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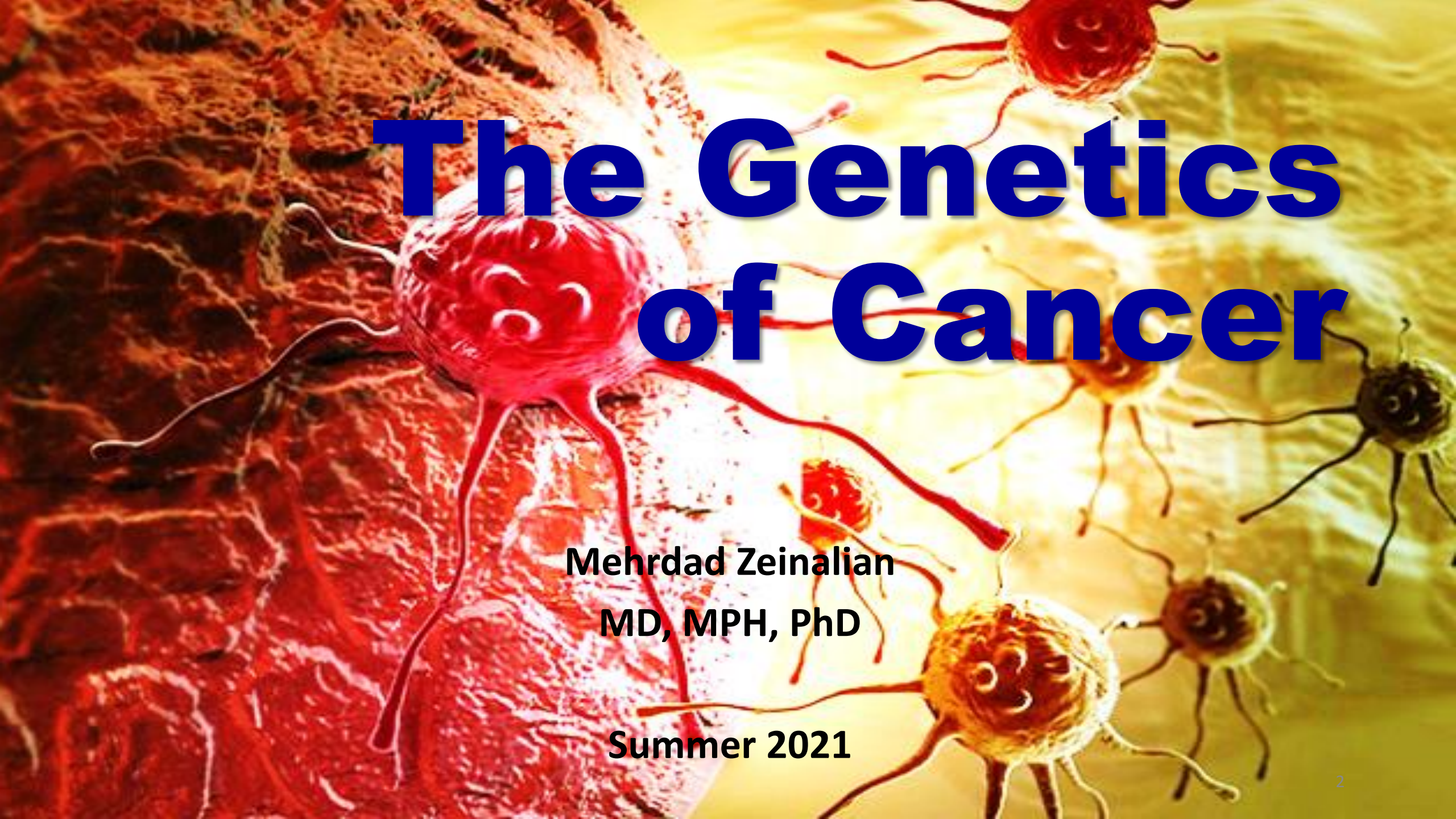
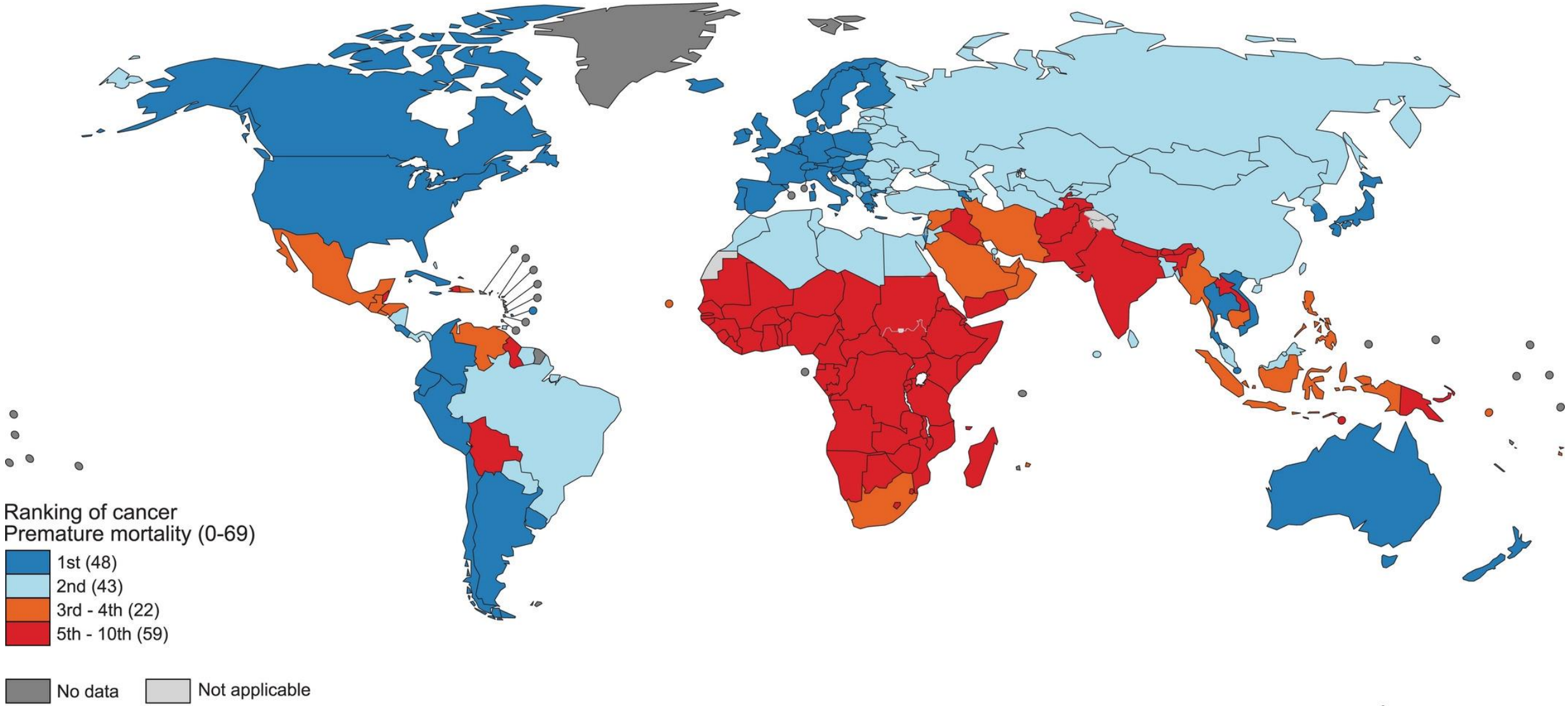


The Genetics of Cancer

Mehrdad Zeinalian
MD, MPH, PhD

Summer 2021



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Data source: GHO
Map production: CSU
World Health Organization

World Health Organization

Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
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[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
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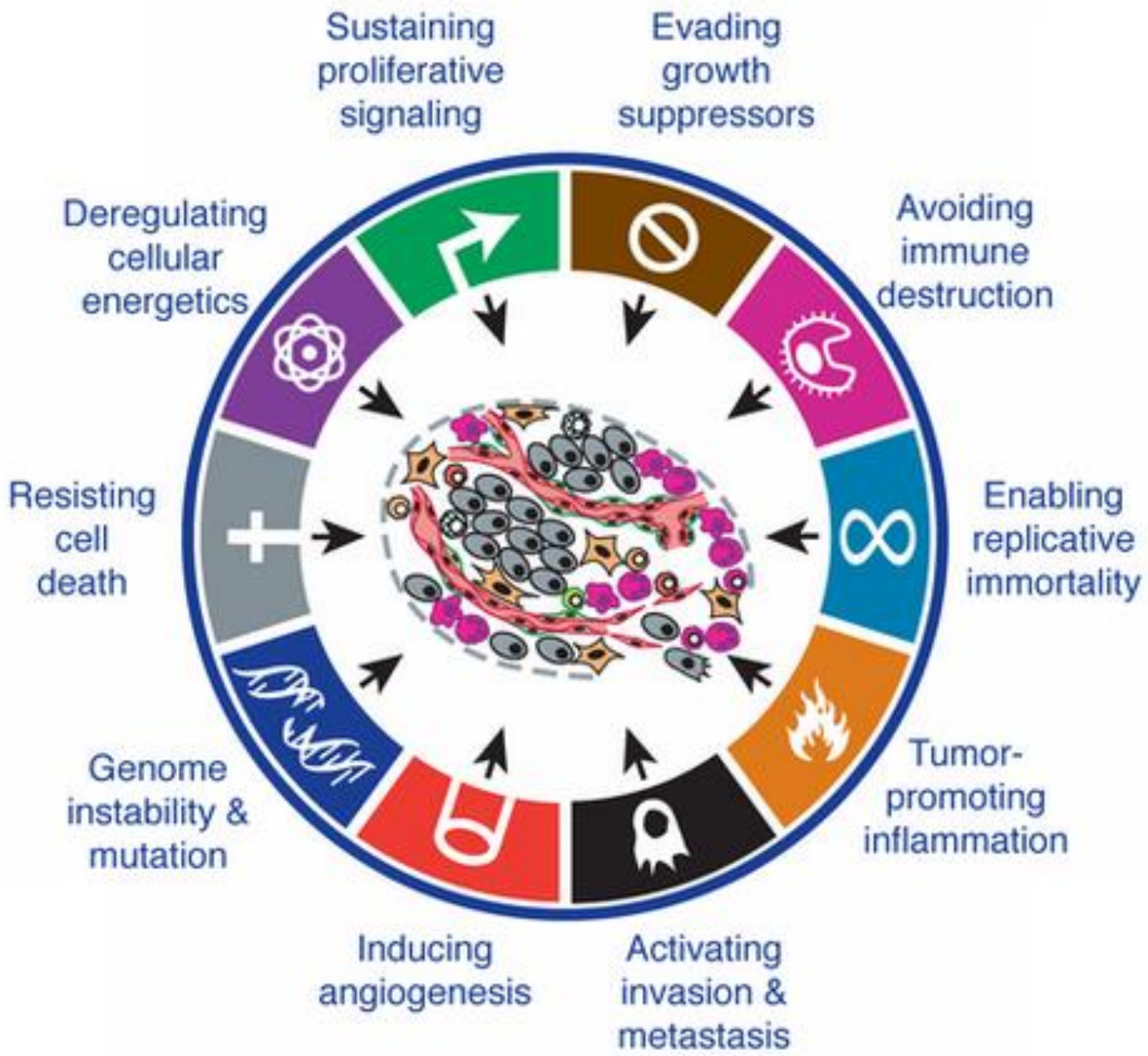
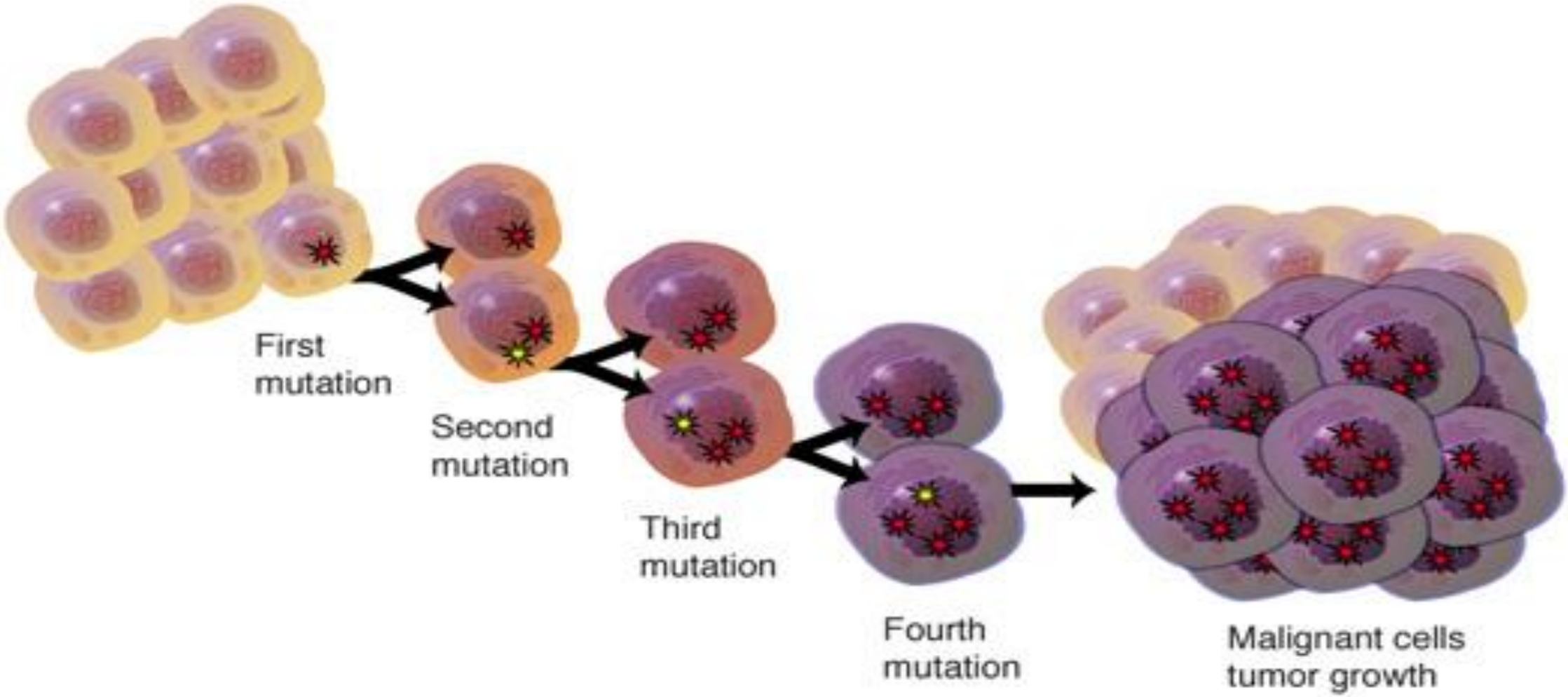
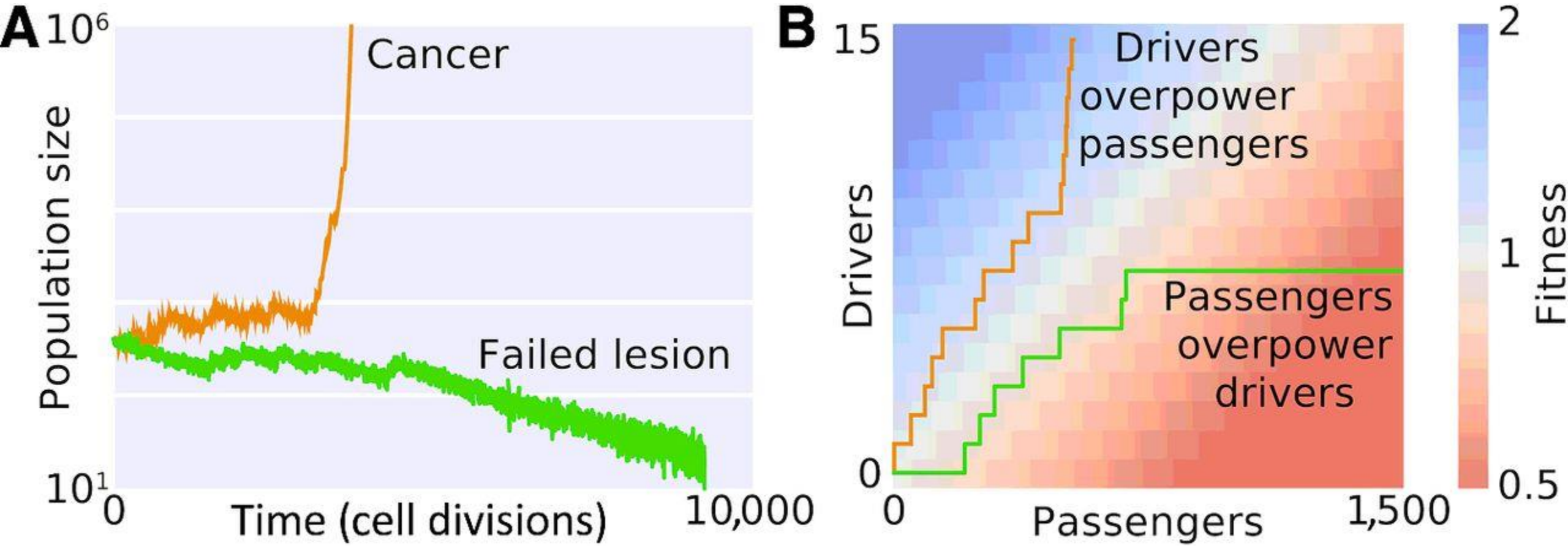
DOI 10.1016/j.cell.2011.02.013

