SOLID TUMOR MARKERS

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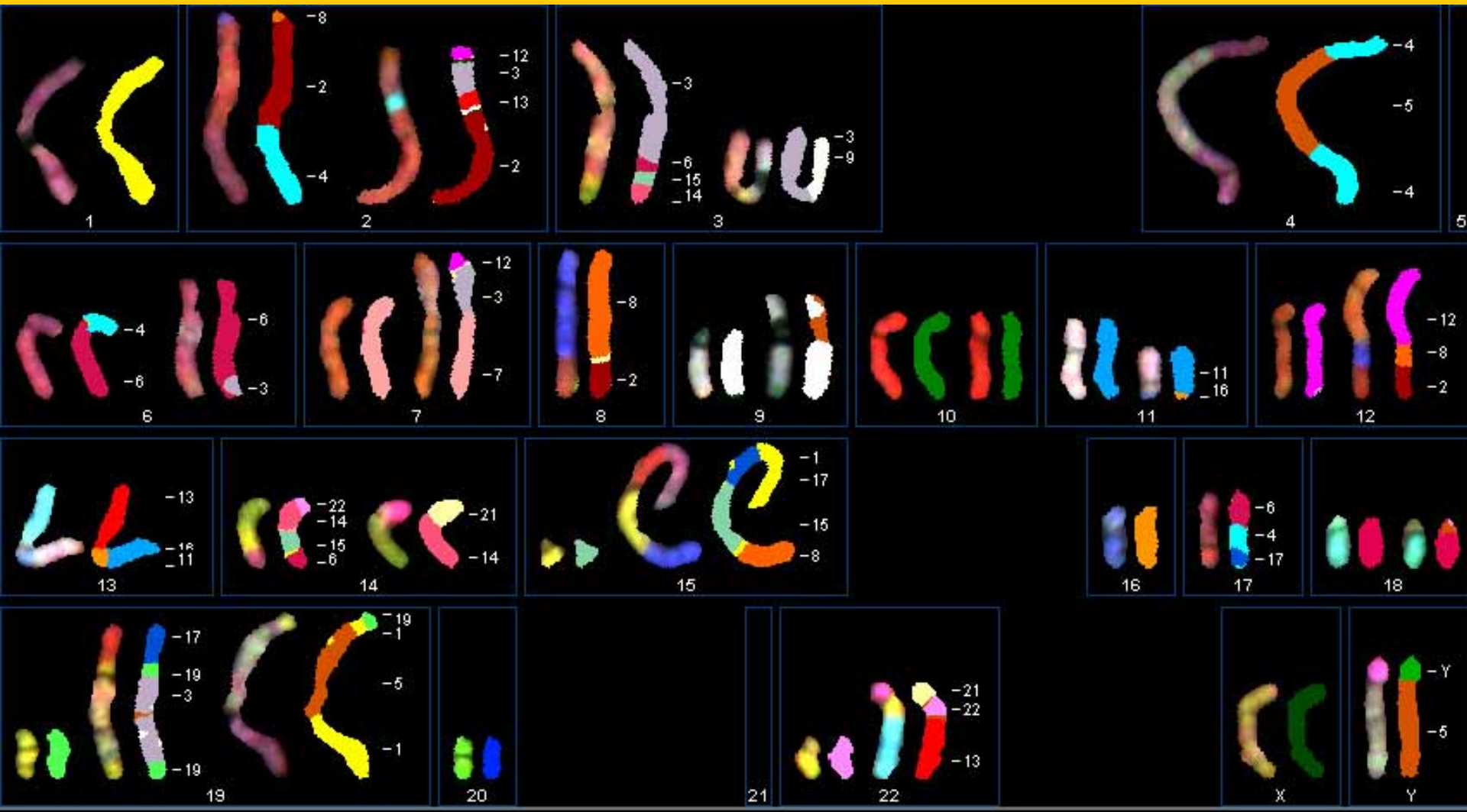
CANCER…???

