Characteristics of cancer cells

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Educational Aims

- Cancer cells vs healthy cells
- Cancer energy production
- Cancer genetics
- Carcinogenesis
- Metastasis
- Stage and grade

Cancer and Cancer Cells

- Cancer is a disease that occurs when cells become abnormal and grow out of control. Normal cells grow—and then die—when they are given signals to do so. Cancer cells ignore these signals and continue to multiply. Cancer cells also may form a tumor at the original site and then spread and form new tumors in other places

Types of Cancer Cells

- Carcinomas

Carcinomas are cancers that arise in epithelial cells that line body cavities. The most common type of cancer cells, carcinomas are named after the type of epithelial cells that mutated. These include:

- Adenocarcinoma: Cancer that affects epithelial cells in glandular tissue, such as the breast, colon, and prostate
- Basal cell carcinoma: Cancer that affects epithelial cells in the basal (lower) layer of the epidermis (skin)
- Squamous cell carcinoma: Cancer that affects squamous epithelial cells, which are found just beneath the outer surface of the skin and in the stomach, intestines, lungs, bladder, and kidneys
- Transitional cell carcinoma: Cancer that affects transitional epithelium (urothelium), which are various-sized, multi-layered epithelial cells in the bladder, ureters, and kidneys

- Sarcomas

Sarcomas are cancers that arise in bone, muscle, blood, fat, and other soft tissue cells known as mesenchymal cells.

- Leukemia

Leukemia cells and leukemic blast cells are abnormal white blood cells that form in bone marrow stem cells, where blood cells are made. Unlike some other cancers, leukemia cells do not bind together to form a tumor.

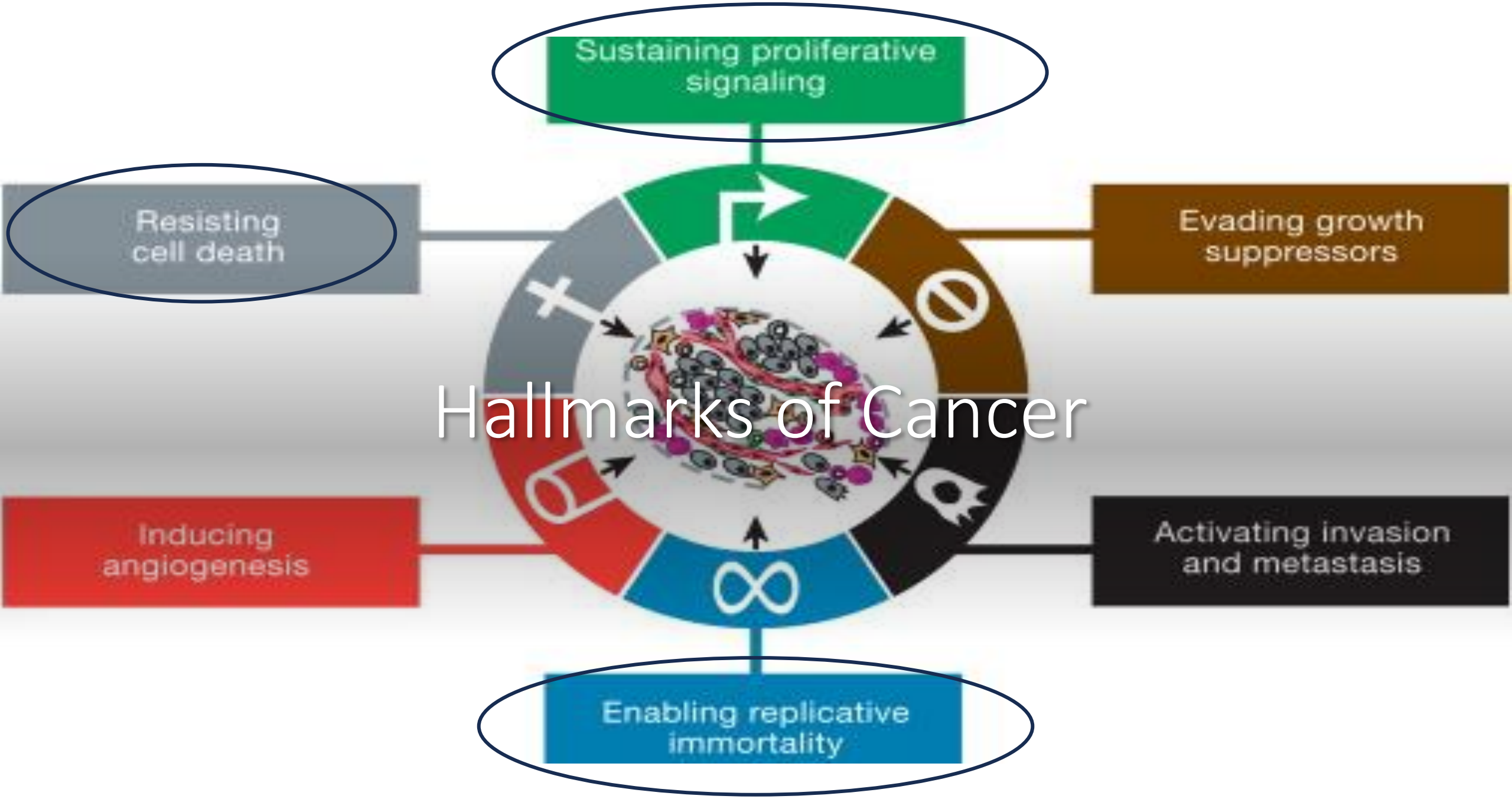
- Lymphomas

Lymphomas are blood-related cancers that arise from lymphoid tissues in the lymphatic system, a part of the immune system that runs throughout the body.

- Multiple Myeloma

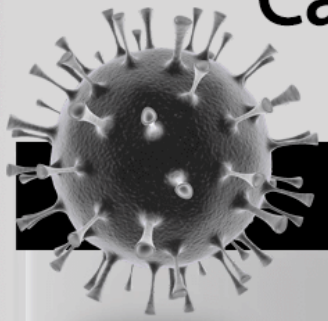
Multiple myeloma is a type of blood cancer that develops in plasma cells—white blood cells that produce antibodies. They occur when a plasma cell becomes abnormal, then divides to replicate, forming myeloma cells.

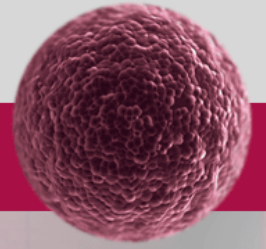
https://www.youtube.com/watch?v=8uWWpdyf6_c



Hallmarks of Cancer

Cancer Cell & Normal Cell Characteristics





Cancer Cell	Normal Cell
Shape: Irregular	**Shape:** Regular
Nucleus: Larger, darker	**Nucleus:** Proportionate size
Growth: Out of control	**Growth:** In control, systematic
Maturation: Immature - Doesn't mature	**Death:** Mortal (Apoptosis)
Communication: Doesn't communicate	**Maturation:** Mature (Cell differentiation)
Visibility: Invisible to immune cells	**Communication:** Communicates
Blood Supply: Tumor angiogenesis	**Visibility:** Visible to immune cells, with ID
Oxygen: Doesn't like or require oxygen	**Blood Supply:** Angiogenesis during repair
Glucose: Loves, craves glucose	**Oxygen:** Requires oxygen
Energy Efficiency: Very low (5%)	**Glucose:** Requires some glucose
Amount of ATP: 2 units of ATP	**Energy Efficiency:** Very high (95%)
Cell Environment: Acidic	**Amount of ATP:** 36 units of ATP
Nutrient Preference: Glucose	**Cell Environment:** Alkaline
	Nutrient Preference: Fat, Ketone, Glucose

