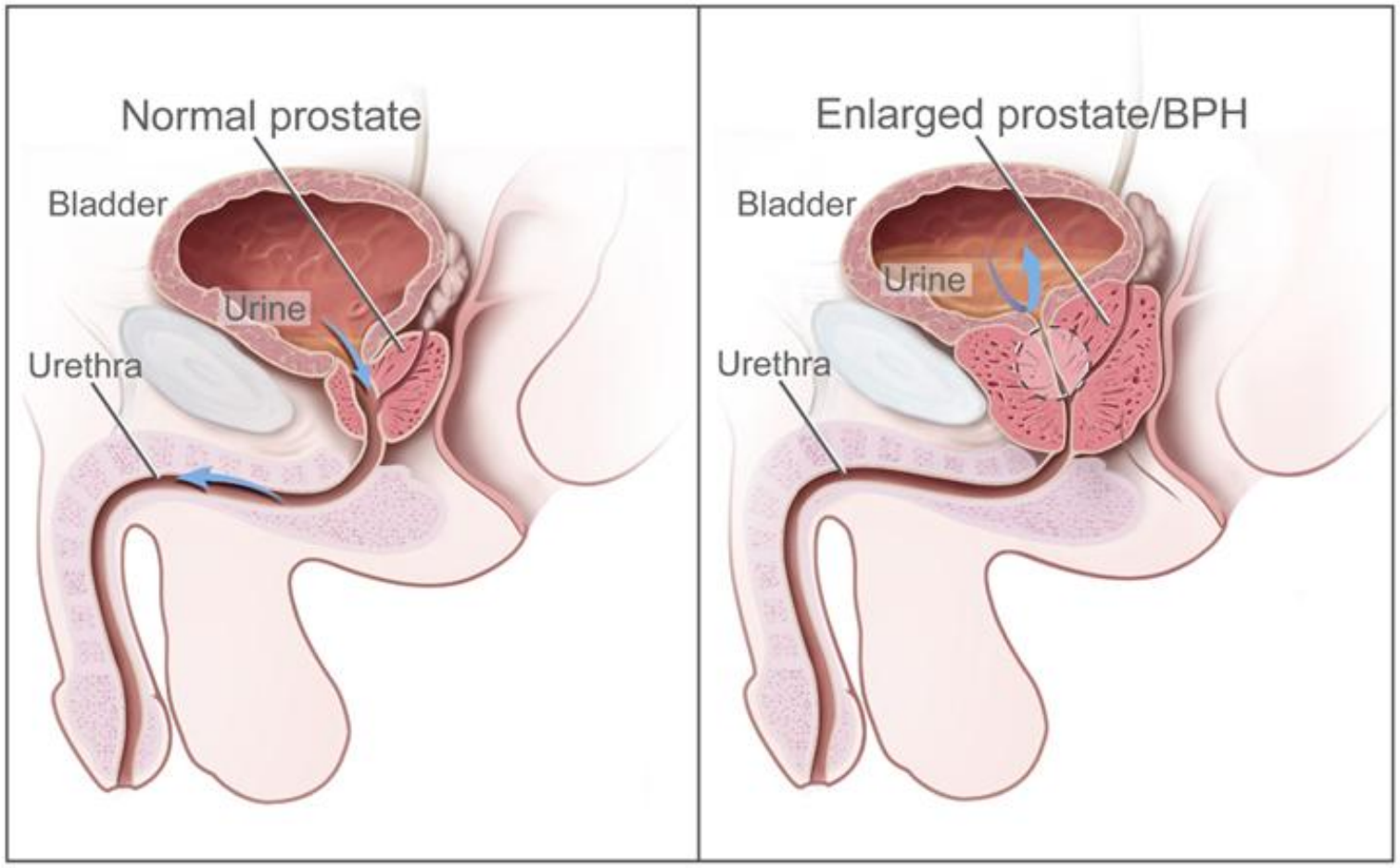
Prostate Specific Antigen

- ✓ PSA: Prostate Specific Antigen (µg/L)
- ✓ PAPm: Prostatic Acid Phosphatase by monoclonal immunoassay (µg/L)
- ✓ PAPe: Enzymatic Prostatic Acid Phosphatase (U/L)



Prostate Specific Antigen

- ✓ Using serum PSA together with DRE (digital rectal exam) is considered more accurate and sensitive than DRE alone.



Prostate Specific Antigen

- ✓ Concentration of PSA:
- ❑ Levels under 4 μg/L are usually considered **normal**
- ❑ Levels over 10 μg/L are usually considered **high**
- ❑ Levels between 4 and 10 μg/L are usually considered **intermediate**

- ✓ If a man had a PSA level above 4.0 μg/L, doctors would often recommend a prostate biopsy to determine whether prostate cancer was present.
- ✓ A **continuous rise** in a man's PSA level over time may also be a sign of prostate cancer.

Prostate Specific Antigen

- ✓ The concentration of PSA serves as a guide and is more useful in evaluating the presence of metastasis.
- ✓ Patient with PSA concentration less than **20 µg/L** rarely have bone metastasis.
- ✓ The greatest clinical use of PSA involves monitoring of definitive treatment for prostate cancer, such as:
  1. Radical prostatectomy
  2. Radiation therapy
  3. Antiandrogen therapy
- ✓ After radical prostatectomy, the PSA concentration should fall to below the detection limit of assay within **2 to 3 weeks**.
- ✓ Sandwich immunoassays using labels such as enzymes, fluorescence or chemiluminescence are used to measure PSA.

Prostate Specific Antigen

Improving the PSA Test:

1) Free versus total PSA
2) PSA density of the transition zone
3) Age-specific PSA reference ranges
4) PSA velocity and PSA doubling time
5) Pro-PSA
6) IsoPSA
7) PSA in combination with other protein biomarkers

Improving the PSA Test

- Free versus total PSA:

The amount of **free PSA** divided by the **total amount of PSA**. Some evidence suggests that a **lower proportion** of free PSA may be associated with more aggressive cancer.