The hallmarks of cancer comprise six biological capabilities acquired during the multistep development of human tumors. The hallmarks constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Underlying these hallmarks are genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions. Conceptual progress in the last decade has added two emerging hallmarks of potential generality to this list—reprogramming of energy metabolism and evading immune destruction. In addition to cancer cells, tumors exhibit another dimension of complexity: they contain a repertoire of recruited, ostensibly normal cells that contribute to the acquisition of hallmark traits by creating the "tumor microenvironment." Recognition of the widespread applicability of these concepts will increasingly affect the development of new means to treat human cancer.


Sustaining proliferative signaling
Evading growth suppressors
Avoiding immune destruction
Enabling replicative immortality
Tumor-promoting inflammation
Activating invasion & metastasis
Inducing angiogenesis
Genome instability & mutation
Resisting cell death
Deregulating cellular energetics

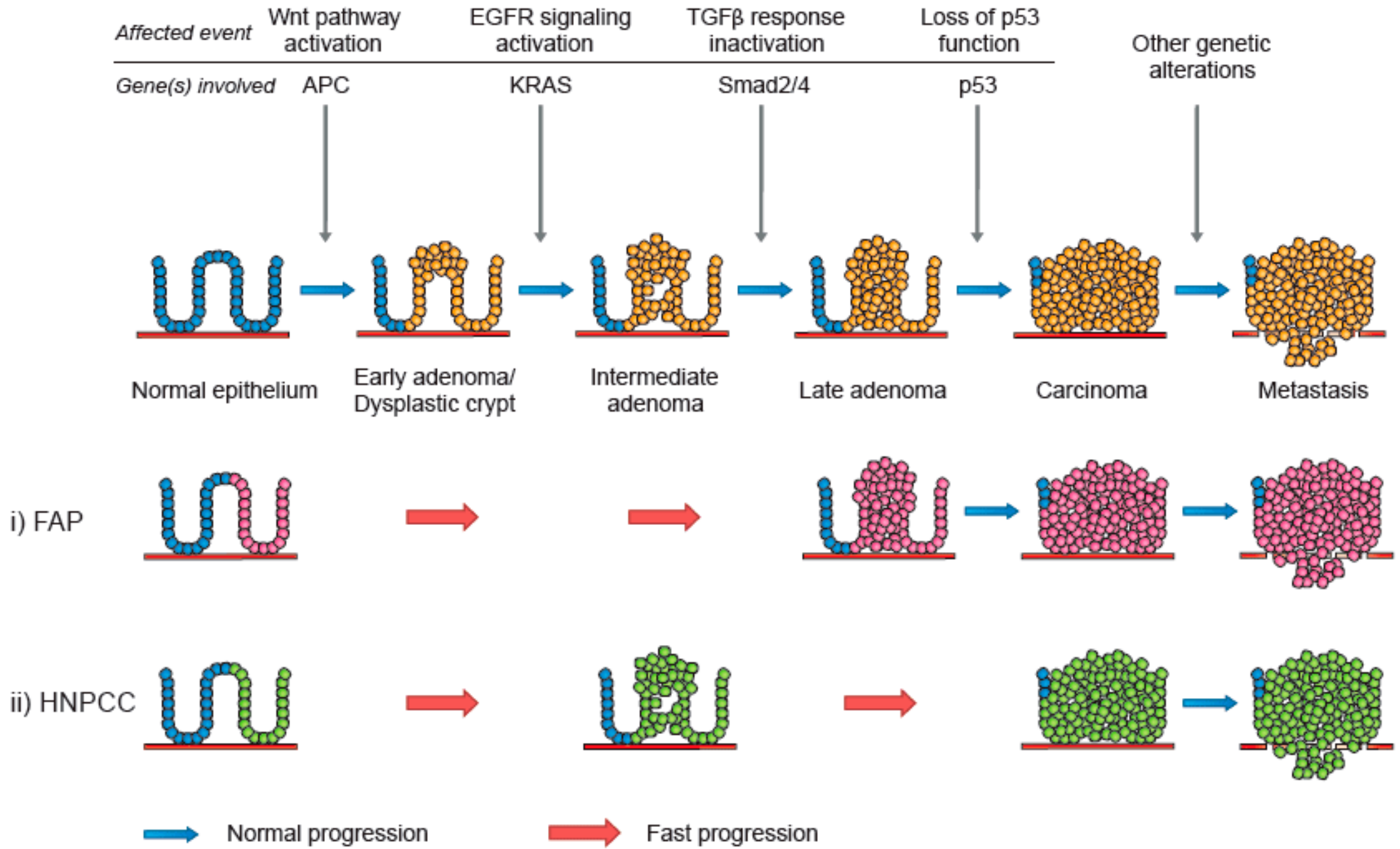

First mutation
Second mutation
Third mutation
Fourth mutation
Malignant cells tumor growth

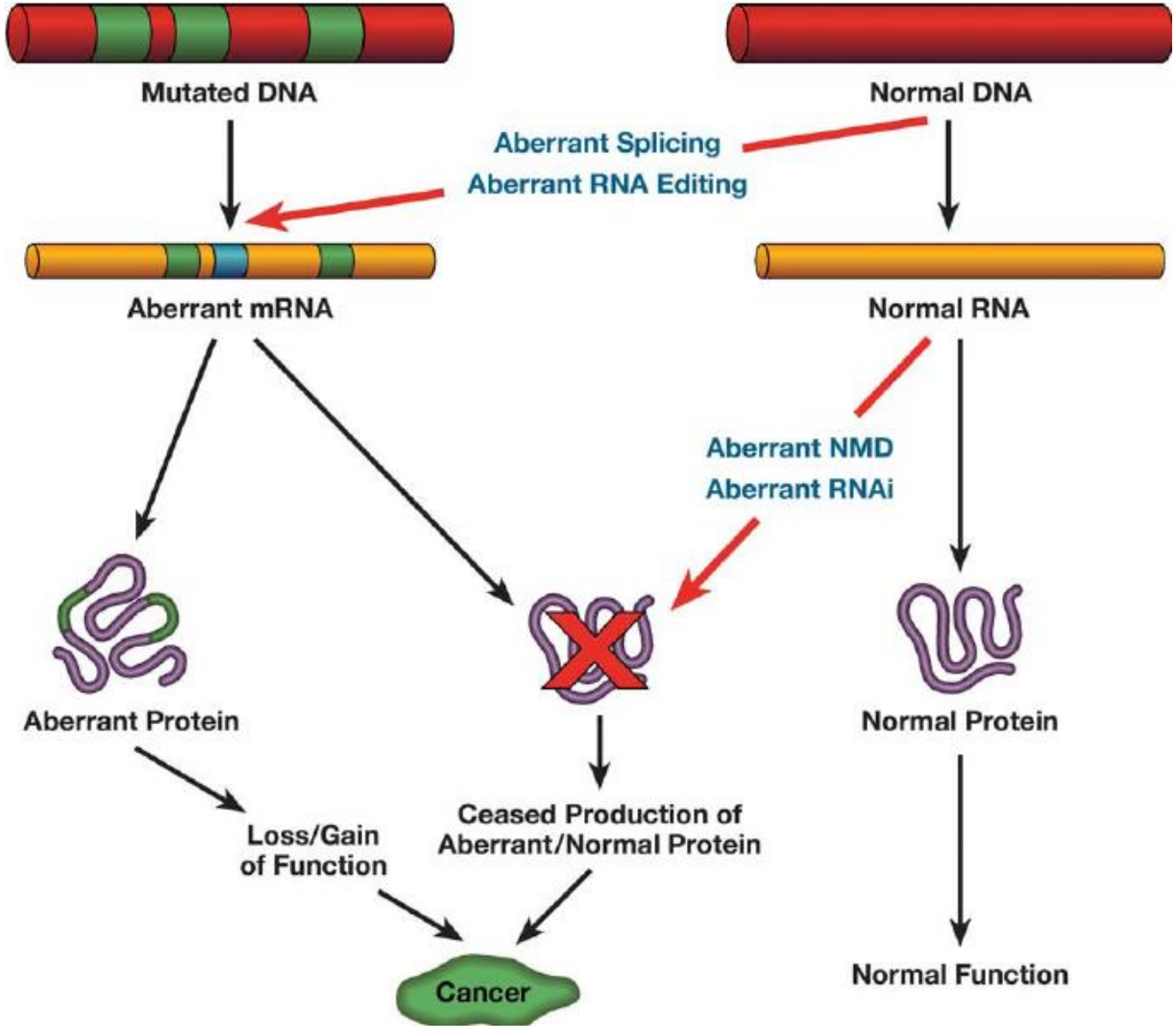

TAXI
Passenger
Mutation!?!
Driver
mutation?!?



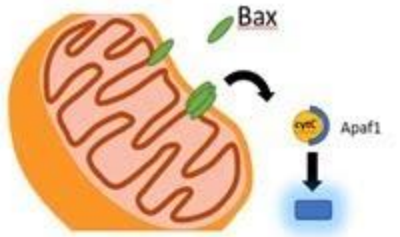
Accumulation of passenger mutations can slow cancer progression and lead to cancer meltdown.

https://cancerres.aacrjournals.org/content/77/18/4763


Affected event
Wnt pathway activation
EGFR signaling activation
TGFβ response inactivation
Loss of p53 function
Other genetic alterations
Gene(s) involved
APC
KRAS
Smad2/4
p53
Normal epithelium
Early adenoma/ Dysplastic crypt
Intermediate adenoma
Late adenoma
Carcinoma
Metastasis
i) FAP
ii) HNPCC
Normal progression
Fast progression



https://www.researchgate.net/figure/Schematic-representation-of-RNA-based-mechanisms-and-their-potential-regulatory-role-in_fig1_7105999