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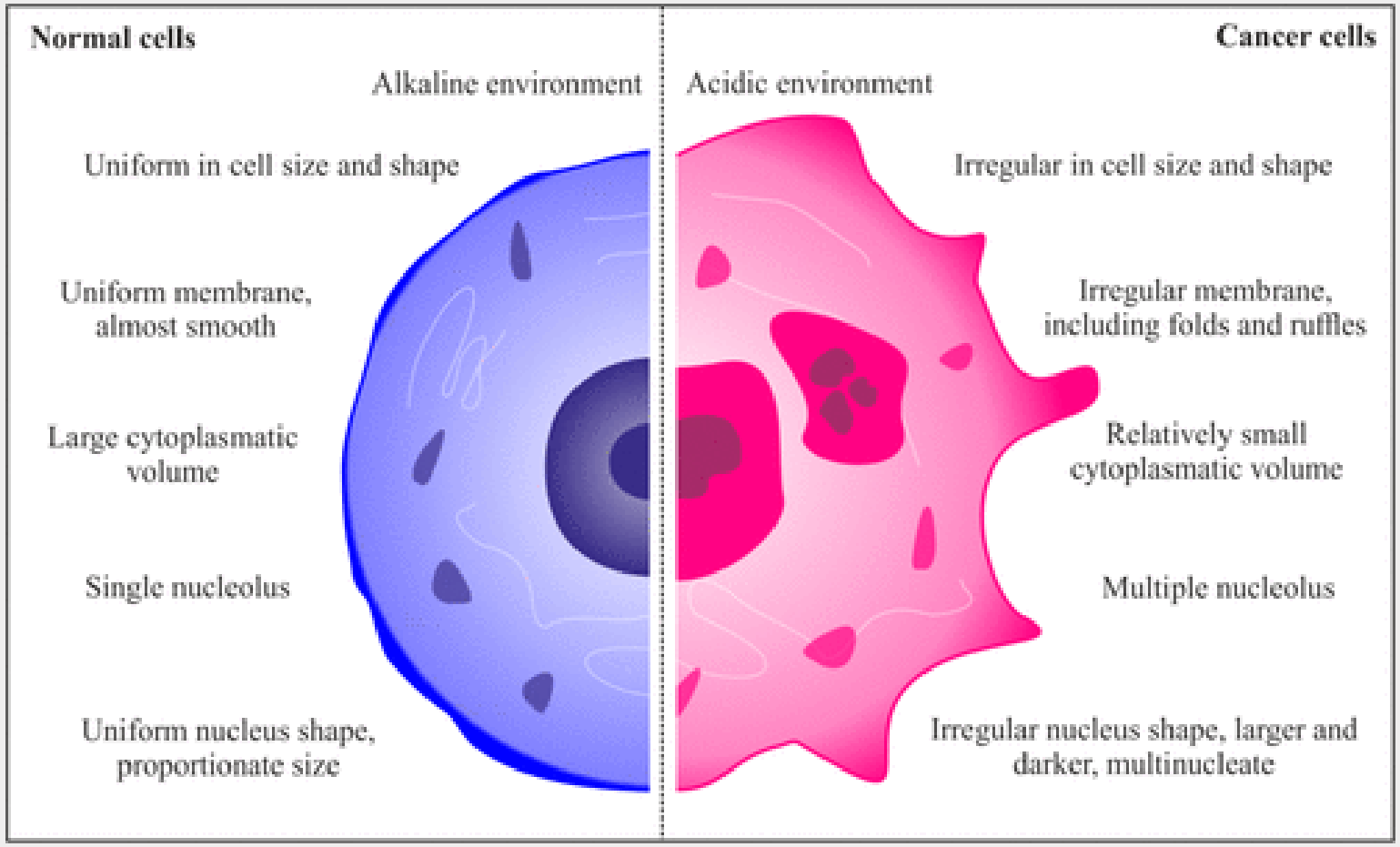
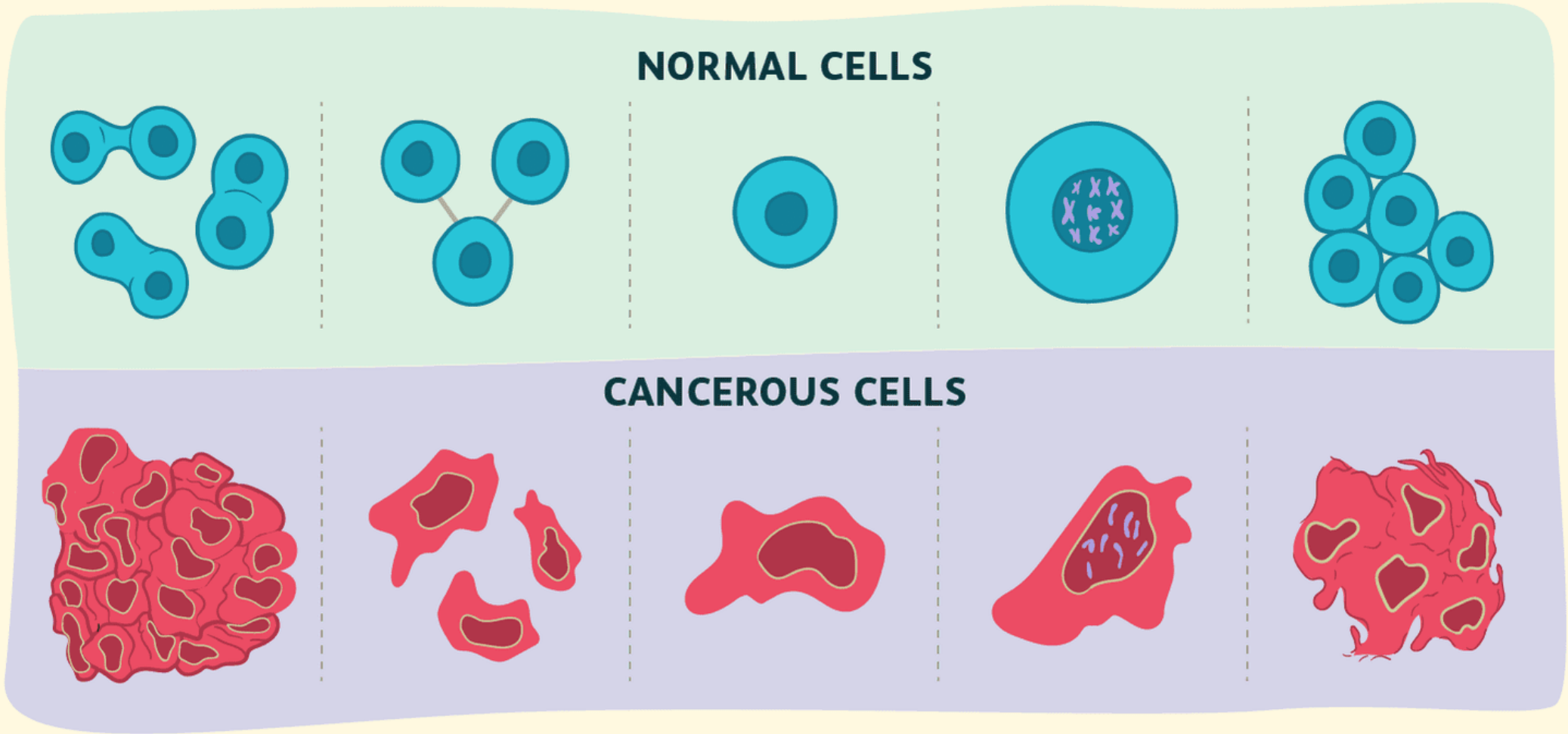
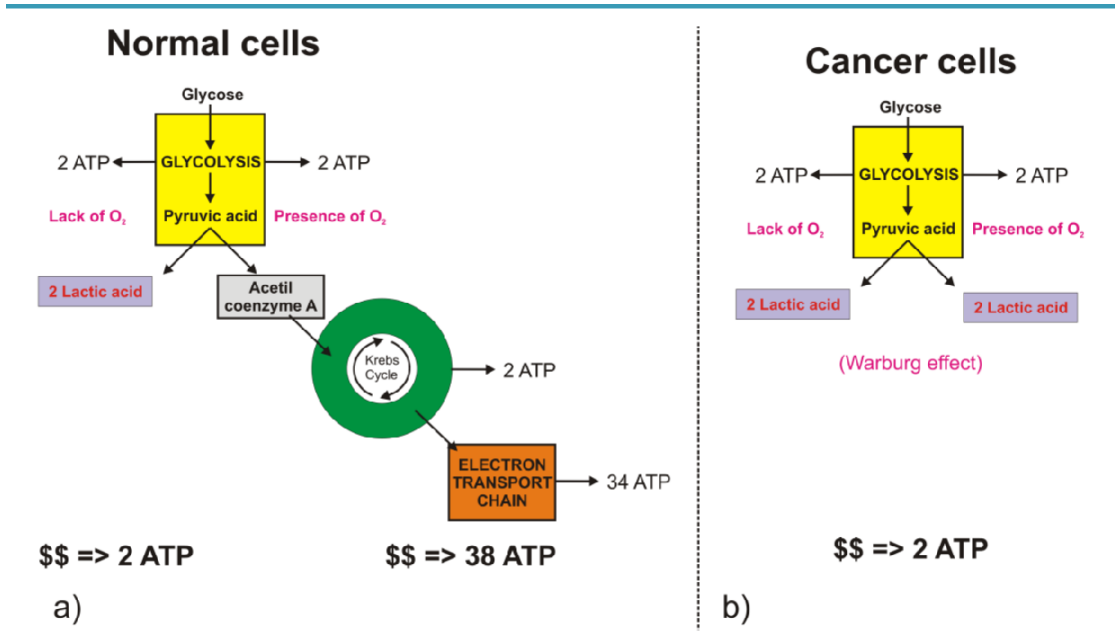