- PSA density of the transition zone:

The blood level of PSA divided by the volume of the **transition zone** of the prostate. Some evidence suggests that this measure may be more accurate at detecting prostate cancer than the standard PSA test.

Improving the PSA Test

- PSA velocity and PSA doubling time:

PSA velocity is the rate of change in a man's PSA level over time, expressed as **µg/L per year**. PSA doubling time is the period of time over which a man's PSA level **doubles**. Some evidence suggests that the rate of increase in a man's PSA level may be helpful in predicting whether he has prostate cancer.

- PSA in combination with other protein biomarkers:

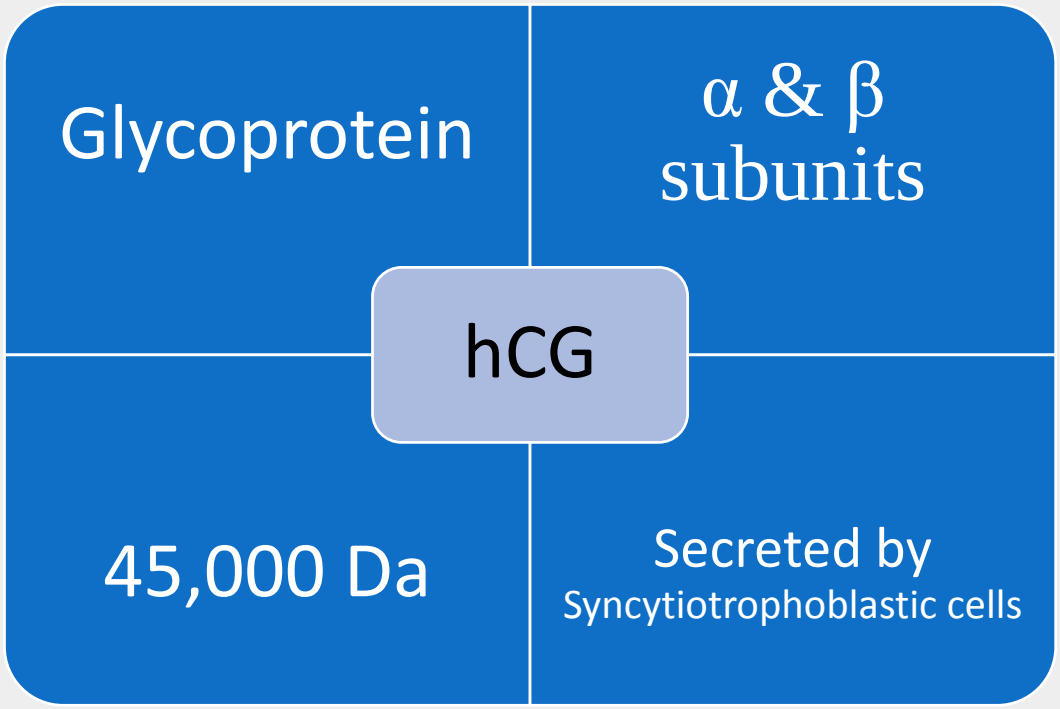
Tests that combine measurements of PSA in blood with measurements of other biomarkers linked to prostate cancer in **blood or urine** are being studied for their ability to distinguish high-risk disease. These other biomarkers include **kallikrein-related peptidase 2**, **prostate cancer antigen 3 (PCA3)**, and the **TMPRSS2-ERG gene fusion**.

Hormones as Tumor Markers

Hormone	Type of Cancer
ACTH	Cushing syndrome, lung (small cell)
ADH	Lung (small cell), adrenal cortex, pancreatic, duodenal
Calcitonin	Medullary thyroid
GH	Pituitary adenoma, renal, lung
Prolactin	Pituitary adenoma, renal, lung
VIP	Pancreatic, bronchogenic, pheochromocytoma, neuroblastoma
Parathyroid hormone	Liver, renal, breast, lung

Hormones: Human Chorionic Gonadotropin

Elevated human chorionic gonadotropin (hCG) are seen in pregnancy, **trophoblastic disease** and **germ cell tumors**. hCG is a useful tumor marker for the tumors of the placenta (trophoblastic tumors) and for some tumors of the testis.



Human Chorionic Gonadotropin

α subunit → Common to LH, FSH & TSH

β subunit → Unique to hCG

Human Chorionic Gonadotropin

- **Gestational trophoblastic disease** (GTD) is a broad term encompassing both benign and malignant growths arising from products of conception in the uterus.

- Two factors have consistently been associated with an increased risk of GTD:
  1) Maternal age
  2) History of hydatidiform mole

Human Chorionic Gonadotropin

Clinical Applications of hCG:

- ✓ Patients with **trophoblastic tumors** typically have elevated concentration of hCG, more than 1 million IU/L.
- ✓ Elevated serum concentration of hCG are found in 45% to 60% of biliary and pancreatic cancers and in 10% to 30% of many other cancers, including bladder, renal, prostate, liver, colorectal, non-small cell lung, breast, and head and neck cancers.
- ✓ hCG is most useful for **monitoring** treatment and **progression** of trophoblastic disease.
- ✓ A patient with initial hCG concentration greater than 400,000 IU/L is considered at high risk for **treatment failure**.

Human Chorionic Gonadotropin

Analytical Methods for hCG:

- ✓ As a tumor marker, a total β-hCG assay is preferred because many cancer patient produce notable amounts of free β-subunit.
- ✓ Most hCG assays use sandwich immunoassay method.