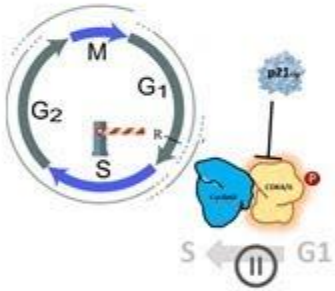


Apoptosis ← Caspase activation

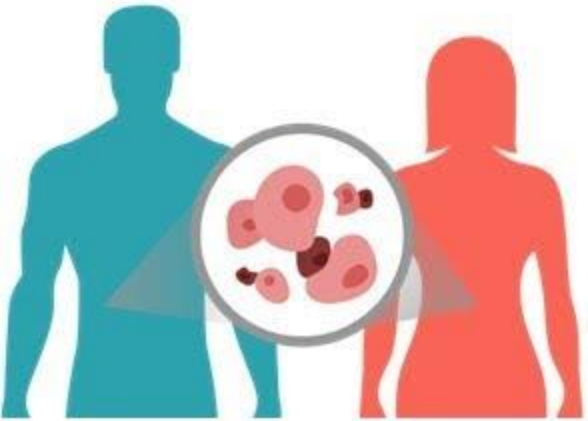
Tumour suppressor genes

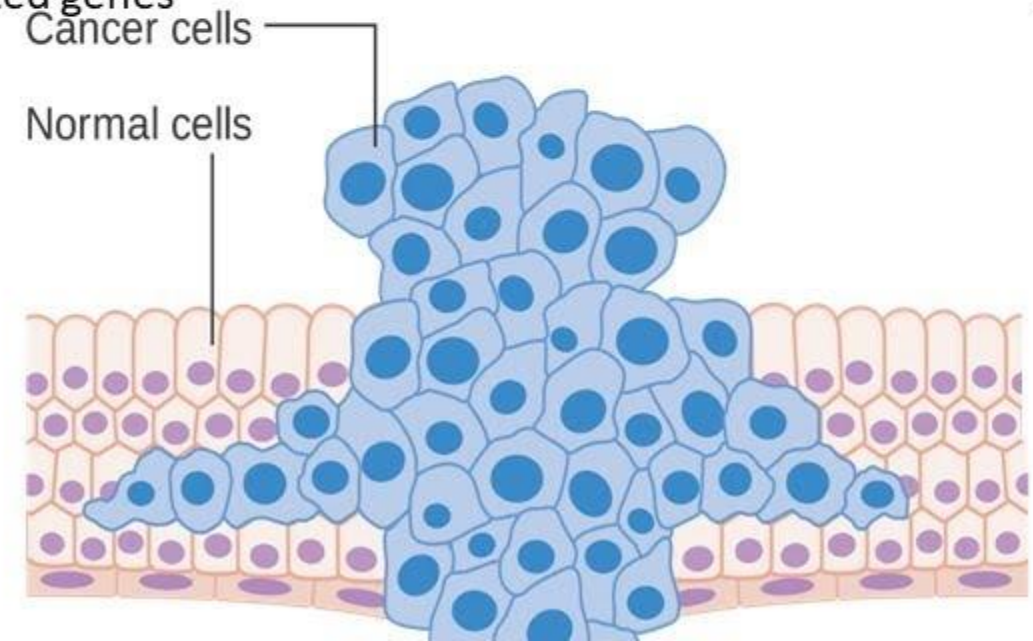
Gate keeper

Directly suppress growth



Cell cycle regulator genes
Checkpoint control genes
Apoptosis related genes

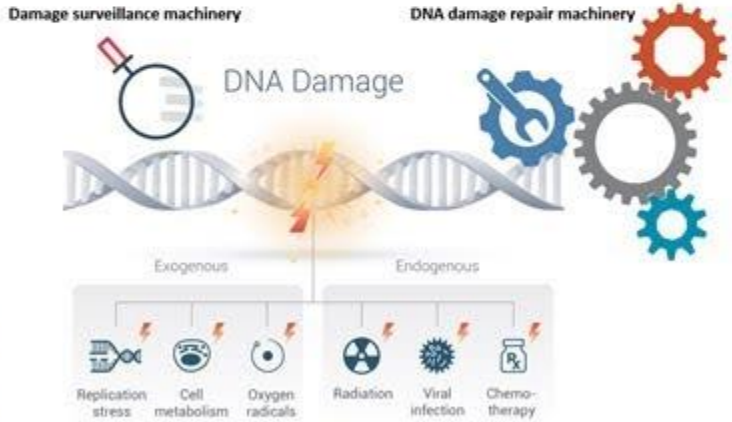




Care taker

Maintain overall genetic stability

DNA repair proteins



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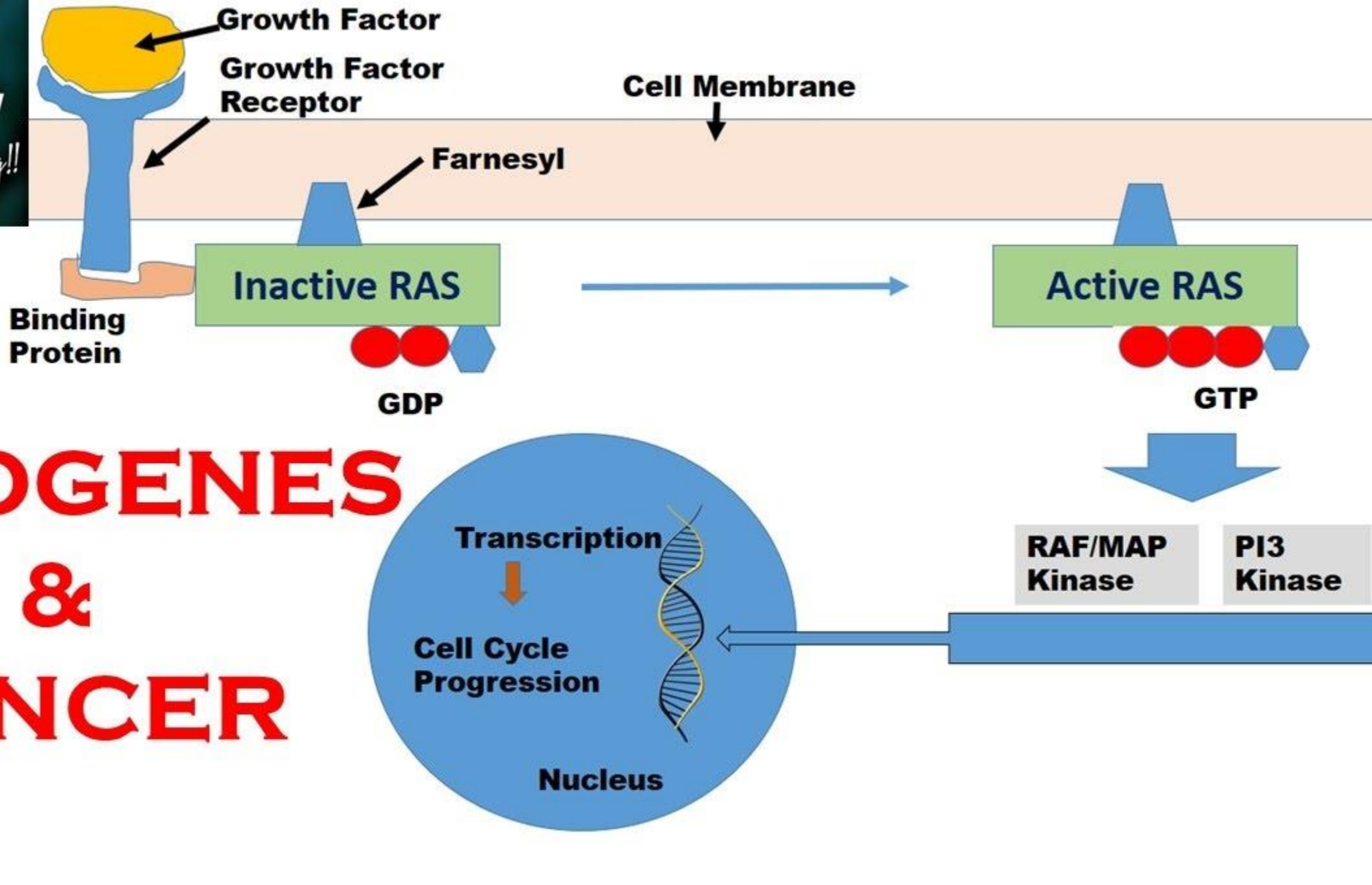
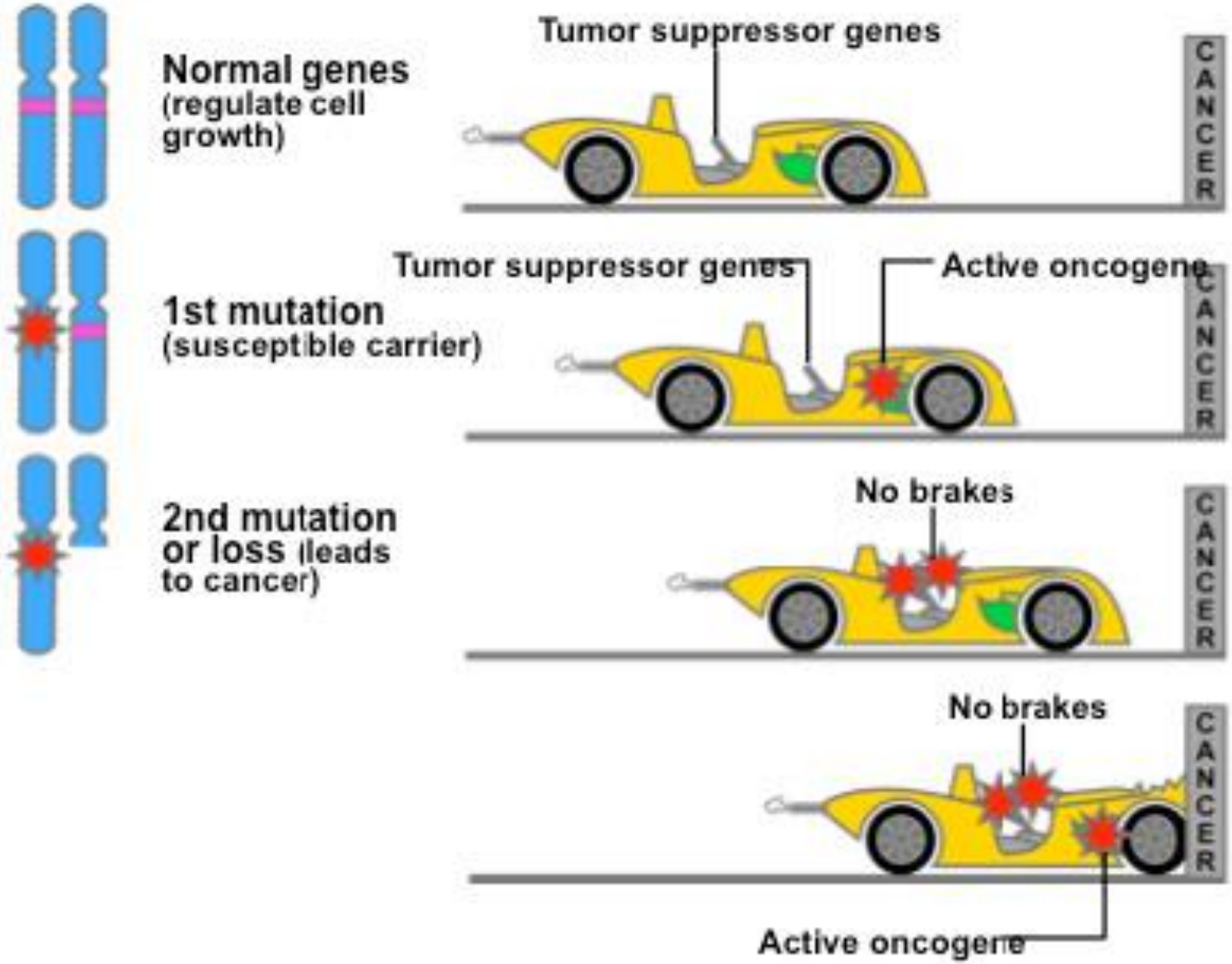
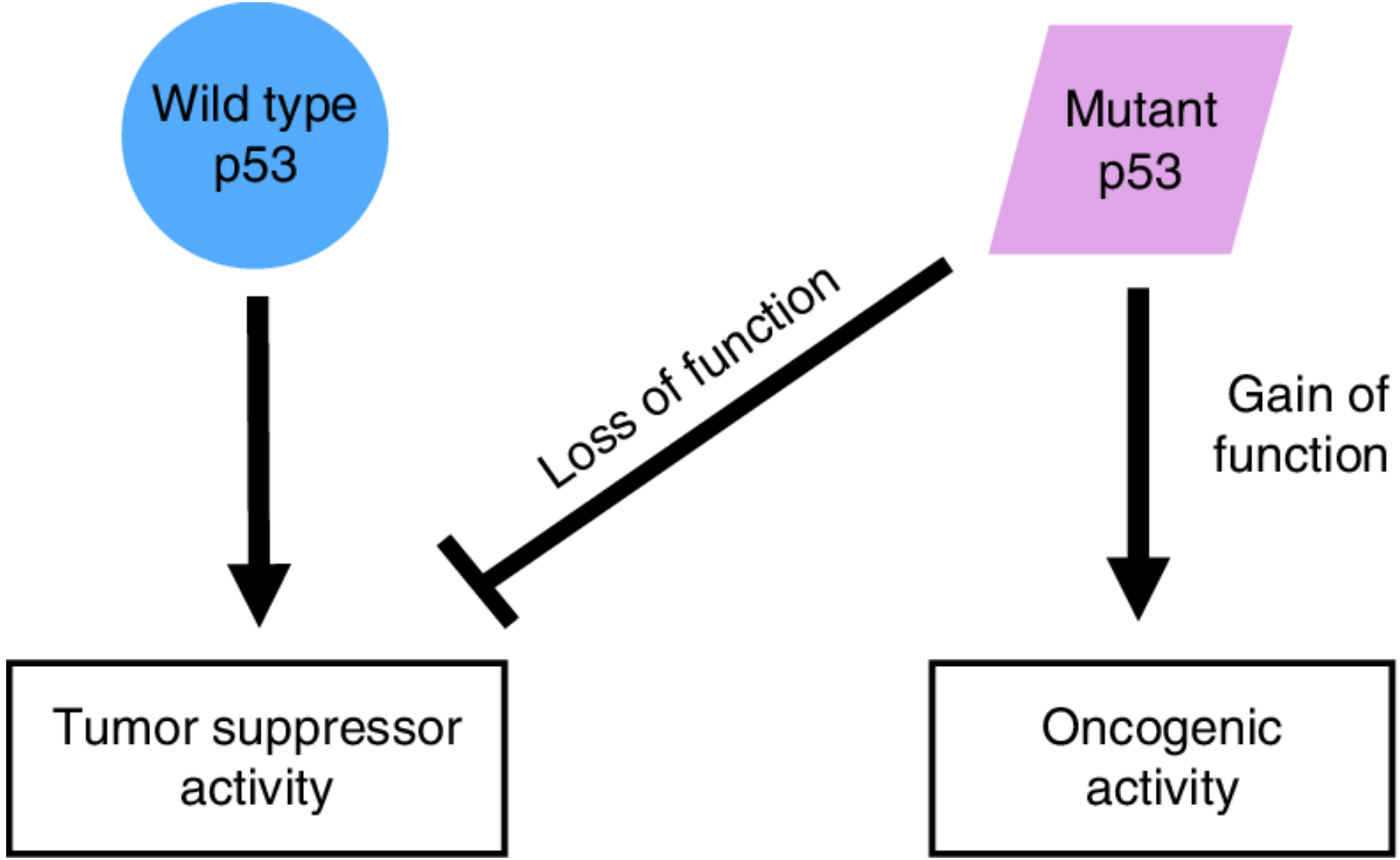
ONCOGENES & CANCER




Normal genes
(regulate cell
growth)
Tumor suppressor genes
CANCER
1st mutation
(susceptible carrier)
Tumor suppressor genes
Active oncogene
CANCER
2nd mutation
or loss (leads
to cancer)
No brakes
CANCER
No brakes
CANCER
Active oncogene