Normal cells
Cancer cells
Alkaline environment
Acidic environment
Uniform in cell size and shape
Irregular in cell size and shape
Uniform membrane, almost smooth
Irregular membrane, including folds and ruffles
Large cytoplasmatic volume
Relatively small cytoplasmatic volume
Single nucleolus
Multiple nucleolus
Uniform nucleus shape, proportionate size
Irregular nucleus shape, larger and darker, multinucleate


NORMAL CELLS
CANCEROUS CELLS
Many cells that continue to grow and divide
Variations in size and shapes of cells
Nucleus that is larger and darker than normal
Abnormal number of chromosomes arranged in a disorganized fashion
Cluster of cells without a boundry

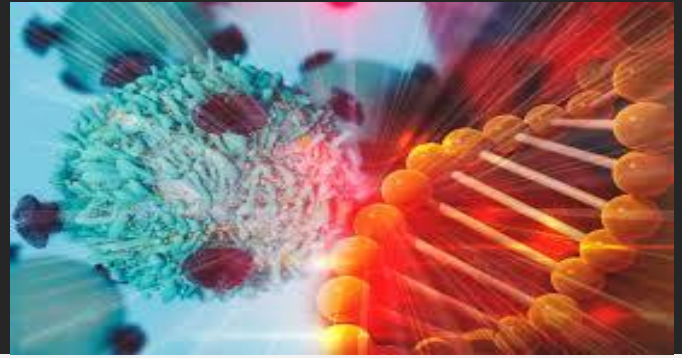
Cancer cells and normal cells differ in their energy production processes

- **Normal cells generate energy by converting glucose into a molecule called ATP through a process called cellular respiration. This process requires oxygen and produces carbon dioxide as a waste product. In contrast, cancer cells can generate energy through a process called glycolysis, which doesn't require oxygen. This process produces lactic acid as a waste product, which can build up and create an acidic environment that can damage nearby tissues. Furthermore, cancer cells may also rely on other sources of energy such as glutamine, a type of amino acid. Overall, the differences in energy production between cancer cells and normal cells are one of the factors that contribute to the abnormal growth and behavior of cancer cells.**

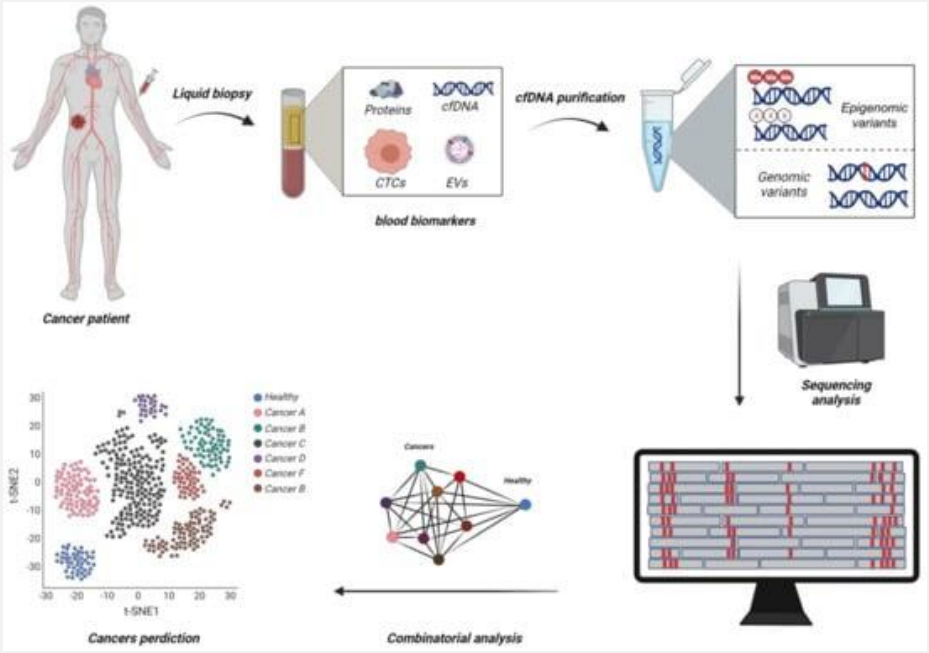


2: Difference in glucose metabolic pathways as a function of oxygen abundance in a) normal cells, and b) cancer cells.

Cancer genetics



In a typical study of cancers in humans, the sequences of all 20,000 genes were determined in about 3,300 different tumors, and then compared with the gene sequences in noncancerous tissue from the same patient. Almost 300,000 mutations were detected in all.



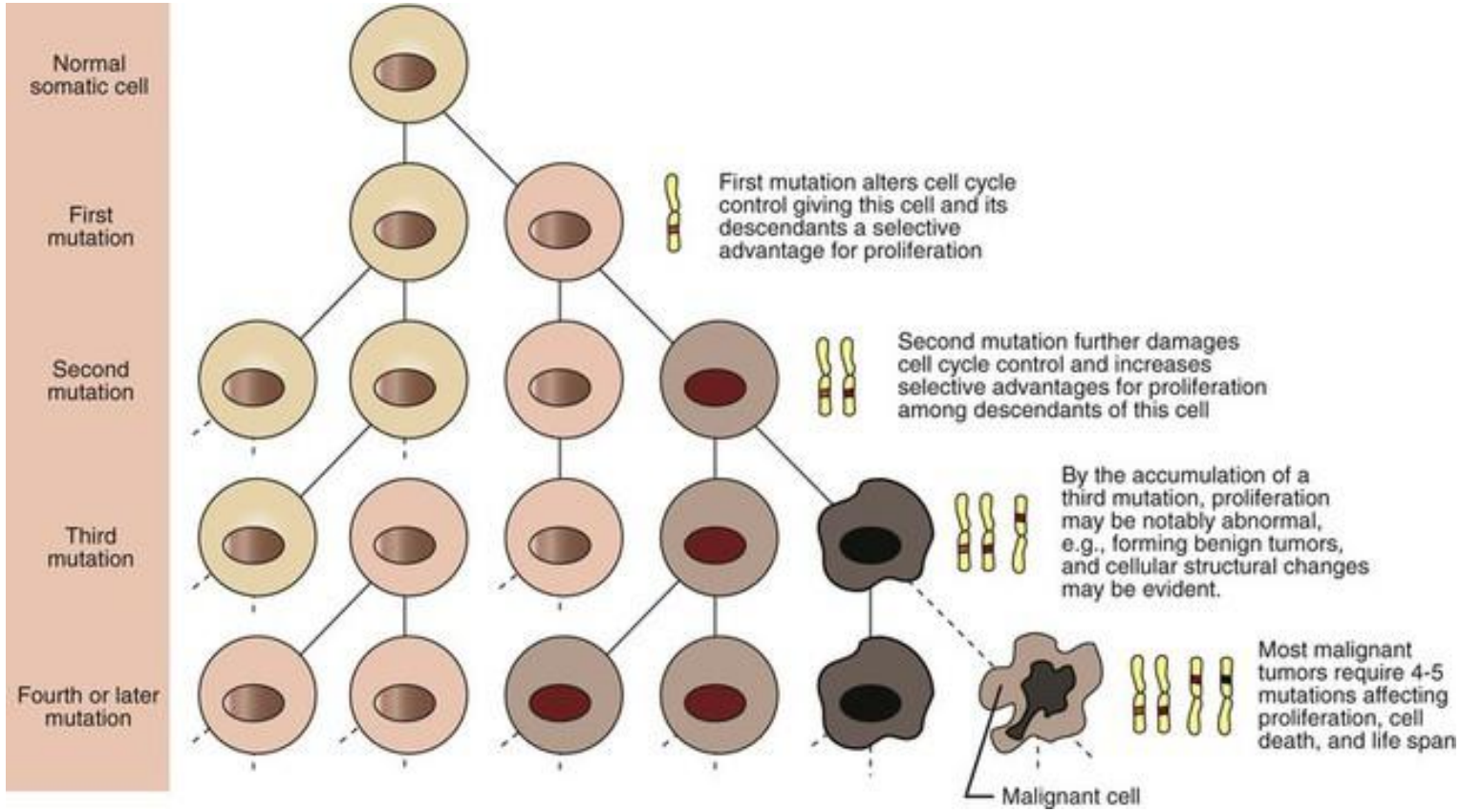
Only a small fraction of these mutations, the driver mutations, were the *cause* of unregulated cell division; the vast majority (>99.9%) were "passenger mutations," which occurred randomly and did not confer a selective growth advantage on the tissue in which they occurred.