- ✓ Additional forms of hCG including:
  1) Intact hCG
  2) Nicked hCG
  3) α-hCG
  4) cfβ-hCG (core fragment β-hCG)

Oncofetal Antigens as Tumor Markers

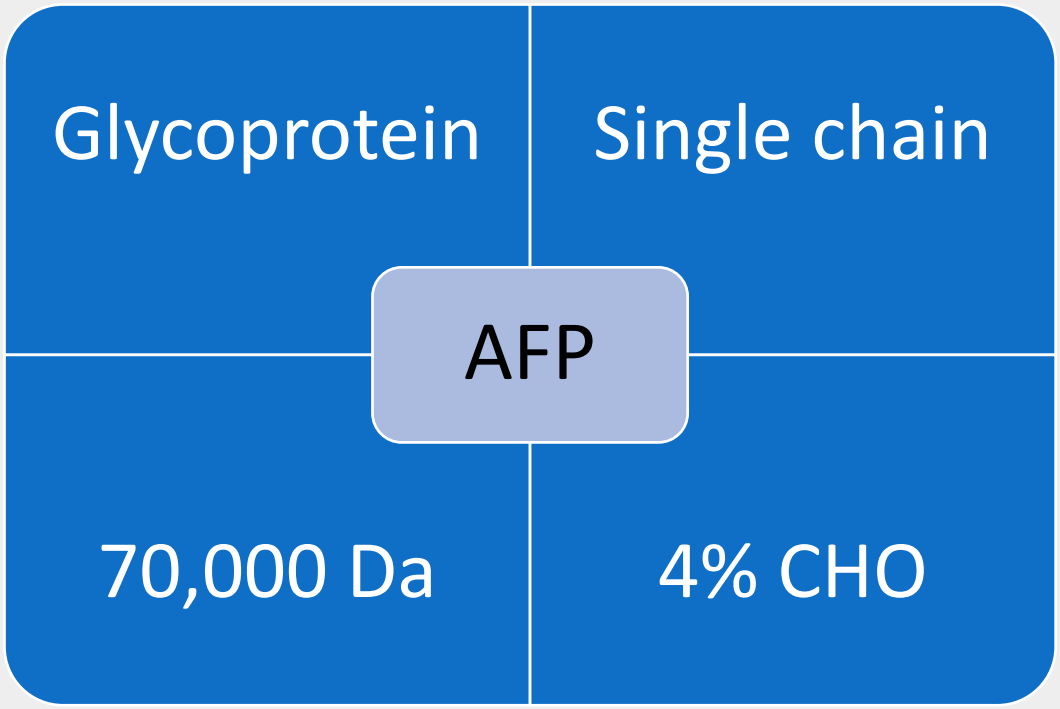
Oncofetal antigens are proteins produced during **fetal life**. In cancer patients, these proteins often **reappear**, showing that certain genes are **reactivated** as the result of the **malignant transformation** of cells.

Antigen	Type of Cancer
AFP	Hepatocellular, germ cell (nonseminoma)
Oncofetal antigen	Colon
Carcinofetal ferritin	Liver
CEA	Colorectal, gastrointestinal, pancreatic, lung, breast
Pancreatic oncofetal	Pancreatic
Squamous cell antigen	Cervical, lung, skin, head and neck
Tennessee antigen	Colon, gastrointestinal, bladder
Tissue polypeptide antigen	Breast, colorectal, ovarian, bladder

Oncofetal Antigens: α-Fetoprotein

α-Fetoprotein (AFP) is a marker for hepatocellular and germ cell (nonseminoma) carcinoma.

AFP is synthesized in large amounts during embryonic development by the fetal yolk sac and liver.



α-Fetoprotein

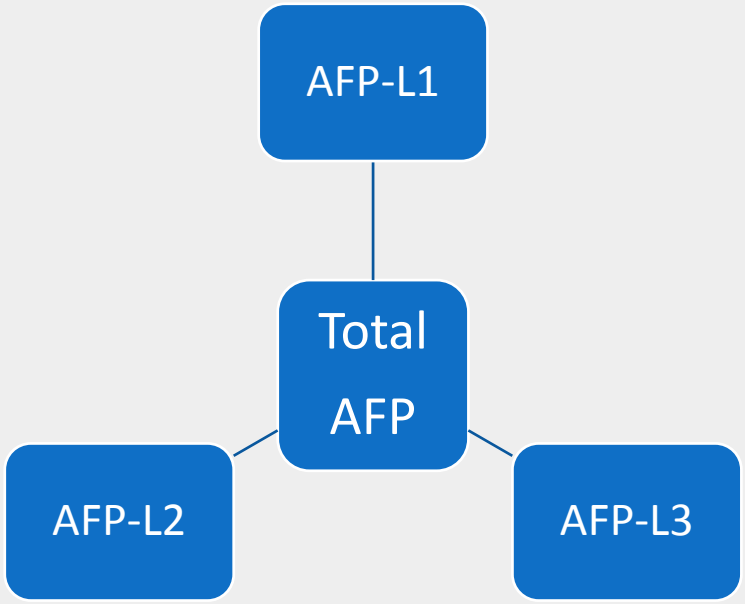
Clinical Applications of AFP:

- ✓ AFP is one of the major proteins in the fetal circulation, but its maximum concentration is about 10% that of albumin.
- ✓ AFP is genetically and structurally related to albumin.
- ✓ The serum AFP concentration is less than **10 µg/L** in healthy adults.
- ✓ Except in the pregnant patients, AFP concentrations greater than **1000 µg/L** are indicative of cancer.

	Serum AFP Concentration as Tumor Marker
Early Marker	10-20 µg/L
Cancer	>1000 µg/L

α-Fetoprotein

- ✓ The combined use of AFP and hCG is useful in monitoring patients with **germ cell tumors**. Elevation of either marker indicates recurrence of disease or development of metastasis.
- ✓ The success of chemotherapy can be assessed by calculating the decrease in concentration of both markers using half-lives of AFP (5 days) and hCG (12 to 20 hours).