4 The relationship between mutant p53 and development of cancer. Mutations in p53 protein often result in either the loss of normal tumor suppressor activity or the gain of new oncogenic functions, both of which can contribute to genomic instability and the carcinogenic process

https://www.researchgate.net/figure/The-relationship-between-mutant-p53-and-development-of-cancer-Mutations-in-p53-protein_fig5_318426635

Genetic changes that can turn proto-oncogenes into oncogenes

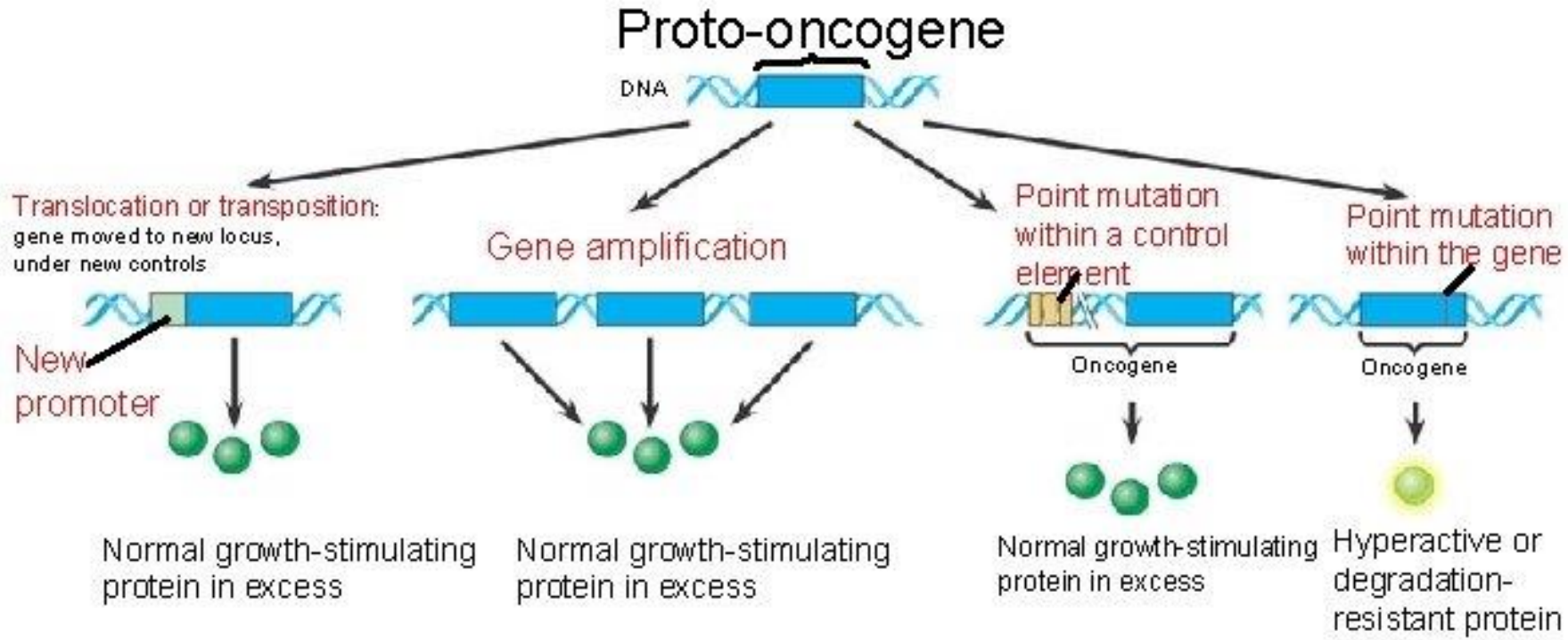
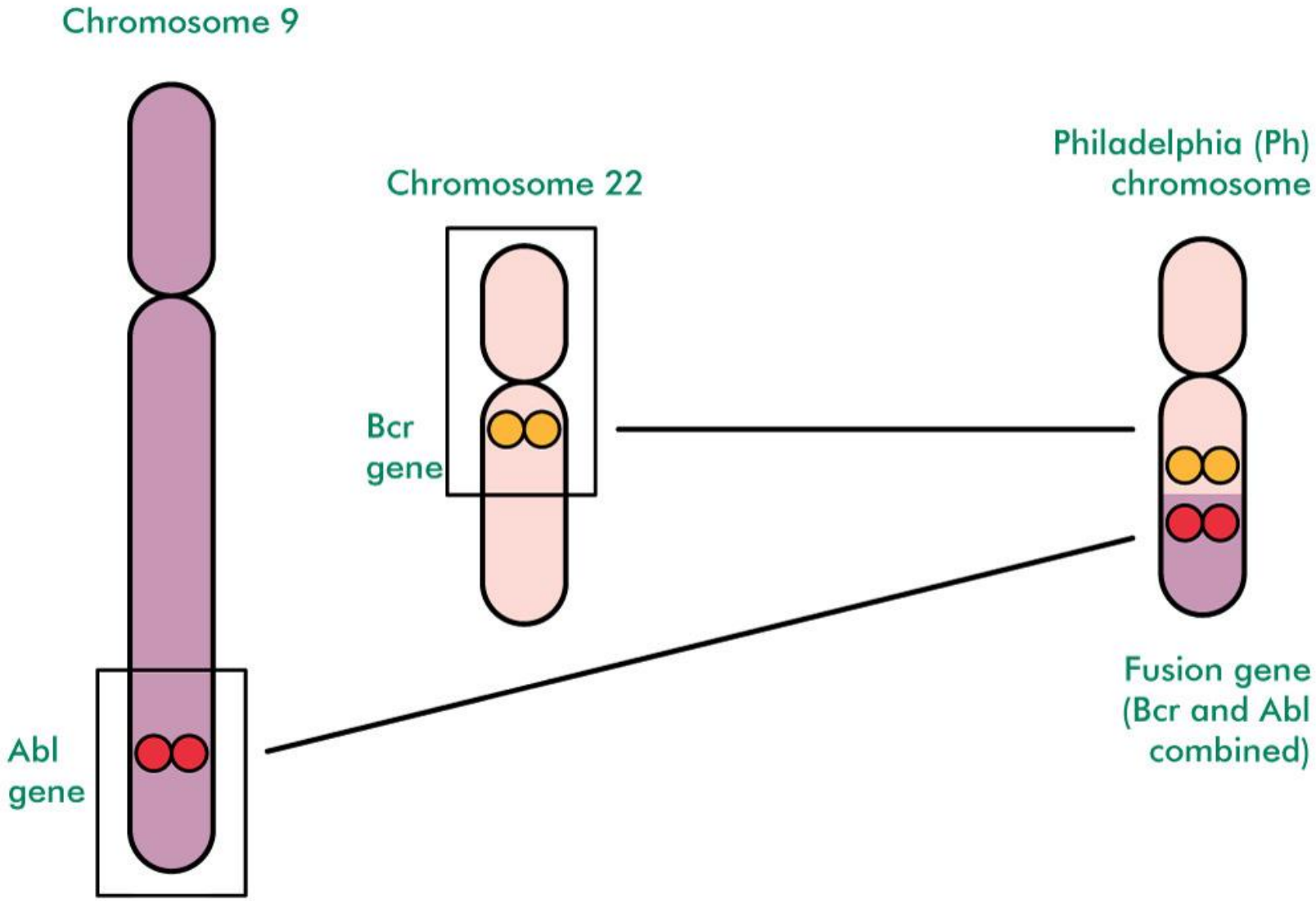
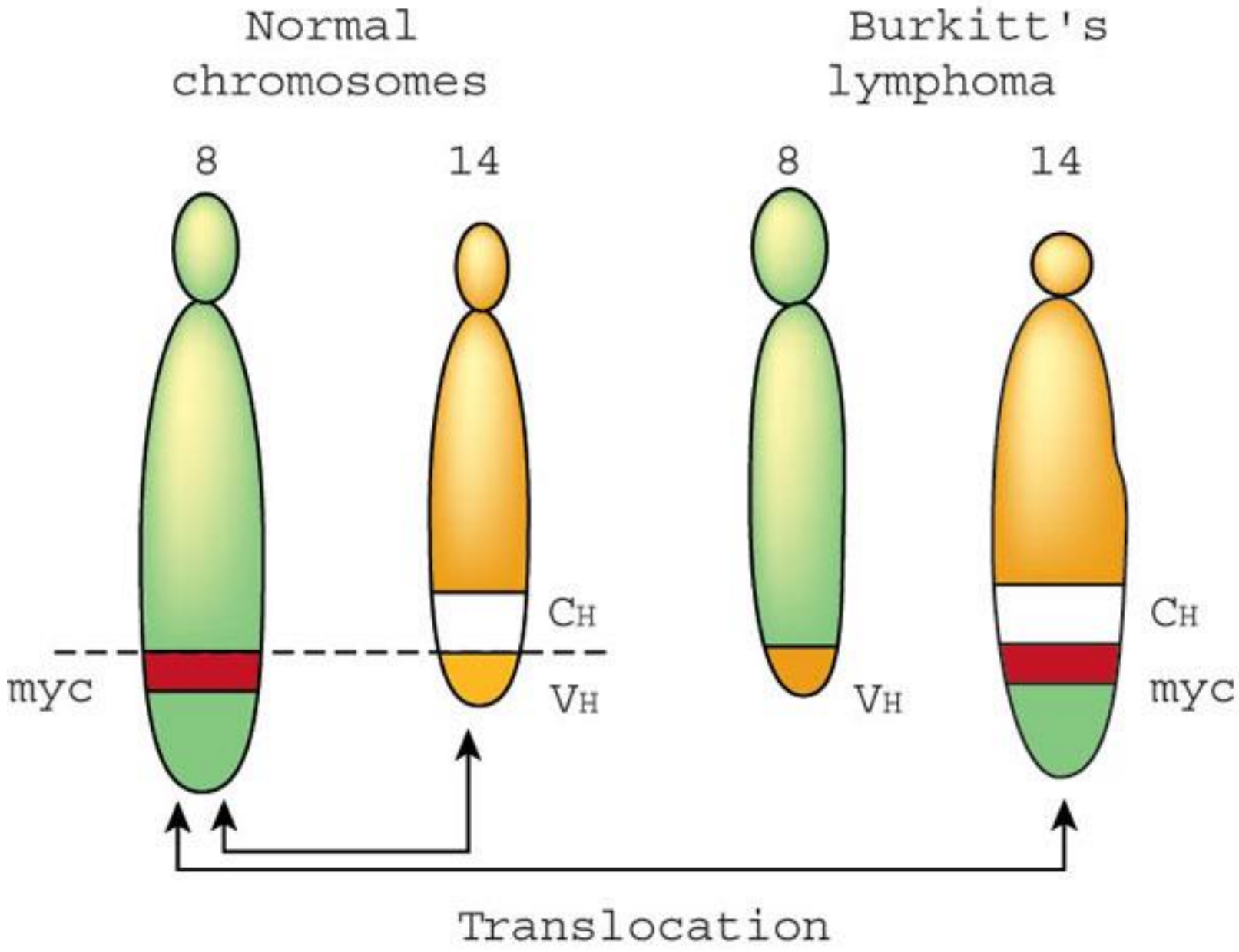


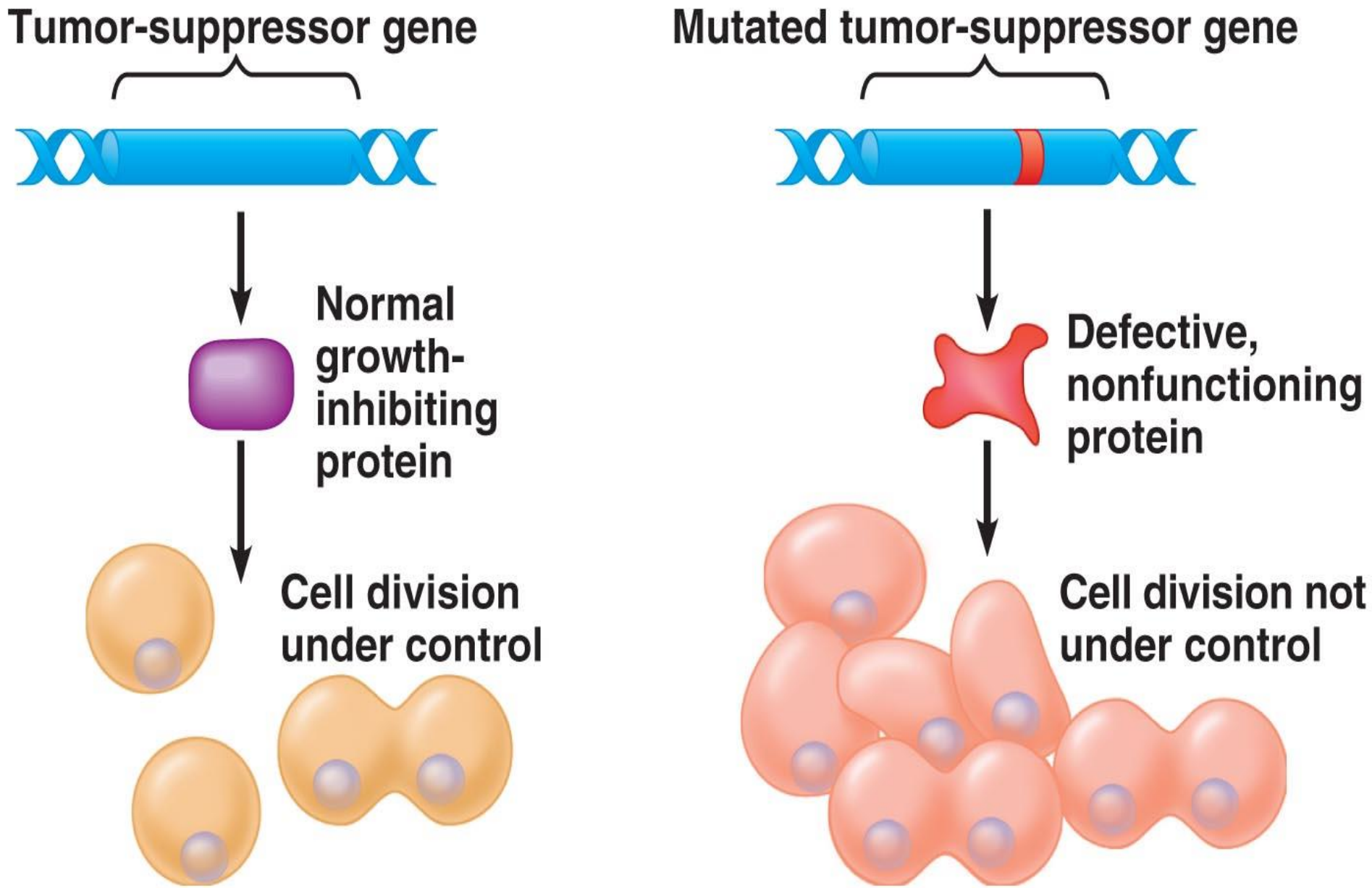
Figure 19.11


Chromosome 9
Chromosome 22
Philadelphia (Ph) chromosome
Bcr gene
Abl gene
Fusion gene (Bcr and Abl combined)