These 140 driver mutations fell in three general categories:

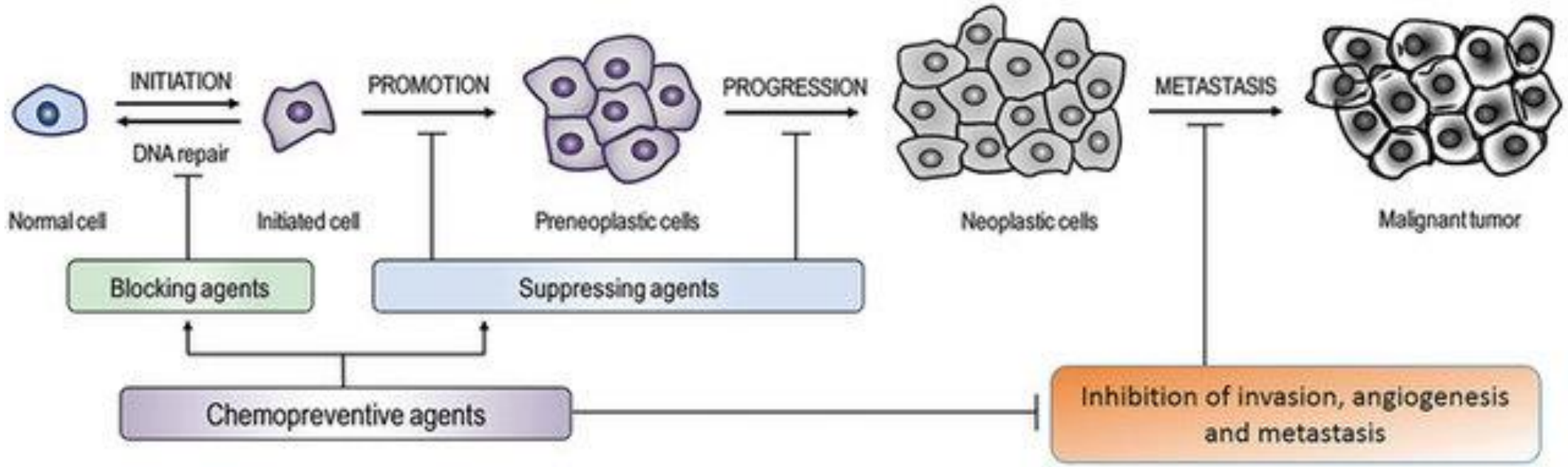
- **those that affect cell survival (in genes encoding Ras, PI3K, MAPK, for example)**
- **those that affect cells' ability to maintain an intact genome (ATM, ATR)**
- **and those that affect cell fate, causing cells to divide, differentiate, or become quiescent (APC is one example).**

✓ **A relatively small number of mutations were very common in multiple types of cancer, in the genes for Ras, p53, and pRb, for example**