α-Fetoprotein

AFP-L1	The majority of total AFP in nonmalignant liver disease
AFP-L2	Mostly derived from yolk sac tumors
AFP-L3	Produced by cancer cells in hepatocellular carcinoma

- The **AFP-L3%** test is indicated for use in risk assessment for development of **hepatocellular carcinoma** in patients who have **chronic liver disease**, and a cutoff of **10%** is used.

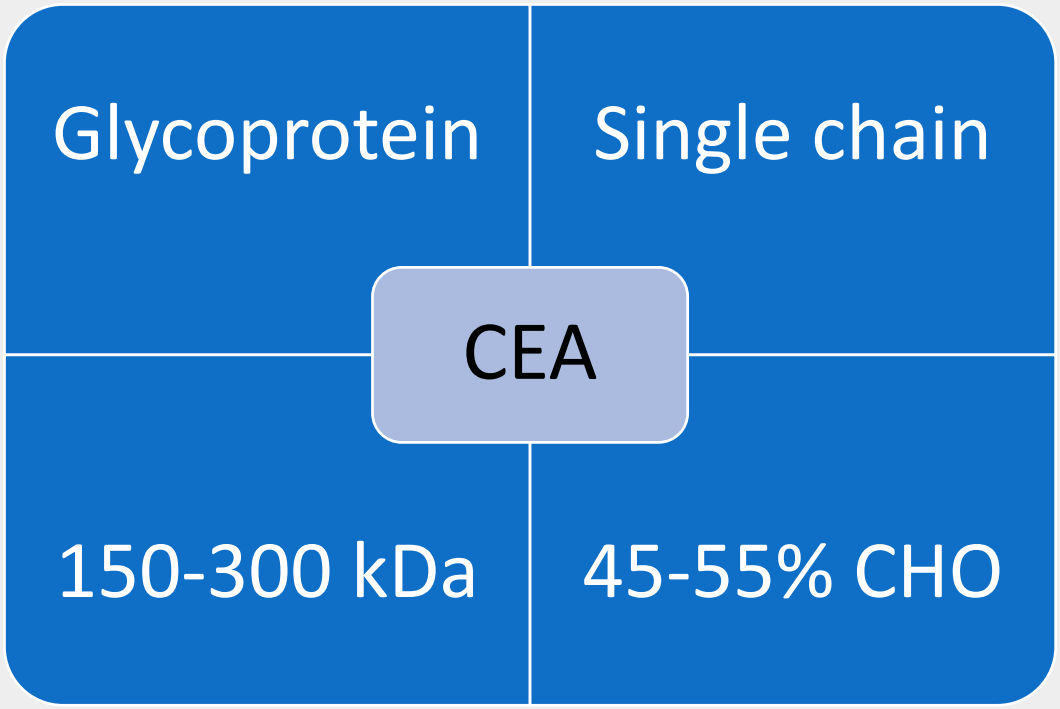
α-Fetoprotein

- ✓ AFP-L3% is measured using a microfluidic-based instrument that utilizes immunochemical and electrophoretic techniques.
- ✓ AFP is reported in units of ng/mL and kIU/L
- ✓ One international unit (IU) of AFP is equivalent to 1.21 ng

Oncofetal Antigens: Carcinoembryonic Antigen

Carcinoembryonic Antigen (CEA) is a marker for colorectal, gastrointestinal, lung, and breast carcinoma.

CEA is part of the immunoglobulin gene superfamily.



Carcinoembryonic Antigen

Clinical Applications of CEA:

- ✓ Persistently elevated concentrations of CEA that are **5 to 10 times** the upper reference limit strongly suggest the presence of **colon cancer**.
- ✓ In colon cancer, CEA concentrations correlate with the **stage** of disease. High **pretreatment** CEA concentrations are associated with greater likelihood of developing **metastasis**.
- ✓ CEA in also useful for **monitoring** breast, lung, gastric, and pancreatic carcinoma. In breast cancer, elevated CEA is associated with metastasis.

Carcinoembryonic Antigen

Serum CEA Concentration	
Nonsmokers	<3 μg/L
Smokers	<5 μg/L

- ✓ Most assays use immunometric format for determination of serum CEA.
- ✓ CEA may be elevated in patients with **benign conditions**, such as cirrhosis, pulmonary emphysema, rectal polyps, benign breast disease, and ulcerative colitis.

Mucins as Tumor Markers

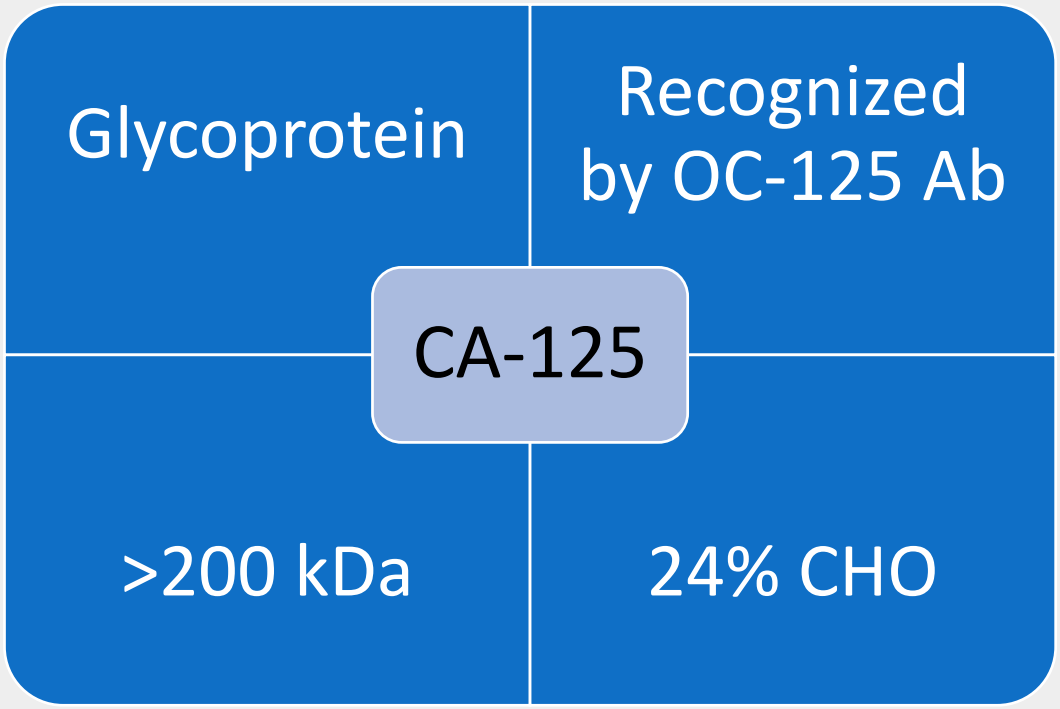
Carbohydrate-related tumor markers may be antigens in the tumor cell surface, or secreted by the tumor cells.