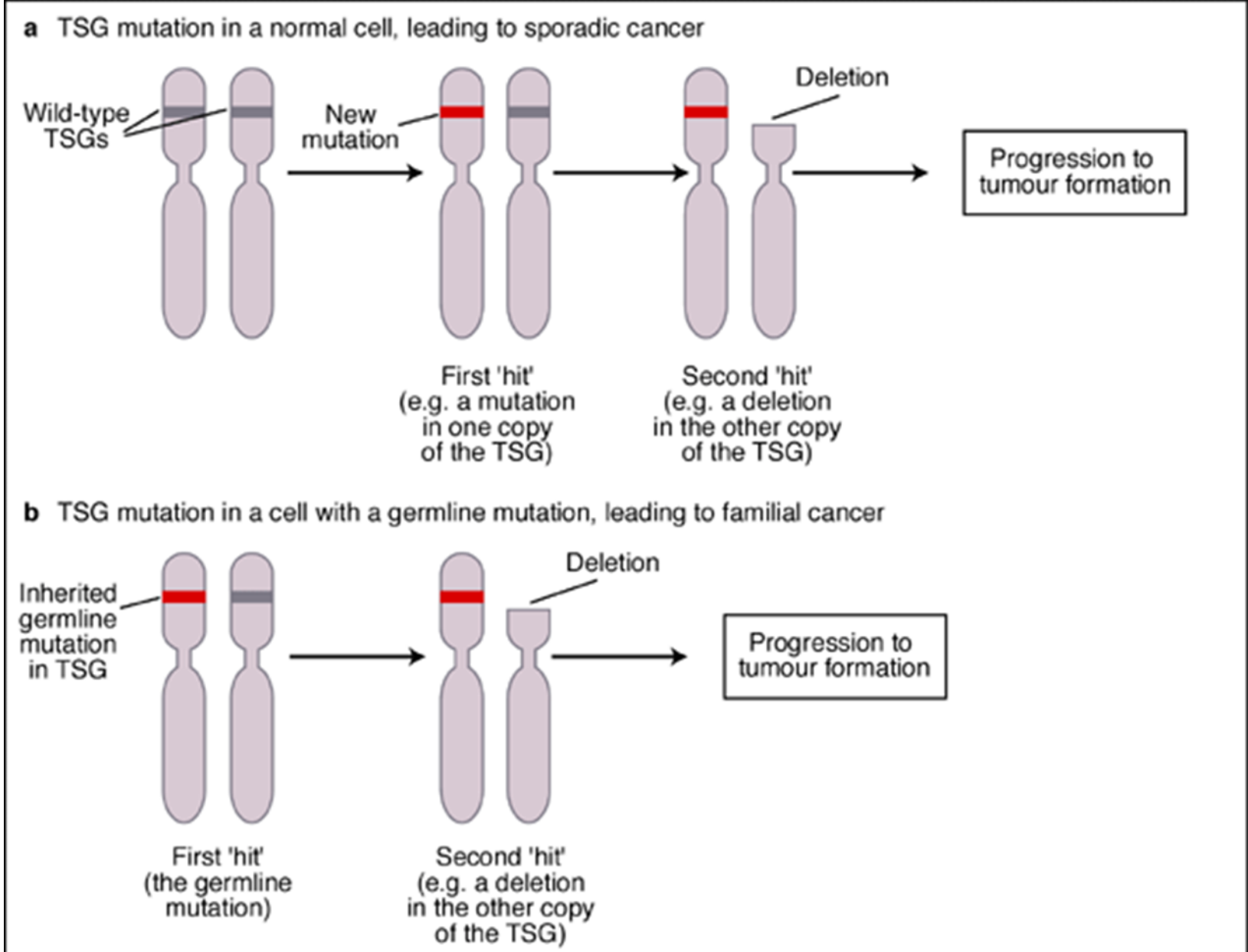

Normal
chromosomes
Burkitt's
lymphoma
8
14
8
14
CH
VH
VH
CH
myc
myc
Translocation

Mechanisms of tumor suppressor gene inactivation

- Deletion
- Point mutation
- Mutation followed by duplication
- Loss of heterozygosity
- DNA methylation
- Post-translational mechanism-binding to DNA viral oncoproteins

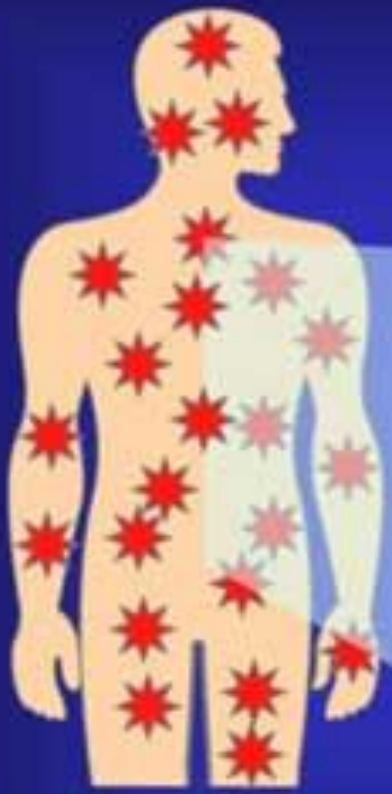


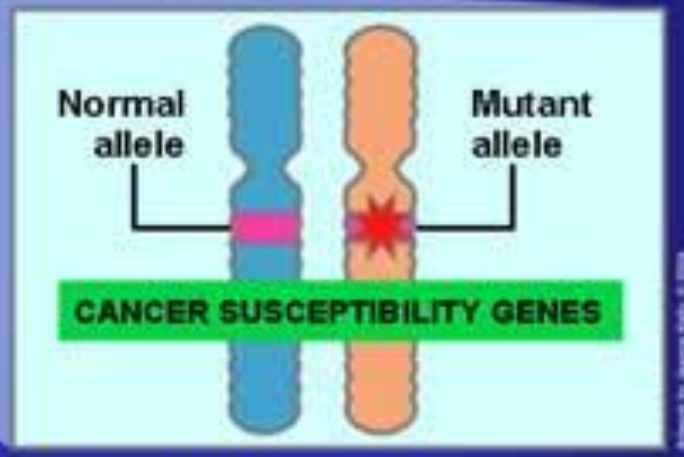
Knudson two-hit Hypothesis



Knudson's two-hit hypothesis for tumourigenesis involving a tumour suppressor gene (TSG)

Loss of Heterozygosity





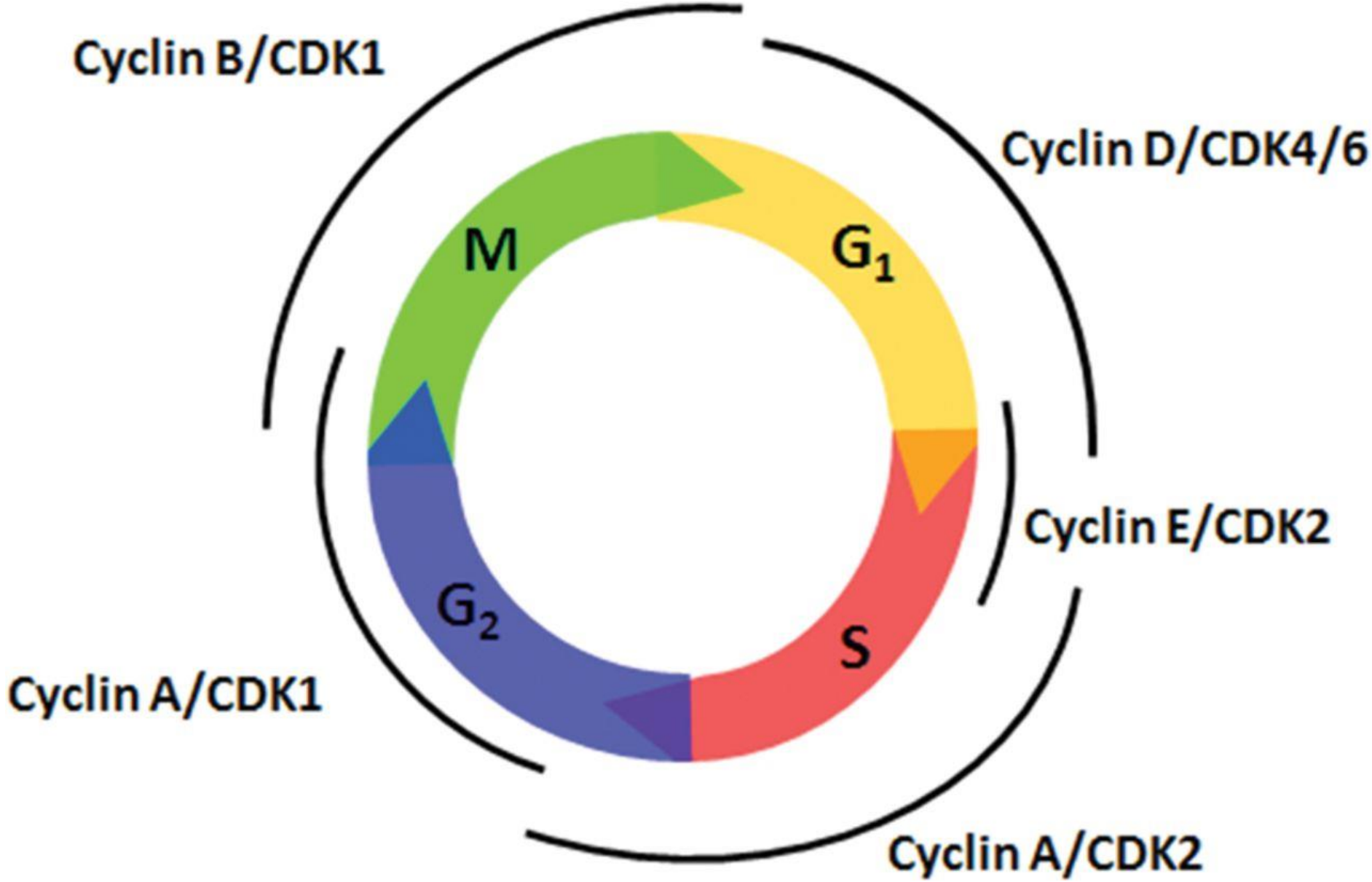
Heterozygous condition: normal gene balances the mutated gene