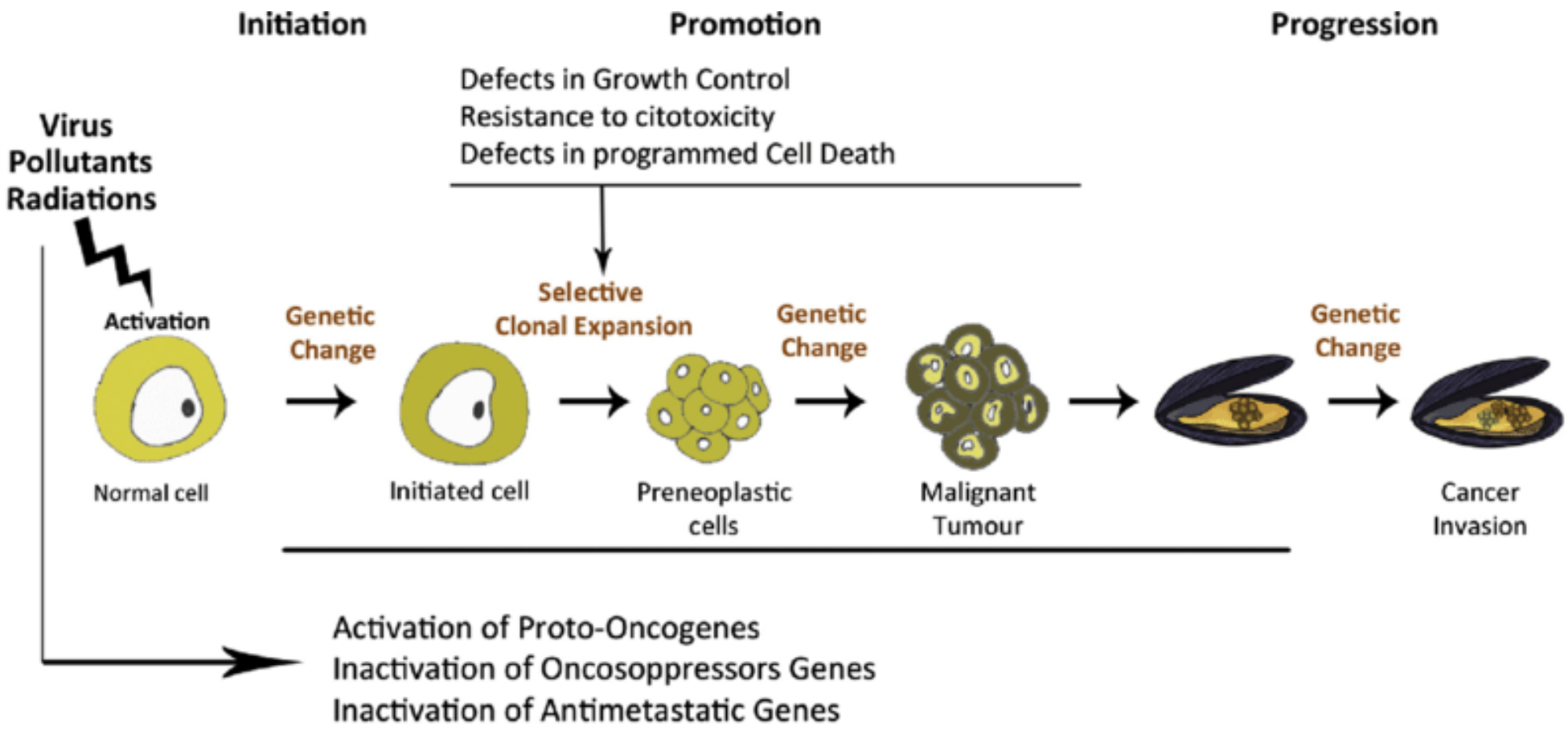
Carcinogenesis and mutations



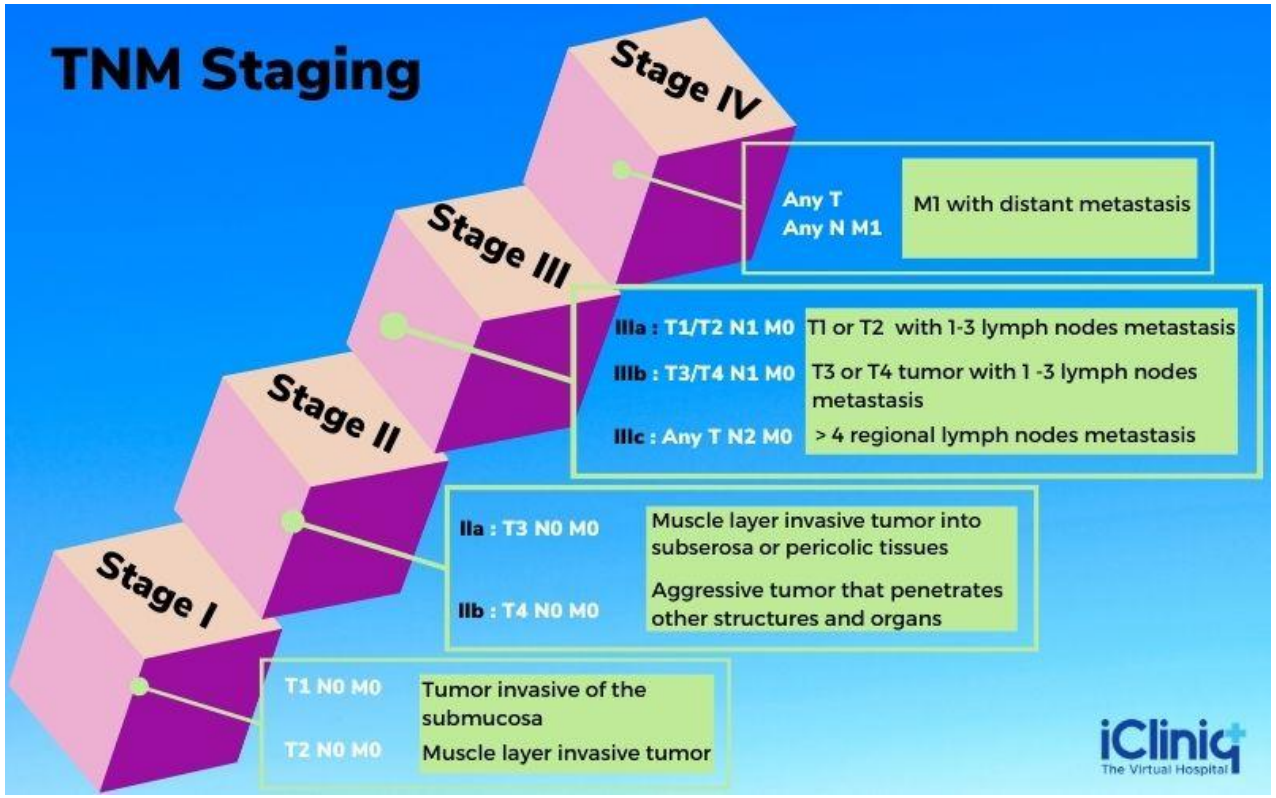
Carcinogenesis phases

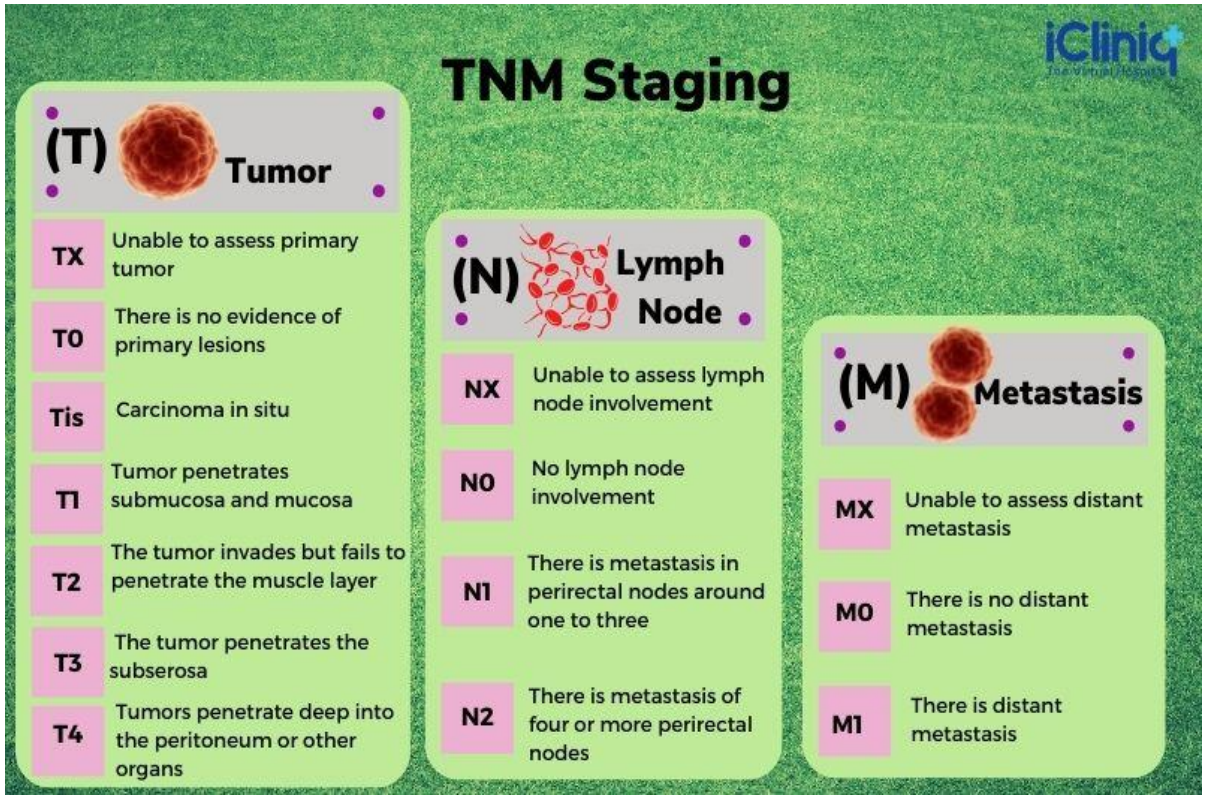


Carcinogenesis phases: initiation, promotion, progression, and metastasis. (A) Initiation involves the alteration, change, or mutation of genes arising spontaneously or induced by exposure to a carcinogenic agent. Genetic alterations can result in dysregulation of biochemical signaling pathways associated with cellular proliferation, survival, and differentiation, which can be influenced by a number of factors, including the rate and type of carcinogenic metabolism and the response of the DNA repair function. (B) The promotion stage is considered to be a relatively lengthy and reversible process in which actively proliferating preneoplastic cells accumulate. Within this period, the process can be altered by chemopreventive agents and affect growth rates. Progression is the phase between a premalignant lesion and the development of invasive cancer. (C) Progression is the final stage of neoplastic transformation, where genetic and phenotypic changes and cell proliferation occur. This involves a fast increase in the tumor size, where the cells may undergo further mutations with invasive and metastatic potential. Chemopreventive agents should be able to preferentially act within the initiation and promotion processes of carcinogenesis. (D) Metastasis involves the spread of cancer cells from the primary site to other parts of the body through the bloodstream or the lymph system. Chemopreventive agents are known to inhibit angiogenesis and invasion of primary tumors, and thus could be utilized to inhibit the metastasis of cancer.