Mucin	Type of Cancer
CA 125	Ovarian, endometrial
CA 15-3	Breast, ovarian
CA 549	Breast, ovarian
CA 27.29	Breast
MCA	Breast, ovarian
DU-PAN-2	Pancreatic, ovarian, gastrointestinal, lung

Mucins: CA-125

CA-125 is a marker for monitoring ovarian cancer.

CA-125 is produced by epithelial ovarian tumors and other pathological and normal tissue of mullerian duct origin.



CA-125

Clinical Applications of CA-125:

- ✓ In ovarian carcinoma, CA-125 is elevated in 50% of patients with stage *I* disease, 90% with stage *II* disease, and more than 90% with stage *III* and *IV*.
- ✓ The concentration of CA-125 correlates tumor size and staging.
- ✓ In healthy population, the upper limit of CA-125 is **35 kU/L**
- ✓ CA-125 cannot be used to differentiate ovarian cancer from other malignancies. It is elevated in nonovarian carcinoma, such as: endometrial, pancreatic, lung, breast, colorectal, and other gastrointestinal tumors.

CA-125

Improving CA-125 Test:

- ✓ Improving clinical usefulness of CA-125 by:
  1) Combining with transvaginal sonography
  2) Assessing changes in concentrations measured over time
  3) Using multimarker panel

Analytical Method for CA-125:

- ✓ **M11** is a monoclonal antibody as the capture antibody, and **OC 125** is conjugated antibody.

CA 15-3

- ✓ CA 15-3 is found in some **benign** and **malignant** disease.
- ✓ It is most useful in **monitoring therapy** and **disease progression** in **metastatic breast cancer** patients.
- ✓ Elevated CA 15-3 are also found in pancreatic, lung, ovarian, colorectal and liver cancer.
- ✓ The upper limit of CA 15-3 in healthy subjects, is **25 kU/L**, with this cutoff, 5.5% of normal individuals, **23%** of patient with primary breast cancer, and 69% of those with metastatic breast cancer have elevated CA 15-3.
- ✓ CA 15-3 **should not be used** in to diagnosis primary breast cancer.
- ✓ MAb **115D8** and MAb **DF3** are used to detect CA 15-3 through immunoassay methods.

CA 27.29

- CA 27.29 is approved by FDA for clinical use for **detecting recurrent breast cancer** in patients with stage *II* or stage *III* disease and for **monitoring therapy** in patient with stage *IV* (metastatic) disease.
- The upper limit of CA 27.29 is **37.7 kU/L** in healthy population.
- CA 27.29 is detected through immunoassay methods using CA 27.29 MAb.

Oncogenes and Tumor-Suppressor Genes as Tumor Markers

- Oncogenes:

Proto-oncogenes are normal cellular genes that are similar to tumor virus genes. Proto-oncogenes are involved in normal cellular processes such as **proliferation** and **signaling pathways**. **Activator mutations** in proto-oncogenes are found to be associated with cancers.