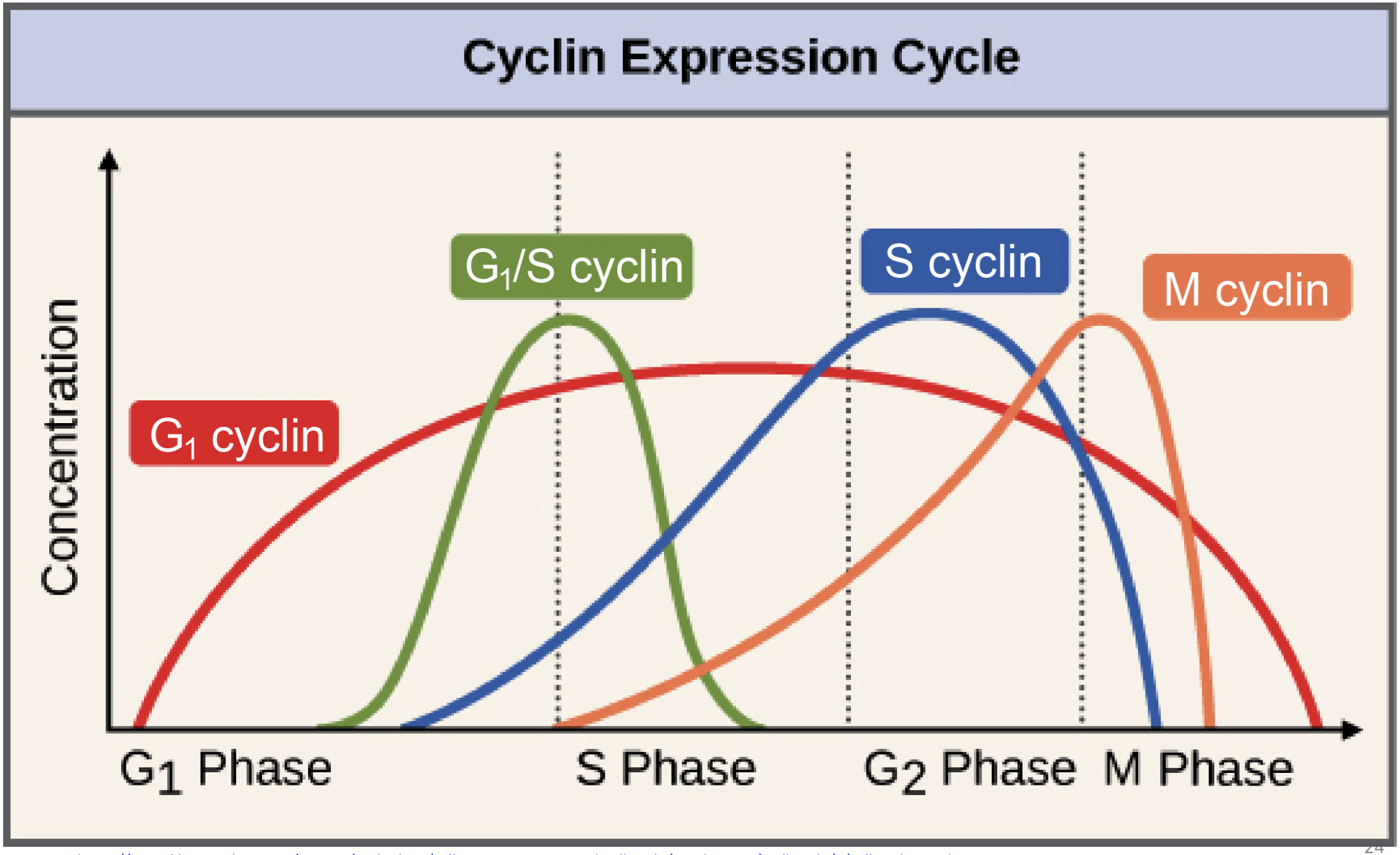
Germline mutation

NATIONAL CANCER INSTITUTE

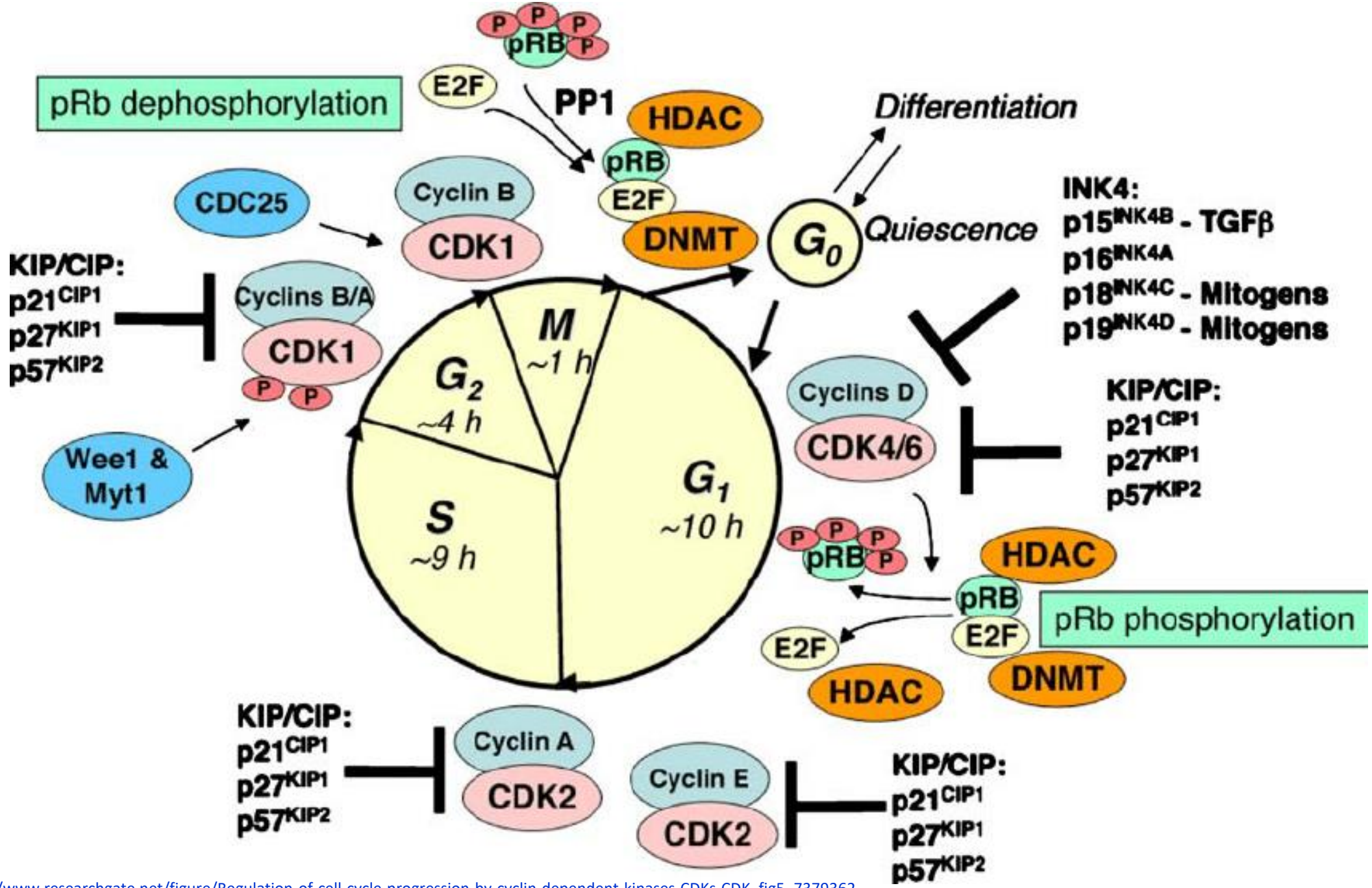
Target gene **expressed**

(Fry, 2011)


Cyclin B/CDK1
Cyclin D/CDK4/6
M
G1
Cyclin E/CDK2
G2
S
Cyclin A/CDK1
Cyclin A/CDK2

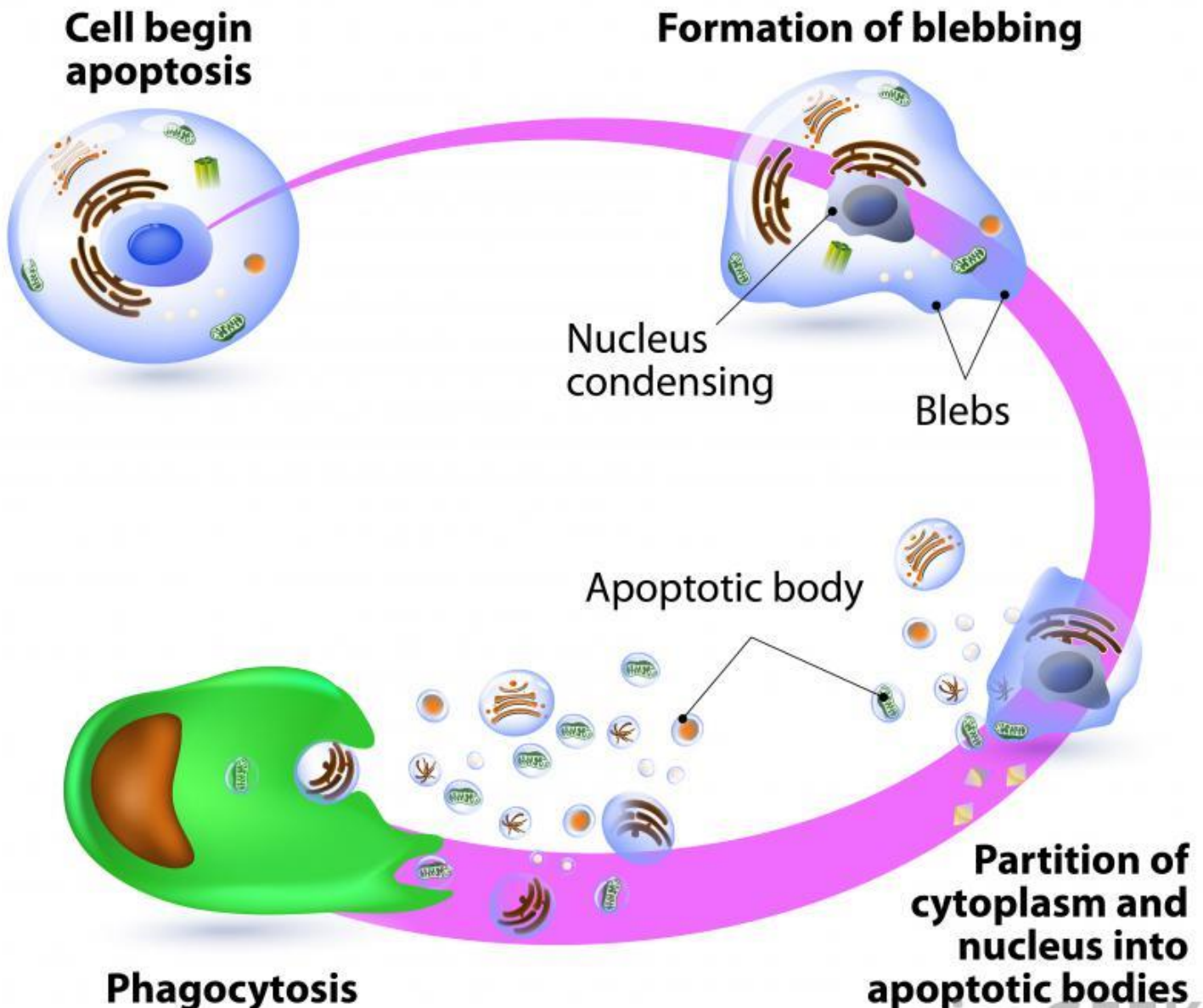


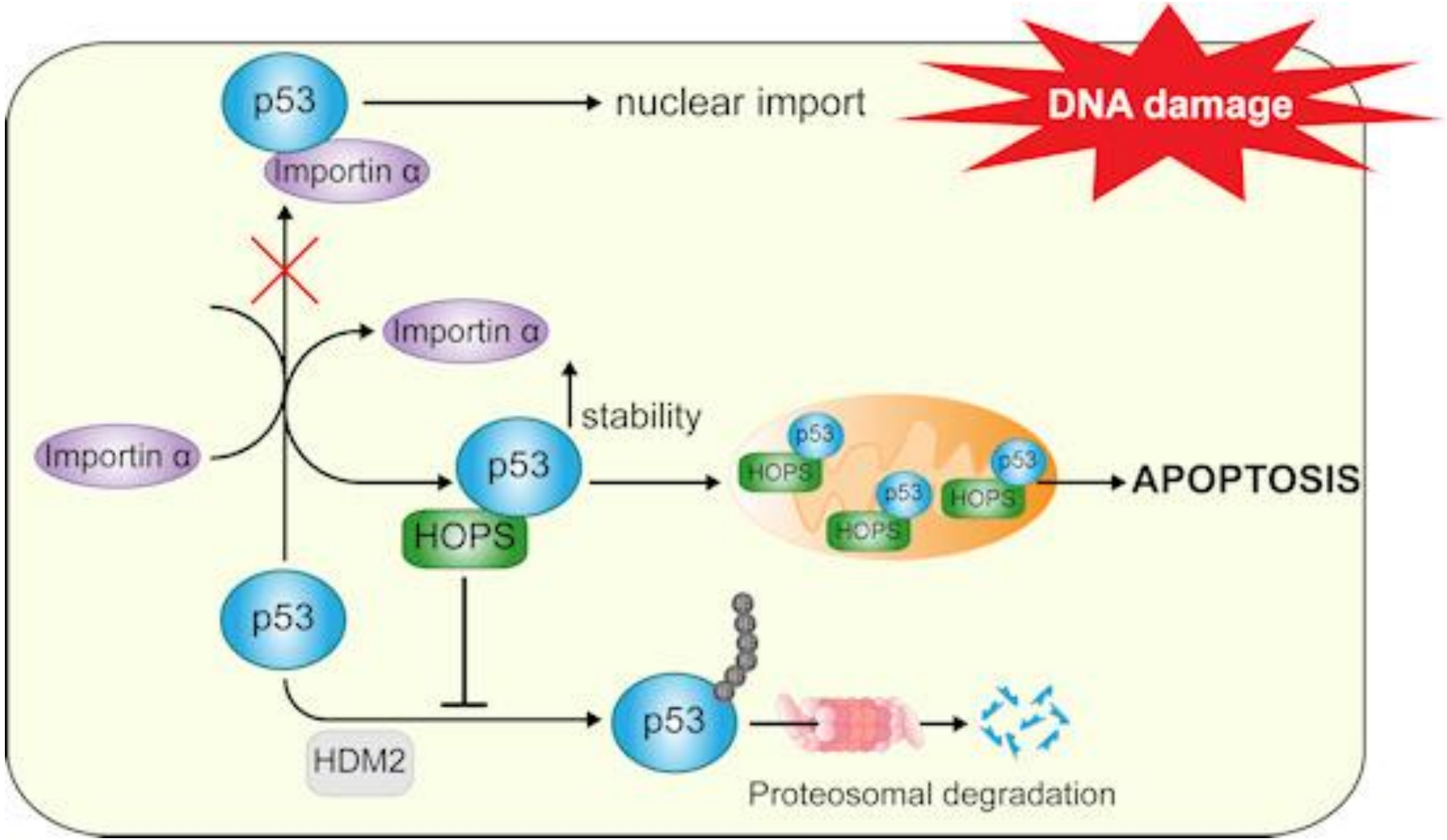
https://www.khanacademy.org/science/ap-biology/cell-communication-and-cell-cycle/regulation-of-cell-cycle/a/cell-cycle-regulators



https://www.researchgate.net/figure/Regulation-of-cell-cycle-progression-by-cyclin-dependent-kinases-CDKs-CDK_fig5_7379362

APOPTOSIS

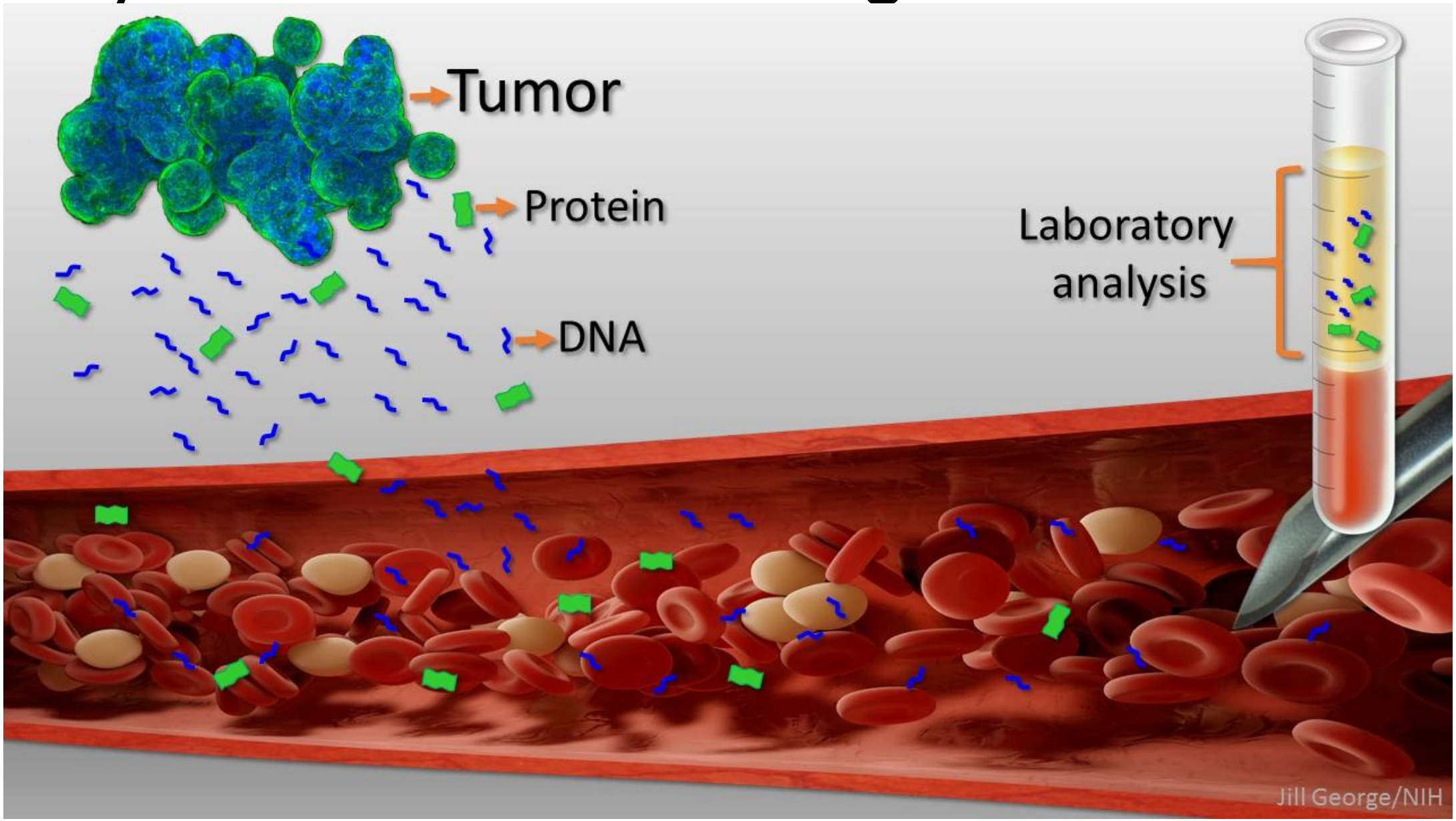

Cell begin apoptosis
Formation of blebbing
Nucleus condensing
Blebs
Apoptotic body
Partition of cytoplasm and nucleus into apoptotic bodies
Phagocytosis
wiseGEEK