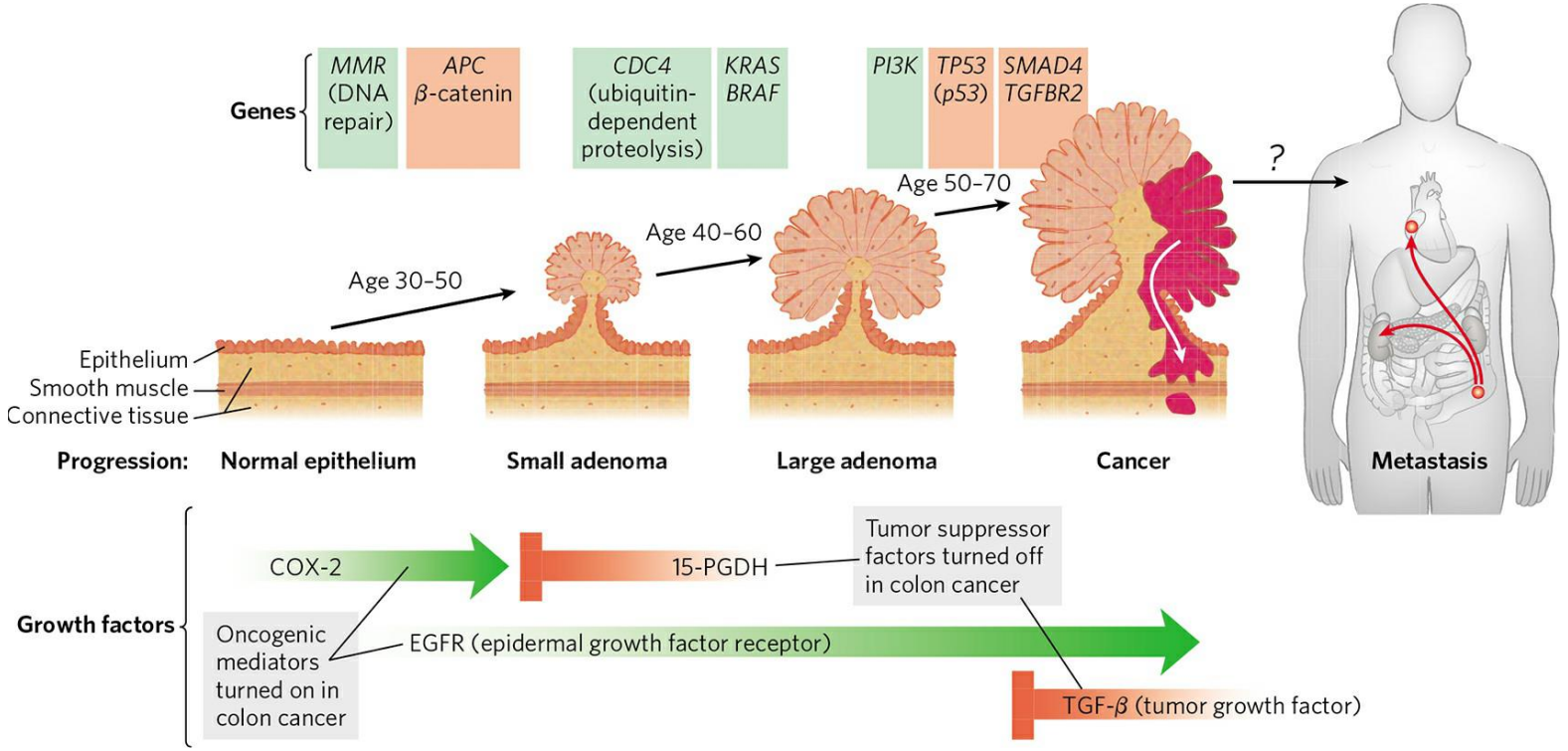

Initiation
Promotion
Progression
Defects in Growth Control
Resistance to citotoxicity
Defects in programmed Cell Death
Virus
Pollutants
Radiations
Activation
Genetic Change
Selective Clonal Expansion
Genetic Change
Genetic Change
Normal cell
Initiated cell
Preneoplastic cells
Malignant Tumour
Cancer Invasion
Activation of Proto-Oncogenes
Inactivation of Oncosoppressors Genes
Inactivation of Antimetastatic Genes

Tumor Stage


TNM Staging
Stage IV
Stage III
Stage II
Stage I
Any T
Any N M1
M1 with distant metastasis
IIIa : T1/T2 N1 M0
T1 or T2 with 1-3 lymph nodes metastasis
IIIb : T3/T4 N1 M0
T3 or T4 tumor with 1 -3 lymph nodes metastasis
IIIc : Any T N2 M0
> 4 regional lymph nodes metastasis
IIa : T3 N0 M0
Muscle layer invasive tumor into subserosa or pericolic tissues
IIb : T4 N0 M0
Aggressive tumor that penetrates other structures and organs
T1 N0 M0
Tumor invasive of the submucosa
T2 N0 M0
Muscle layer invasive tumor
iClinic
The Virtual Hospital

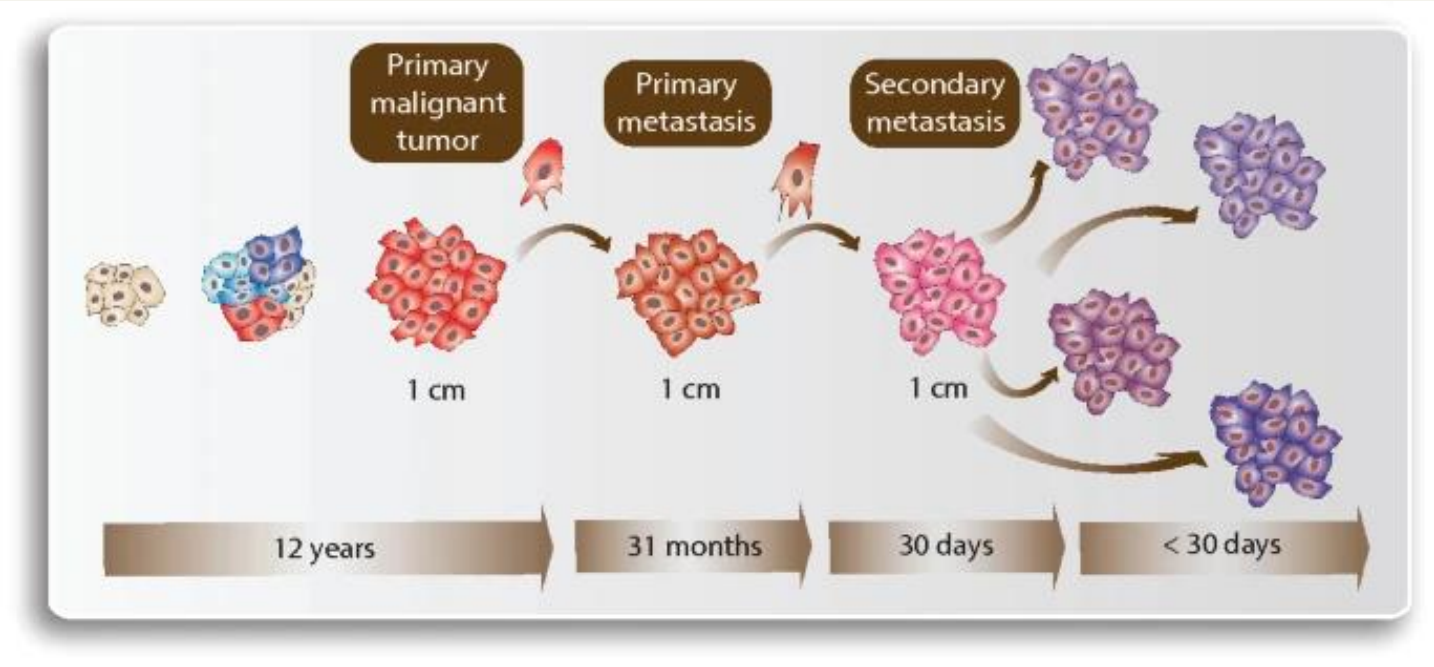

TNM Staging
iClinic
(T) Tumor
TX
Unable to assess primary tumor
T0
There is no evidence of primary lesions
Tis
Carcinoma in situ
T1
Tumor penetrates submucosa and mucosa
T2
The tumor invades but fails to penetrate the muscle layer
T3
The tumor penetrates the subserosa
T4
Tumors penetrate deep into the peritoneum or other organs
(N) Lymph Node
NX
Unable to assess lymph node involvement
N0
No lymph node involvement
N1
There is metastasis in perirectal nodes around one to three
N2
There is metastasis of four or more perirectal nodes
(M) Metastasis
MX
Unable to assess distant metastasis
M0
There is no distant metastasis
M1
There is distant metastasis