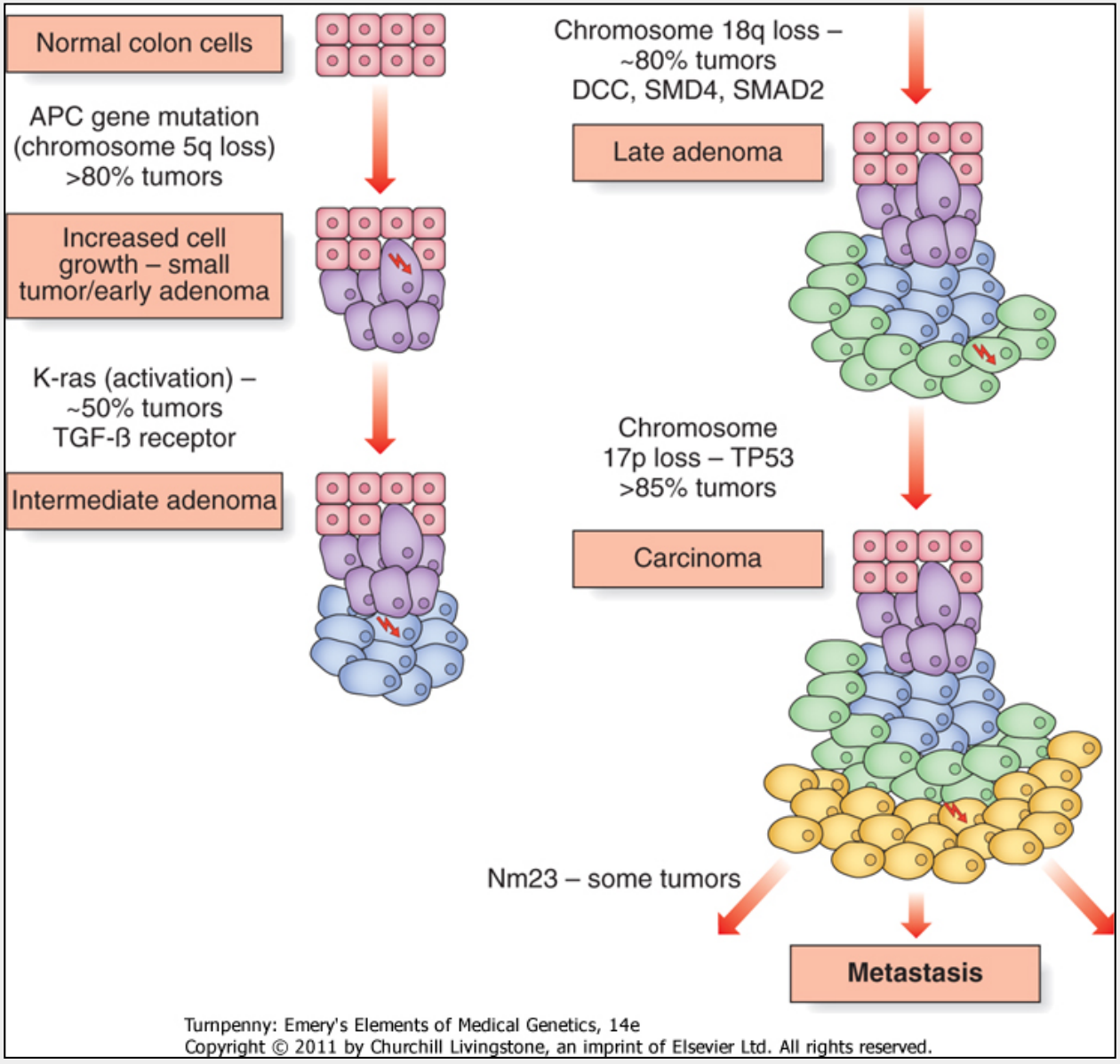
- Tumor-Suppressor Genes:

Healthy cells contain genes that suppress the expression of malignancy. **Deactivating mutations** in tumor-suppressor genes are involved with cancers.

Oncogenes and Tumor-Suppressor Genes as Tumor Markers

Oncogenes	Cellular Function	Related Cancers
RAS	Proliferation, cell growth	AML(N-ras), leukemia(K-ras)
C-myc	Transcriptional regulation	B and T cell lymphoma
HER2 (c-erbB2)	Receptor tyrosine kinase	Breast, ovarian, GI tumors
BCL2	Apoptosis	Leukemia, lymphoma
BCR/ABL	Signal transduction protein	CML, RCC, GIST
Tumor-Suppressor Genes	**Cellular Function**	**Related Cancers**
Rb	Cell cycle regulation	Retinoblastoma
TP53	Transcriptional regulation, apoptosis	Breast, colorectal, lung, liver, …
p21	Cell cycle progression	Breast, pancreatic, …
APC	Cell-cell interaction	Colorectal
NF1	Proliferation, cell growth, negative regulator	Neurofibromatosis type 1
BRCA1/2	DNA repair	Breast cancer
PTEN	Lipid kinase	Glioblastoma, endometrial, prostate