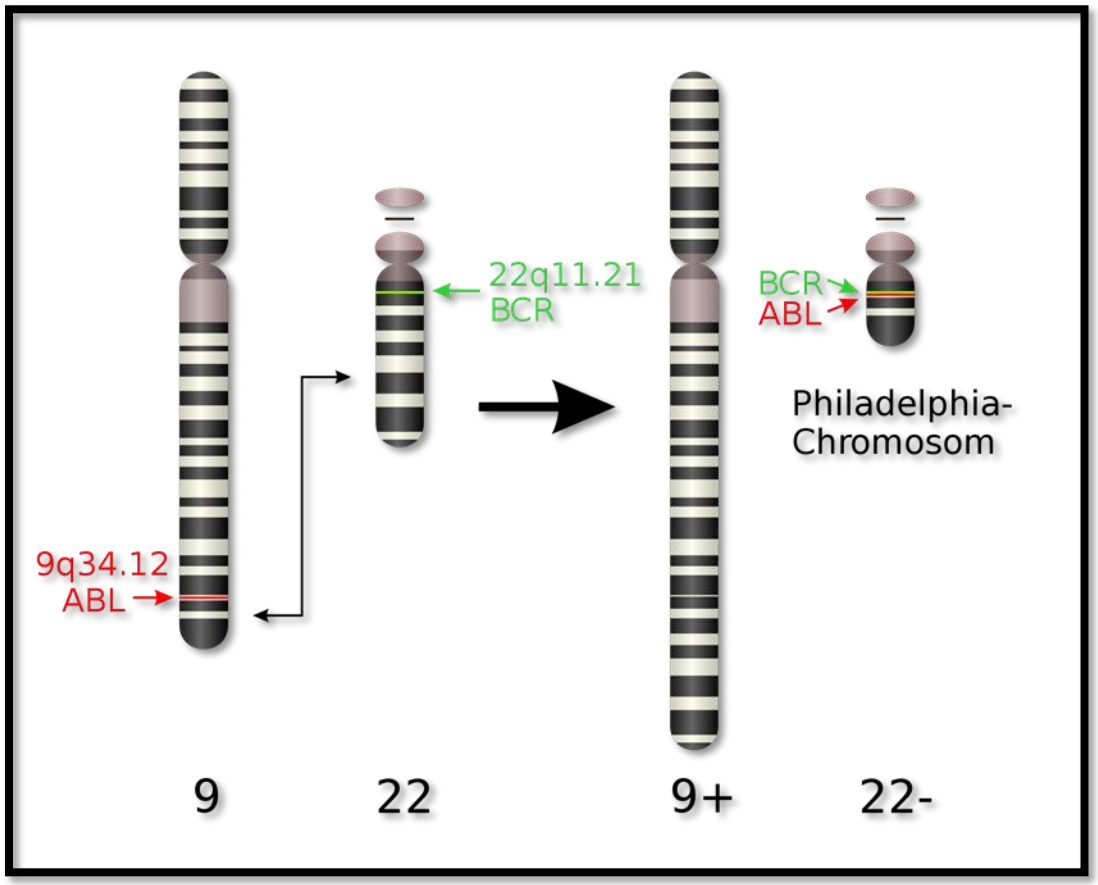
https://www.embopress.org/doi/full/10.15252/embr.201948073

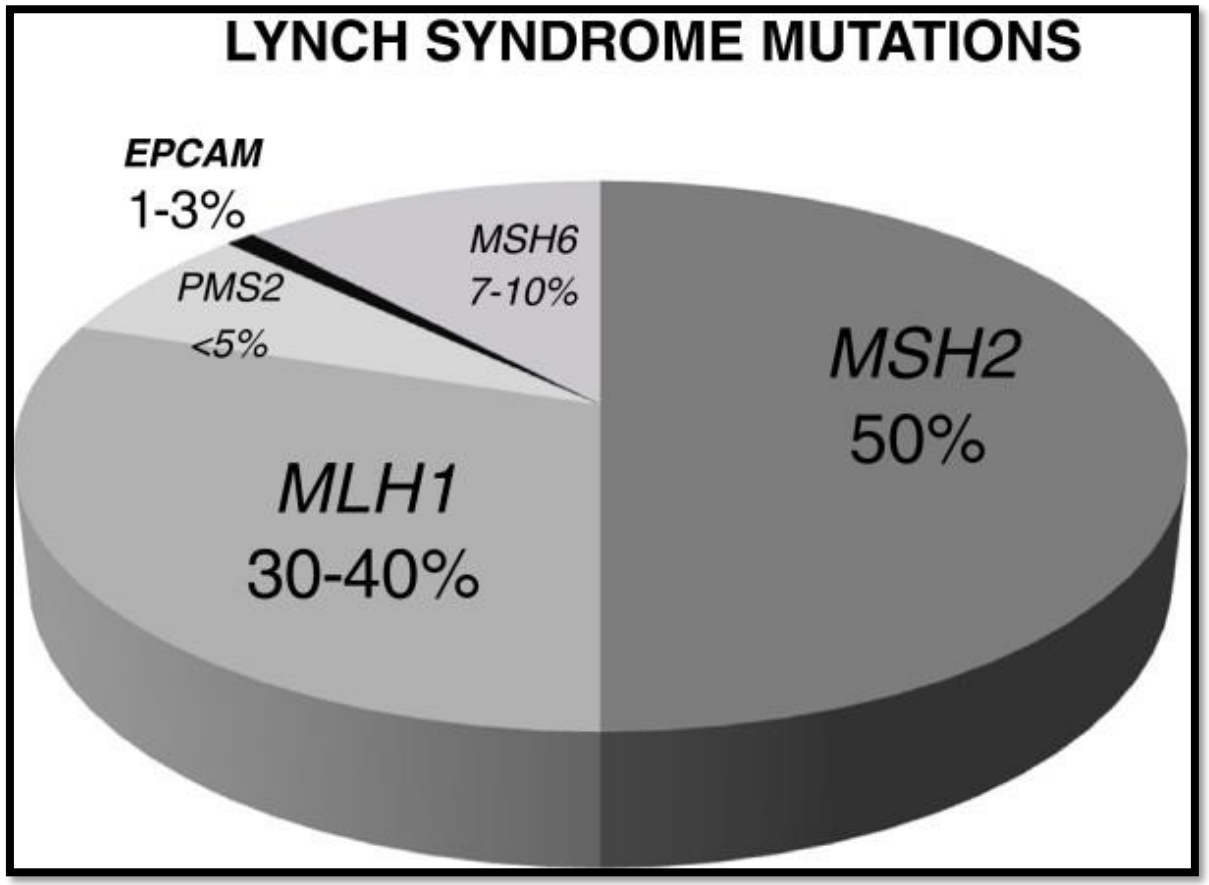
Molecular Medicine Implications in Cancer

Early detection and screening of cancer

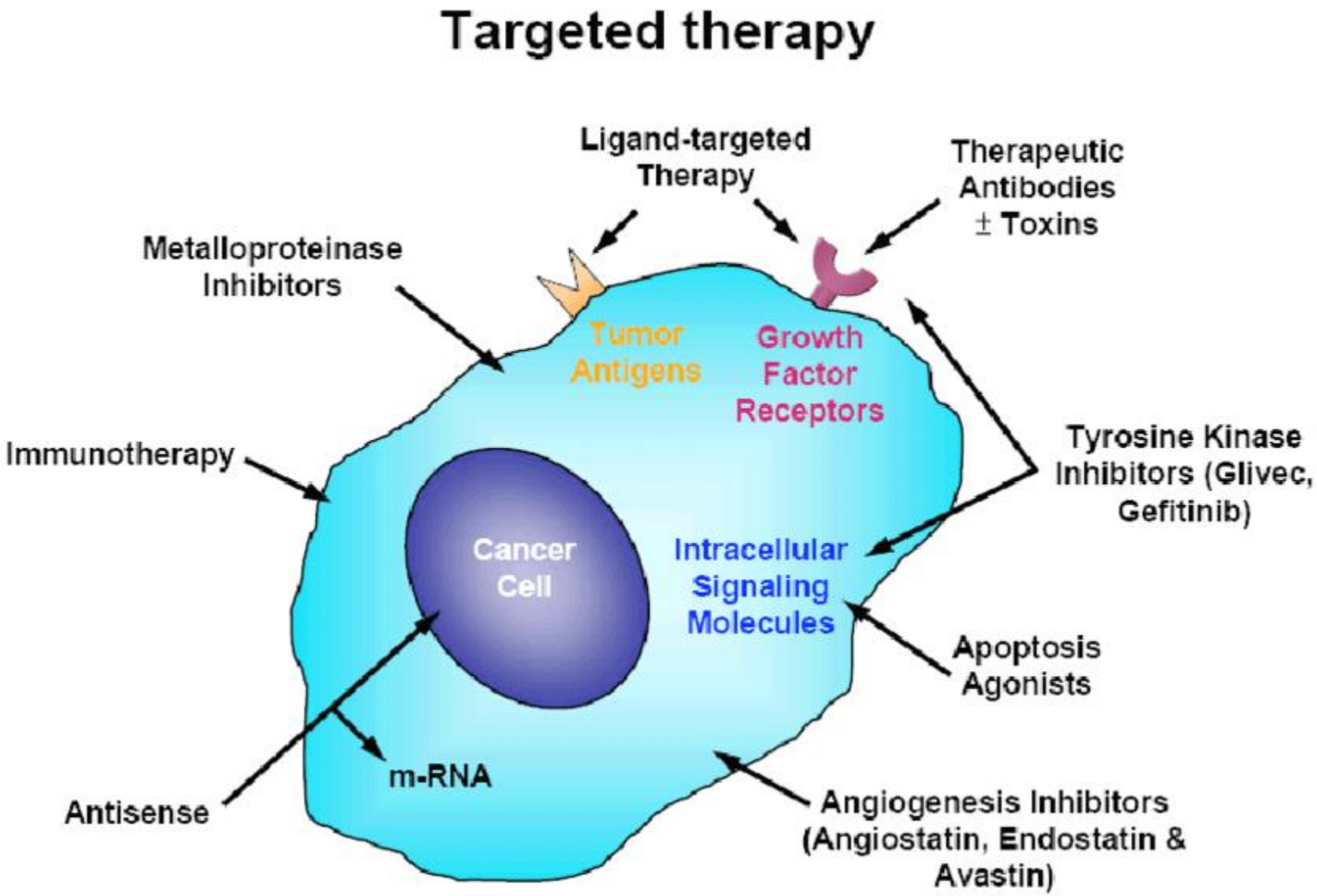


Diagnostic Implications





Therapeutic Implications



lymphpblastic leukaemia; UGT, uridine glucuronyltransferase.

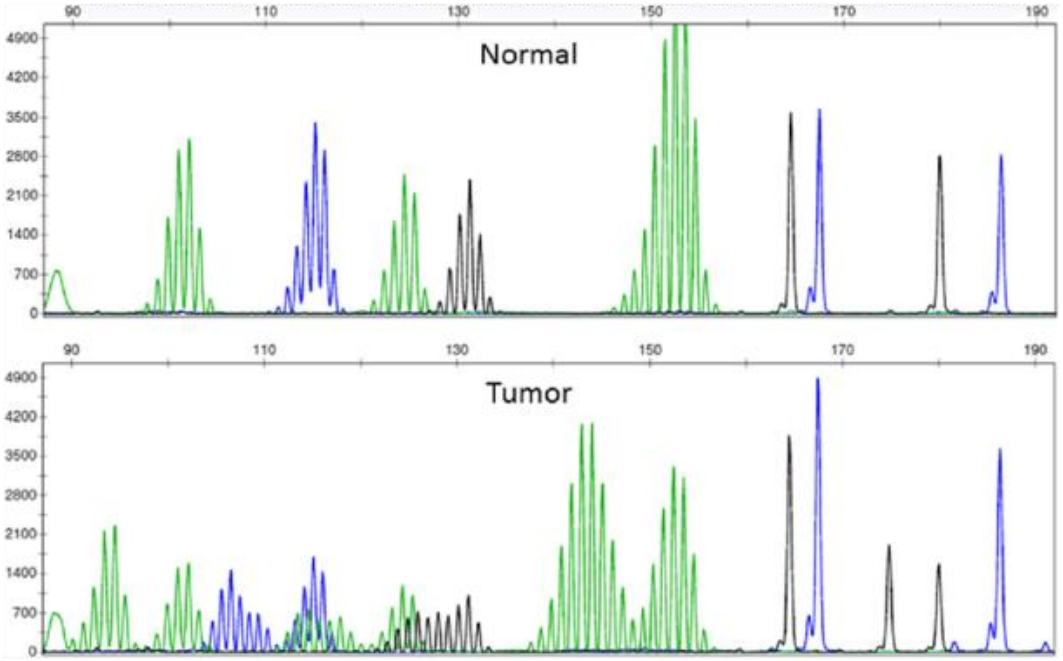
Marker	Malignancy	Therapy	Biological role of marker
ER	Breast	Hormone	Primary target
HER2	Breast	Trastuzumab	Primary target
Mutant *K-RAS*	Non small-cell lung	Gefitinib, erlotinib	Downstream of primary target
Mutant *K-RAS*, *BRAF*, *PIK3*, *PTEN*	Colorectal	Cetuximab, panitumumab	Downstream of primary target
MGMT	Glioma	Alkylating agents	DNA repair
ERCC1	NSCLC	Platinum agents	DNA repair
CYD2D6[a]	Breast cancer	Tamoxifen	Drug metabolism
TPMT	ALL	6-Mercaptopurine, 6-Thioguanine	Drug metabolism
UGT1A1[a]	Colorectal cancer	Irinotecan	Drug metabolism

[a] Specific genotypes.