Multistep transition from normal epithelial cell to colorectal cancer



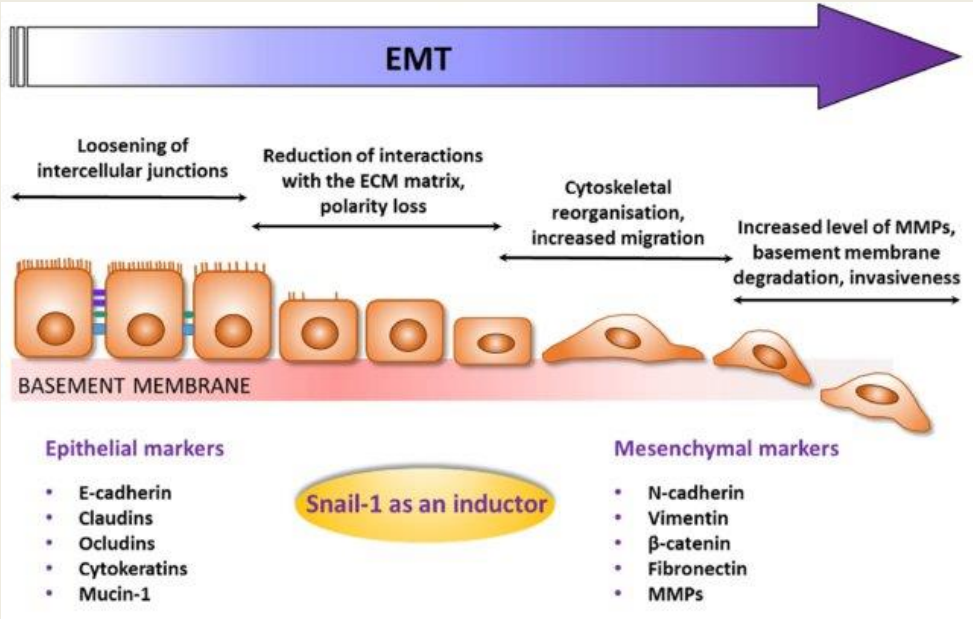
Serial mutations in oncogenes (green) or tumor suppressor genes (red) lead to progressively less control of cell division, until finally an active tumor forms, which can sometimes metastasize (spread from the initial site to other regions of the body). Mutation of the MMR gene leads to defective DNA repair and consequently to a higher rate of mutation. Mutations in both copies of the tumor suppressor gene APC lead to benign clusters of epithelial cells that multiply too rapidly (early adenoma). The CDC4 oncogene results in defective ubiquitination, which is essential to the regulation of cyclin-dependent kinases. The oncogenes KRAS and BRAF encode Ras and Raf proteins, and this further disruption of signaling leads to the formation of a large adenoma, which may be detected by colonoscopy as a benign polyp. Oncogenic mutations in the PI3K gene, which encodes the enzyme phosphoinositide-3 kinase, or in PTEN, which regulates the synthesis of this enzyme, lead to a further strengthening of the signal: divide now. When a cell in one of the polyps undergoes further mutations, such as in the tumor suppressor genes DCC and p53, increasingly aggressive tumors form. Finally, mutations in other tumor suppressor genes such as SMAD4 lead to a malignant tumor and sometimes to a metastatic tumor that can spread to other tissues.

Metastasis



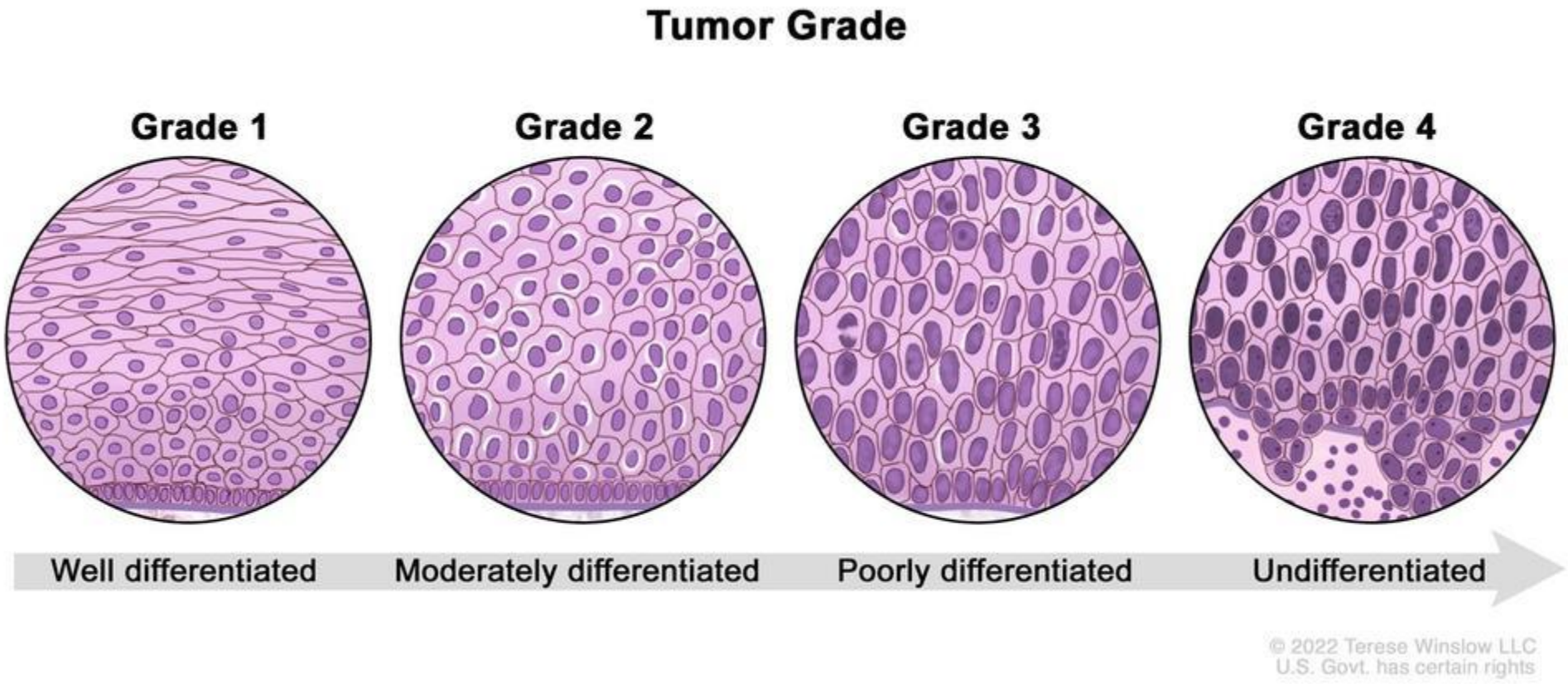
- In the example shown here this happens at a stage of 1 cm tumor diameter and may have taken 12 years. In primary, secondary and tertiary metastasis the cells become increasingly malignant and the tumor doubling time significantly decreases.