Oncogenes and Tumor-Suppressor Genes

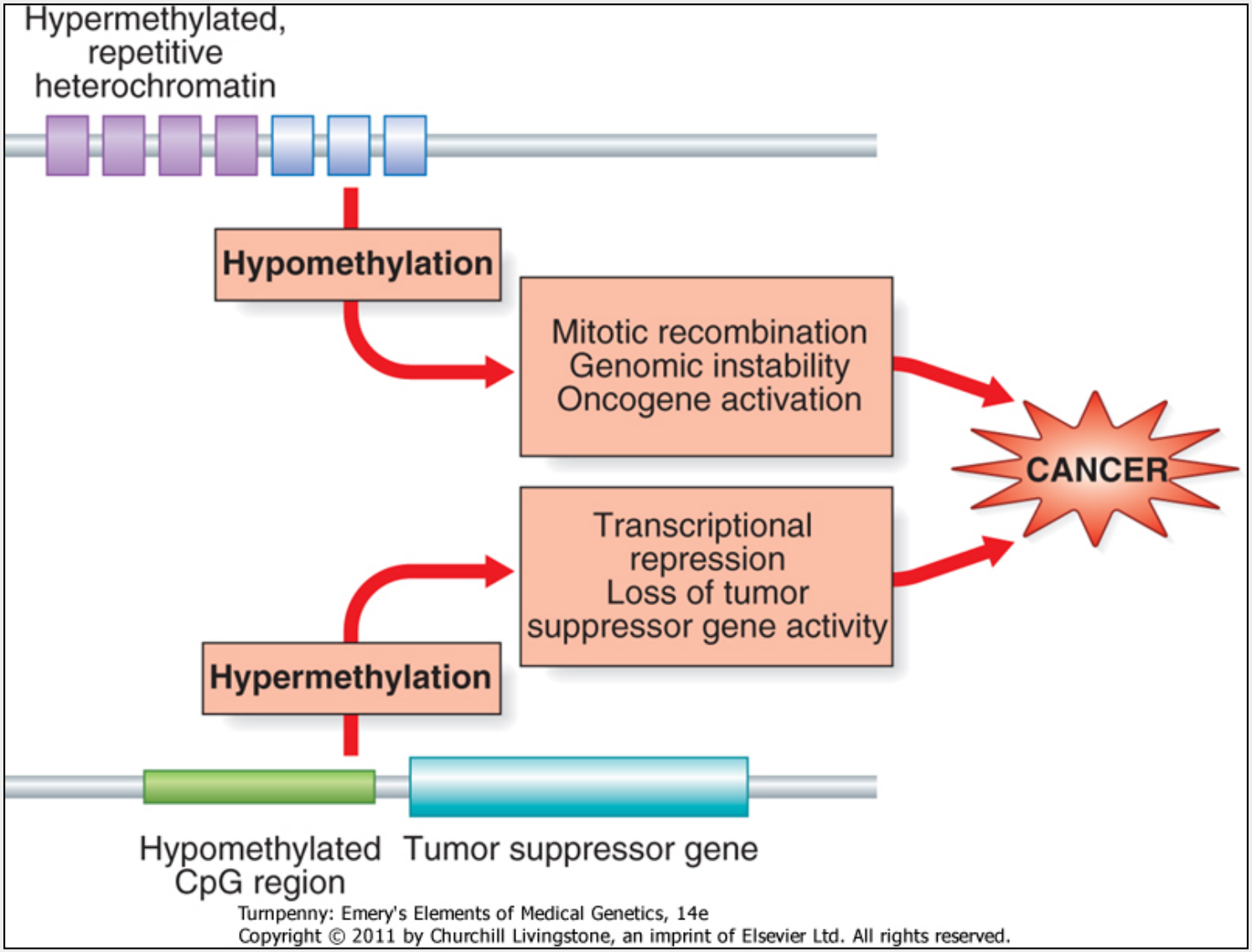


Cell-Free Nucleic Acids

- ✓ Circulating **DNA and RNA** have been proposed as markers for certain types of cancer.
- ✓ To use circulating DNA as a cancer marker, a mechanism must differentiate normal DNA from **neoplastic DNA**:
  1) Microsatellite analysis
  2) Detecting common cancer-causing chromosomal translocations
  3) Detecting epigenetic alterations

- ✓ Cell-free nucleic acids have been detected in bronchial lavage fluid from lung cancer patients and in plasma from colorectal cancer patients.

Epigenetic Effect



Microarray-Based Markers

- ✓ Microarray-based genotyping is a molecular technique used to simultaneously screen hundreds to thousands of gene markers per individual. It is associated with relatively low cost and consequently is useful for large populations.

- ✓ Three well known microarray assay:

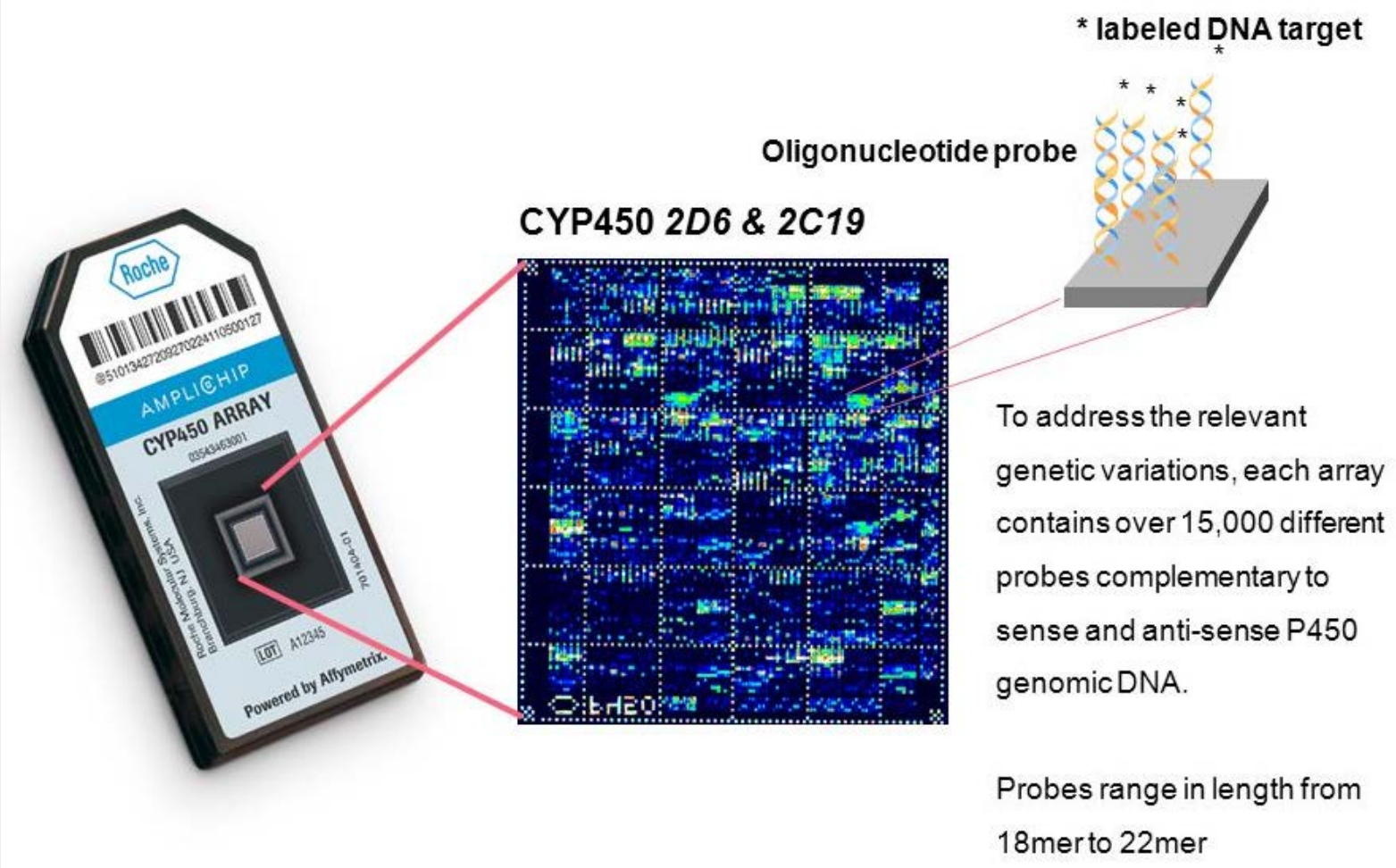
1) Roche Amplichip P450

2) Oncotype Dx

3) MammaPrint

Roche Amplichip P450

Roche Amplichip P450 detects variants in P450 genes that are involved in metabolism of many drugs.