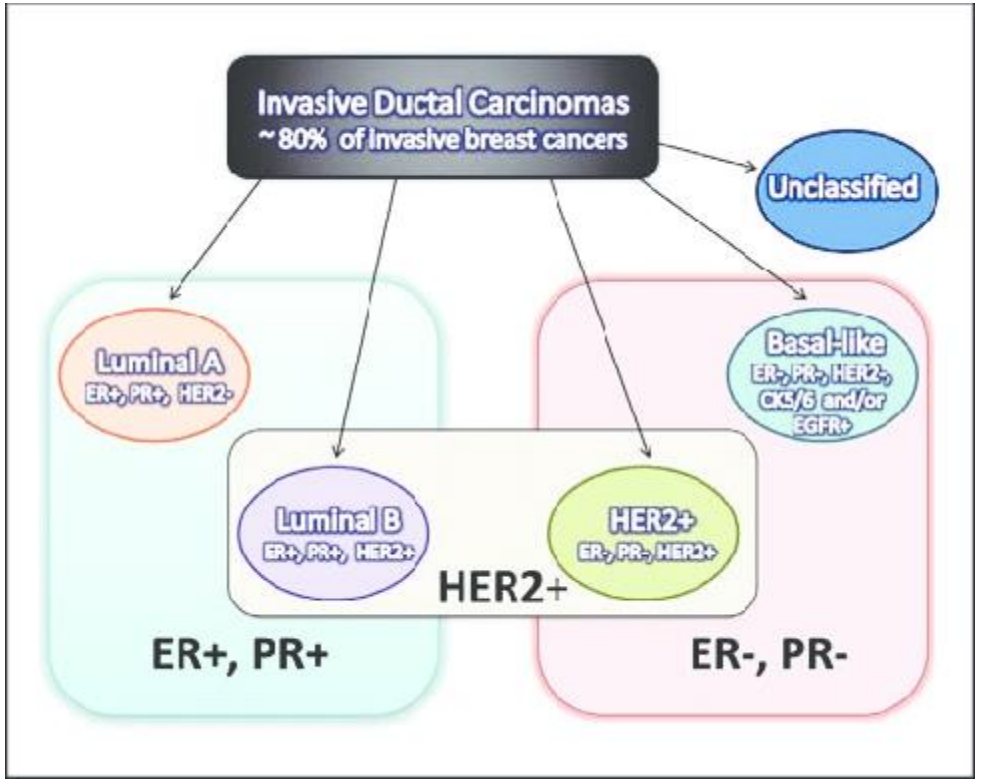
Biological roles of oncological therapy predictive and putative predictive markers.

https://www.semanticscholar.org/paper/Use-of-molecular-markers-for-predicting-therapy-in-Duffy O%27Donovan/e2a11a294bddf8646fd3689ae6656c2098ef8717/figure/0

Prognostic Implications



MSI testing



Preventive Implications

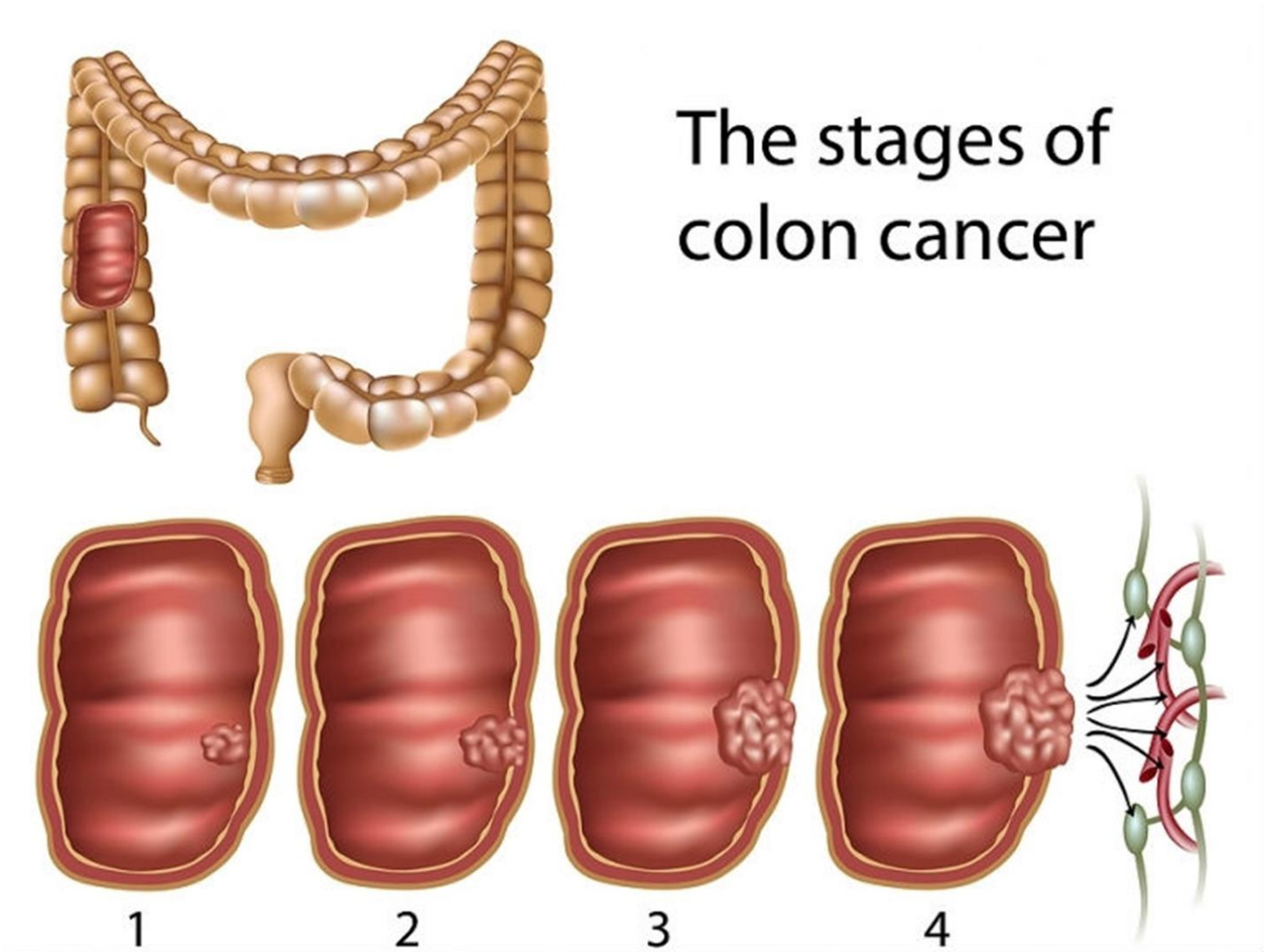


Table 1
Select hereditary cancer syndromes with genetic abnormality, associated cancers, and screening guidelines

Syndrome	Genes (Chromosomal Locus)	Common Cancers	Other Common Manifestations	Cancer Screening Guidelines
Hereditary breast and ovarian cancer syndrome	*BRCA1* (17q21) *BRCA2* (13q13)	Breast cancer and high-grade serous cancer of the ovary	Peritoneal serous carcinoma; primary fallopian tube carcinoma; pancreatic, prostate, and colon cancers	Annual breast MR imaging and/or mammogram starting between the ages of 25–29 y
Lynch syndrome	*MLH1* (3p21) *MSH2* (2p16) *MSH6* (2p16) *PMS2* (7p22)	Colorectal and endometrial cancers	Cancers of the ovary, stomach, and small bowel	Annual colonoscopy in all mutation carriers, beginning at the age of 25 y or 5–10 y before the earliest age of colon cancer onset in the family
FAP	*APC* (5q21)	Multiple colorectal adenomatous polyps and colorectal carcinoma	Gastric and duodenal polyps, osteomas, and desmoid tumors	Annual colonoscopy in patients with classic FAP and their first-degree relatives at the age of 12–14 y Annual upper GI endoscopy and neck US starting at 25–30 y
Li-Fraumeni syndrome	*TP53* (17p13)	Sarcomas, breast cancers, brain tumors, hematologic cancers, and adrenal cortical carcinomas	—	Annual mammography with or without breast MR imaging, starting at age 20–25 y Annual whole-body MR imaging examination is increasingly being considered
Cowden syndrome	*PTEN* gene (10q21)	Breast, thyroid, renal, and endometrial cancers	Trichilemmomas, macrocephaly, Lhermitte-Duclos disease, benign thyroid nodules, fibrocystic breast disease, multiple GI polyps, and uterine fibroids	Annual renal US at 40 y and repeating every 1–2 y Annual endometrial biopsy and/or the transvaginal US starting at age 30 y and colonoscopy starting at 35–40 y
Hereditary diffuse gastric cancer	E-cadherin (16q22)	Aggressive diffuse, infiltrating gastric cancer (signet-ring type)	—	Prophylactic gastrectomy in asymptomatic carriers of CDH1 gene and intensive annual endoscopic surveillance in those who decline gastrectomy Annual breast MR imaging with or without mammogram starting at 30 y

Important Criteria for Cancer Genetics Counseling

- 1) One FDR members affected to cancer in age < 50 or two FDRs in any age
- 2) A family history of cancer in successive generations
- 3) A family history of rare cancers without any known risk factors
- 4) A family history of known hereditary cancer syndromes

(no subject) - zeinalianmehrdad | دانشگاه علوم پزشکی اصفهان | macsa cancer - Google Search | مکسا ارائه دهنده مراقبت های حمایتی

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Cancer Genetics (1).pptx
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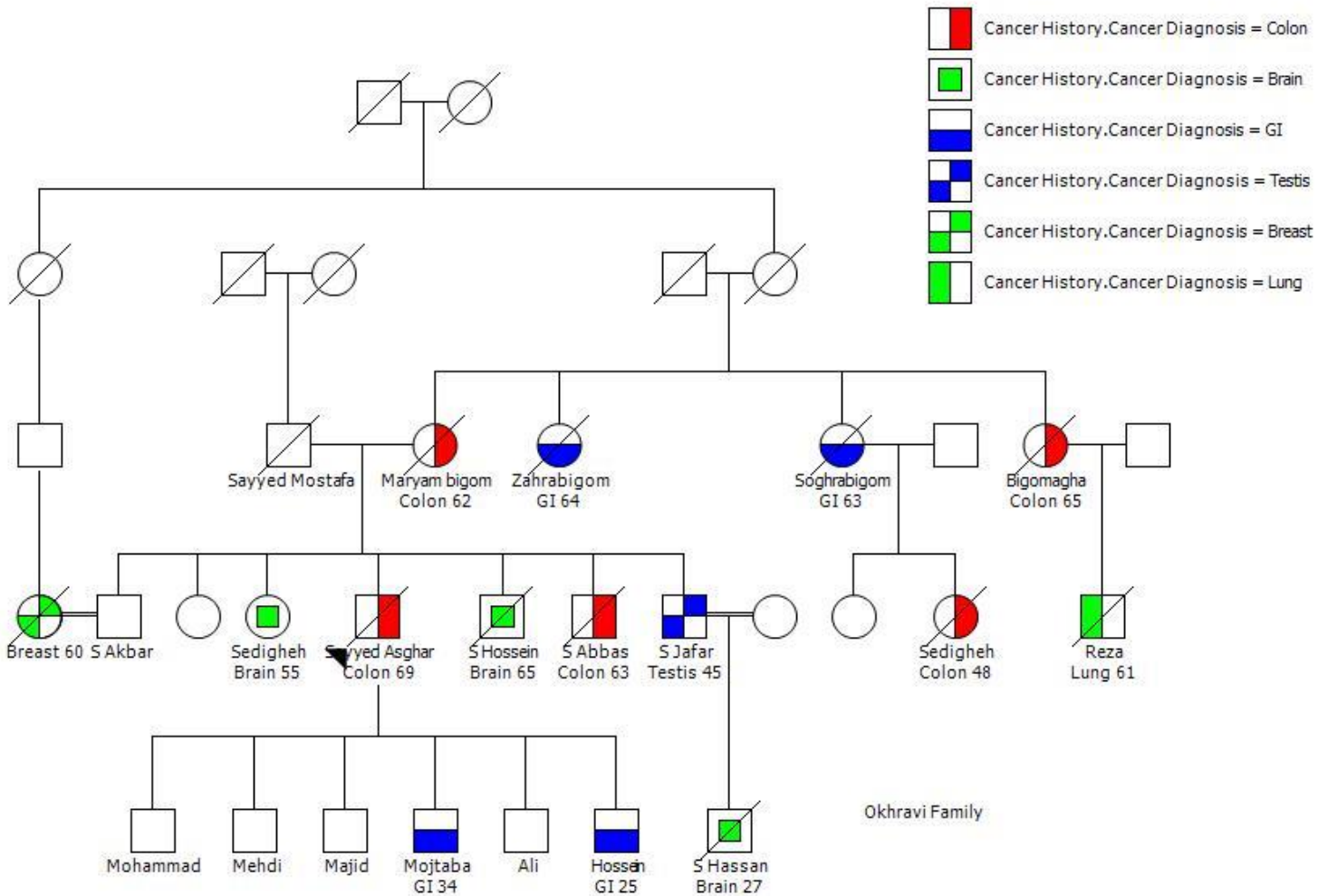
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Cancer History.Cancer Diagnosis = Brain
Cancer History.Cancer Diagnosis = GI
Cancer History.Cancer Diagnosis = Testis
Cancer History.Cancer Diagnosis = Breast
Cancer History.Cancer Diagnosis = Lung
Sayyed Mostafa
Maryam bigom
Colon 62
Zahrabigom
GI 64
Soghrabigom
GI 63
Bigomagha
Colon 65
Breast 60
S Akbar
Sedigheh
Brain 55
Sayyed Asghar
Colon 69
S Hossein
Brain 65
S Abbas
Colon 63
S Jafar
Testis 45
Sedigheh
Colon 48
Reza
Lung 61
Mohammad
Mehdi
Majid
Mojtaba
GI 34
Ali
Hossein
GI 25
S Hassan
Brain 27
Okhravi Family


Questions?
Comments?
Suggestions?


Thanks for your attention