Epithelial-to-mesenchymal transition (EMT) process

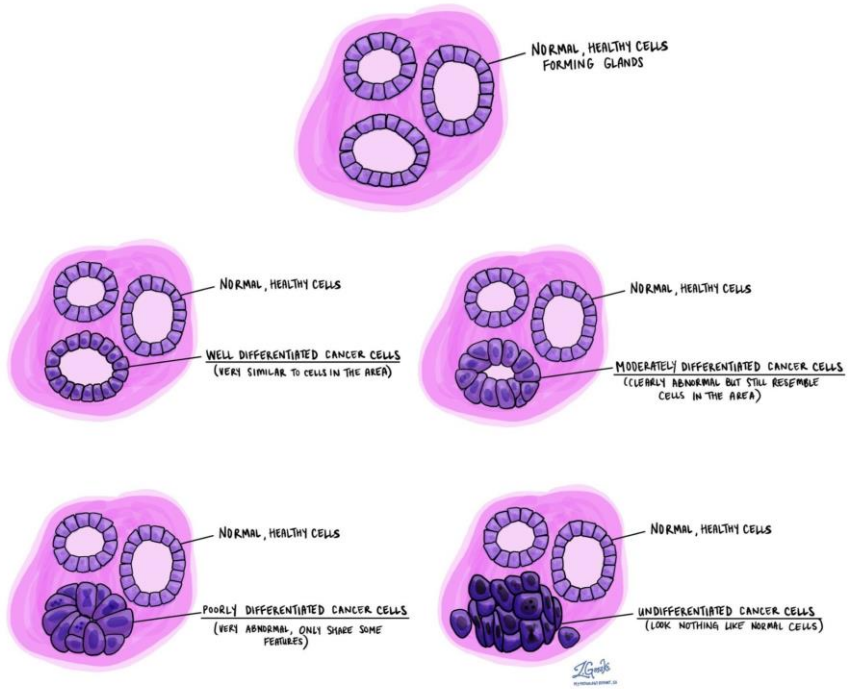


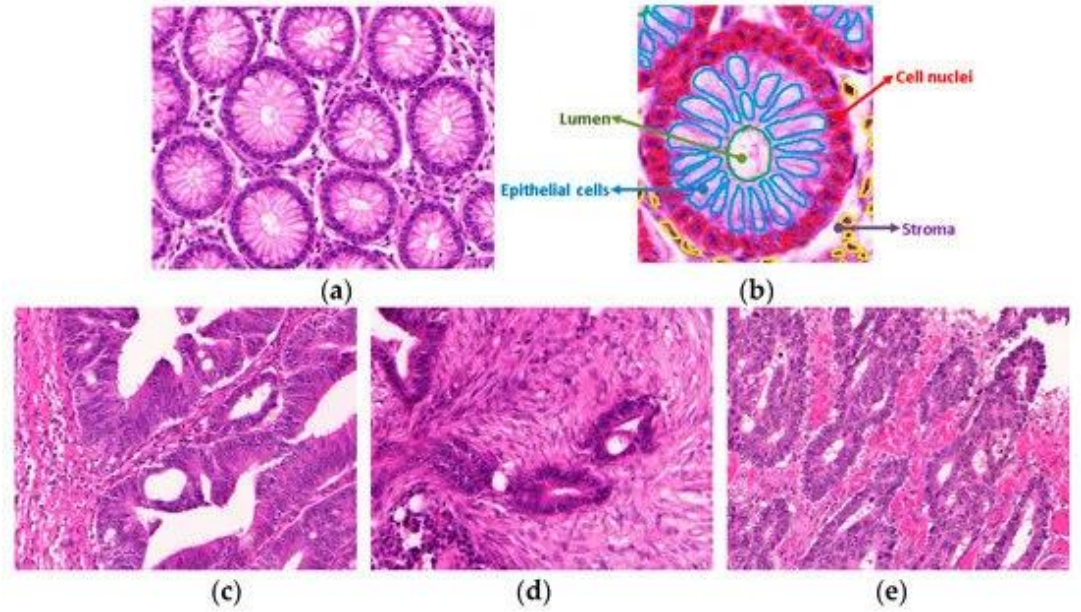
The epithelial-to-mesenchymal transition (EMT) is a physiological process that occurs during early developmental stages. However, it is also characteristic of cancer progression, with it being the main mechanism responsible for invasiveness and metastasis of the neoplasm at the advanced stages. During this transformation, the immotile cells of epithelial origin gradually lose their tight junction connections, their characteristic shape and polarity, and due to the cytoskeleton rearrangements, gain a fibroblast-like mesenchymal phenotype.

<u>In the context of cancer progression, the most important cell ability that is enabled by the EMT is invasion</u>



- ✓ ***Tumor grade describes how normal or abnormal cancer cells look under a microscope.***
- ✓ ***The higher the grade, the more abnormal the cells look and the faster it is likely to grow and spread.***



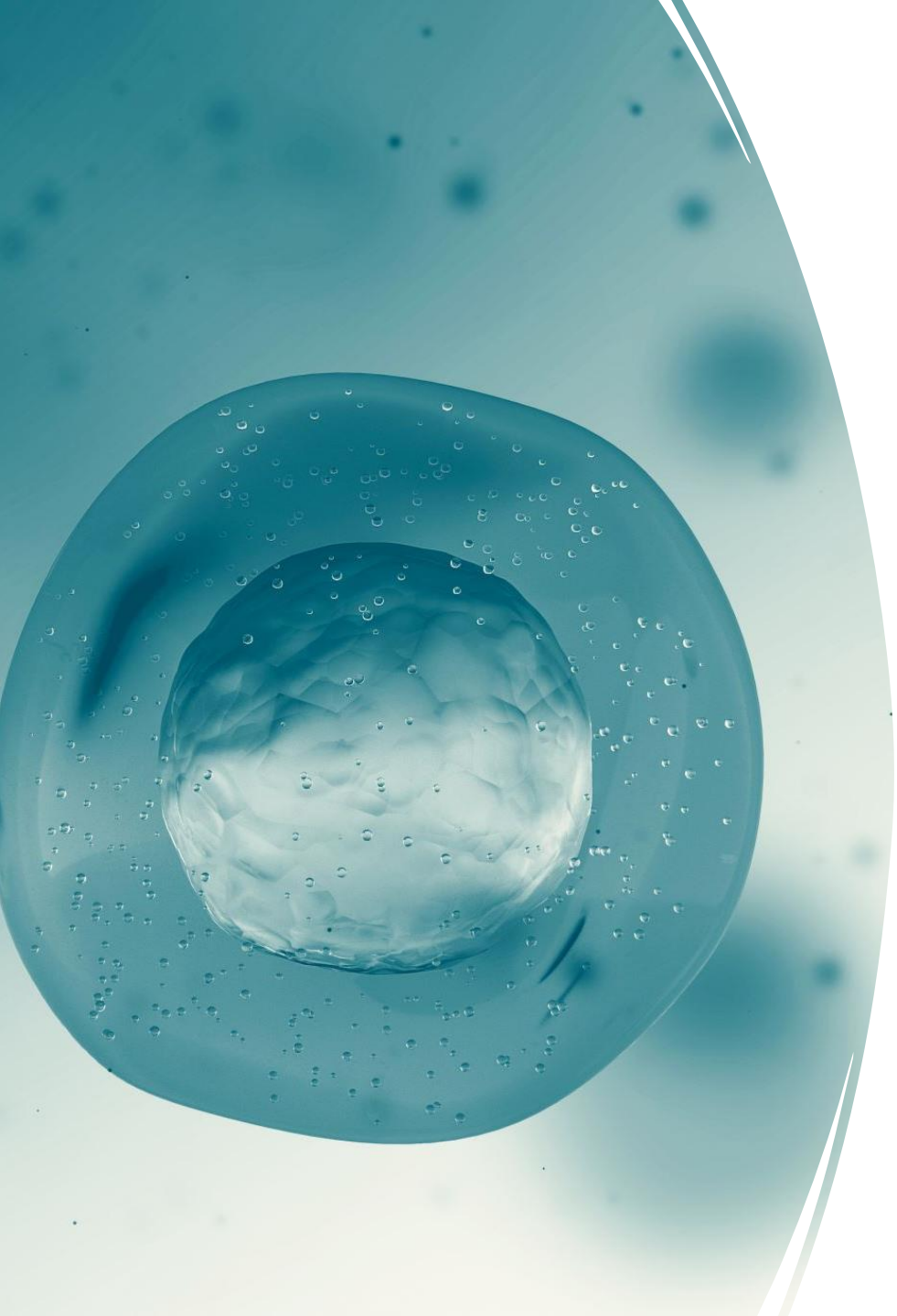


Colon tissue

- **a) Normal colon tissue, (b) detailed structure of a normal colon tissue; malignant colon tissue, (c) moderately differentiated, (d) moderately-to-poorly differentiated, and (e) poorly differentiated.**

Learning Objectives

1. Understanding the characteristics of cancer cells
2. Understanding the differences in their growth patterns, characteristics, and behavior the genetic and environmental factors that contribute to development of cancer cells
3. Knowing the mechanisms of cancer cell growth and metastasis
4. Understanding the meaning of Grade and Stage



Questions

- Normal cells have:

a) Larger cytoplasmic volume and darker nucleus

b) Alkaline environment and multiple nucleolus

c) Acidic environment and larger cytoplasmic volume

d) Alkaline environment and almost smooth membrane

Questions

- How many are the driver mutations?

a) 3,300

b) 140

c) 20,000

d) 3

Questions

- About Grade:

a) The higher the grade, the more abnormal the cells look and the faster it is likely to grow and spread

b) The higher the grade, the more normal the cells look and the faster it is likely to grow and spread

- Thank you for your attention!