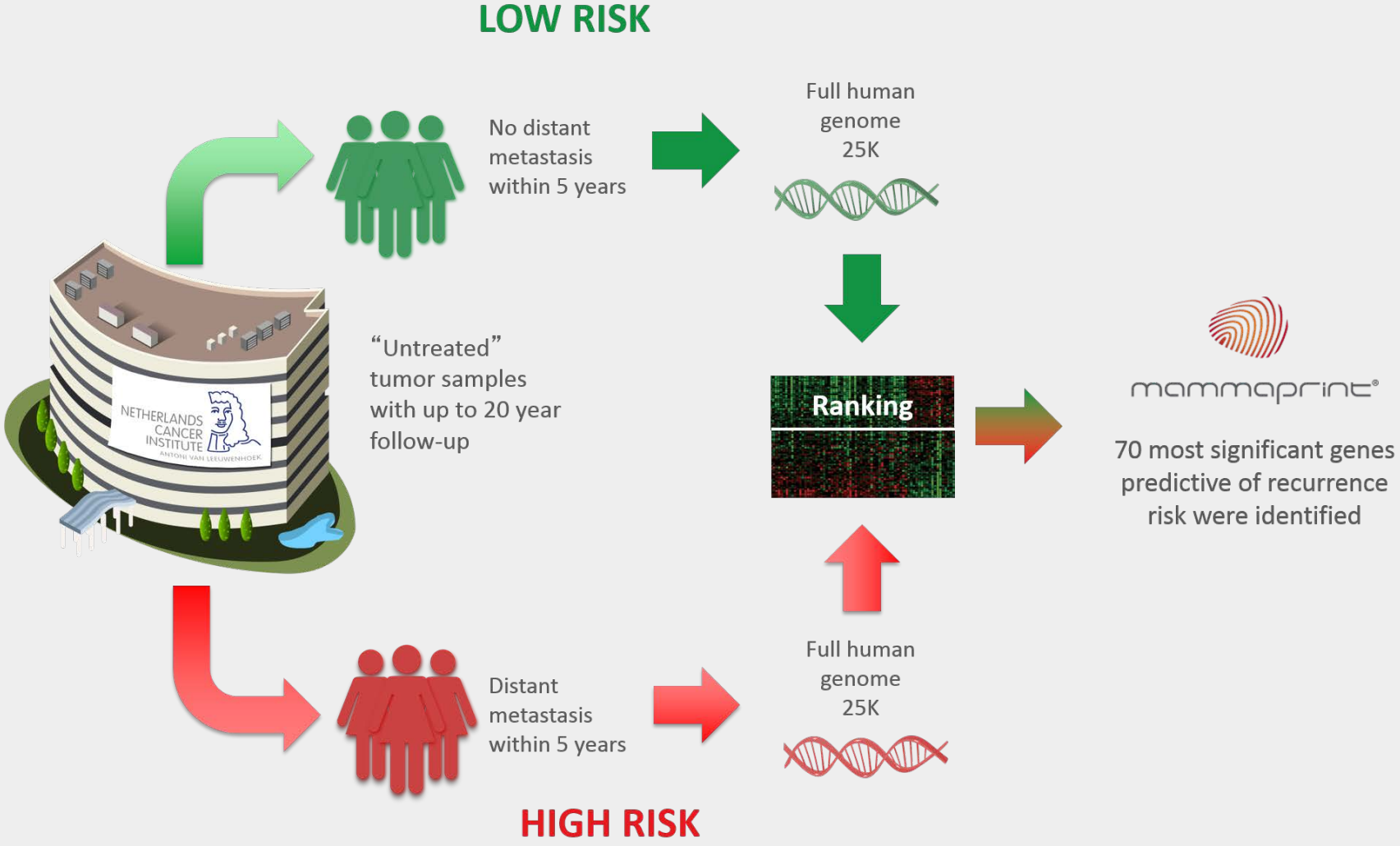
Oncotype Dx

Oncotype Dx is available for breast, prostate, and colon cancer.

EXAMPLE Case Study Comparison - Clinical use of the DCIS Score result	
63-YEAR-OLD PATIENT	**66-YEAR-OLD PATIENT**
Menopausal Status: **Postmenopausal** Tumor Type: **DCIS** Tumor Size: **1.6 cm** ER Status (IHC): **Positive** Nuclear Grade: **2** Comedo Necrosis: **Absent** Margin Width: **2 mm**	Menopausal Status: **Postmenopausal** Tumor Type: **DCIS** Tumor Size: **1.0 cm** ER Status (IHC): **Positive** Nuclear Grade: **2** Comedo Necrosis: **Absent** Margin Width: **2 mm**
DCIS Score result: **3**	DCIS Score result: **57**
10% risk of any local recurrence (DCIS or invasive)	**23%** risk of any local recurrence (DCIS or invasive)
3% risk of an invasive local recurrence	**13%** risk of an invasive local recurrence
Cases submitted by Charles Leonard, MD, from Rocky Mountain Cancer Centers.	

MammaPrint

MammaPrint evaluates the risk of breast cancer recurrence.



Measurement of Tumor Markers in Kermanshah Reference Lab

- AFP
- PSA
- CA125
- CA15-3
- CA19-9
- CEA
- Tg

References

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Any Questions?

Thanks for Your Attention