~600 mutations, chromosomal gains-losses, tert, snps…



CANCER

Cancer MoonShot 2020

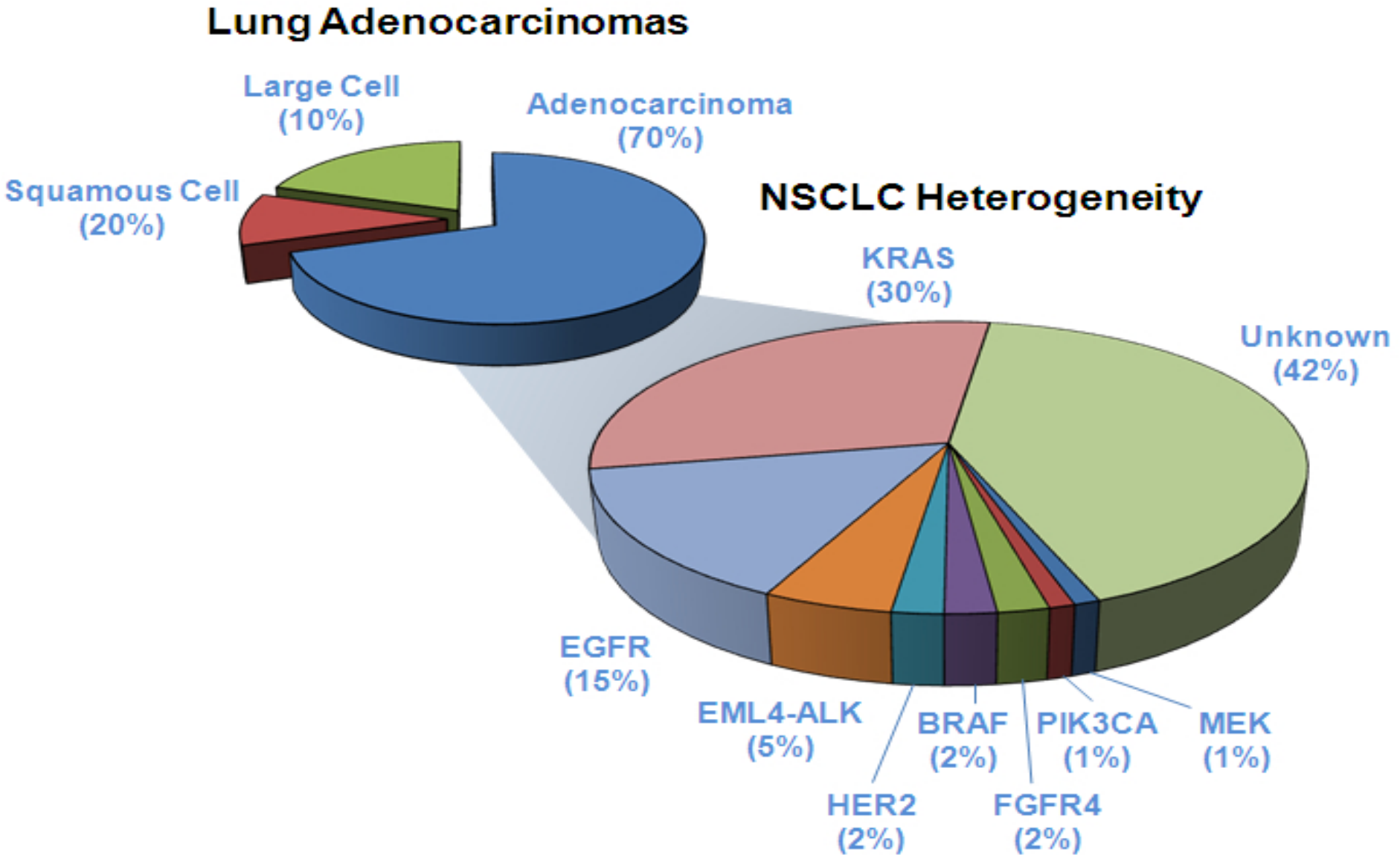
TURKEY…???

ICR The Institute of Cancer Research

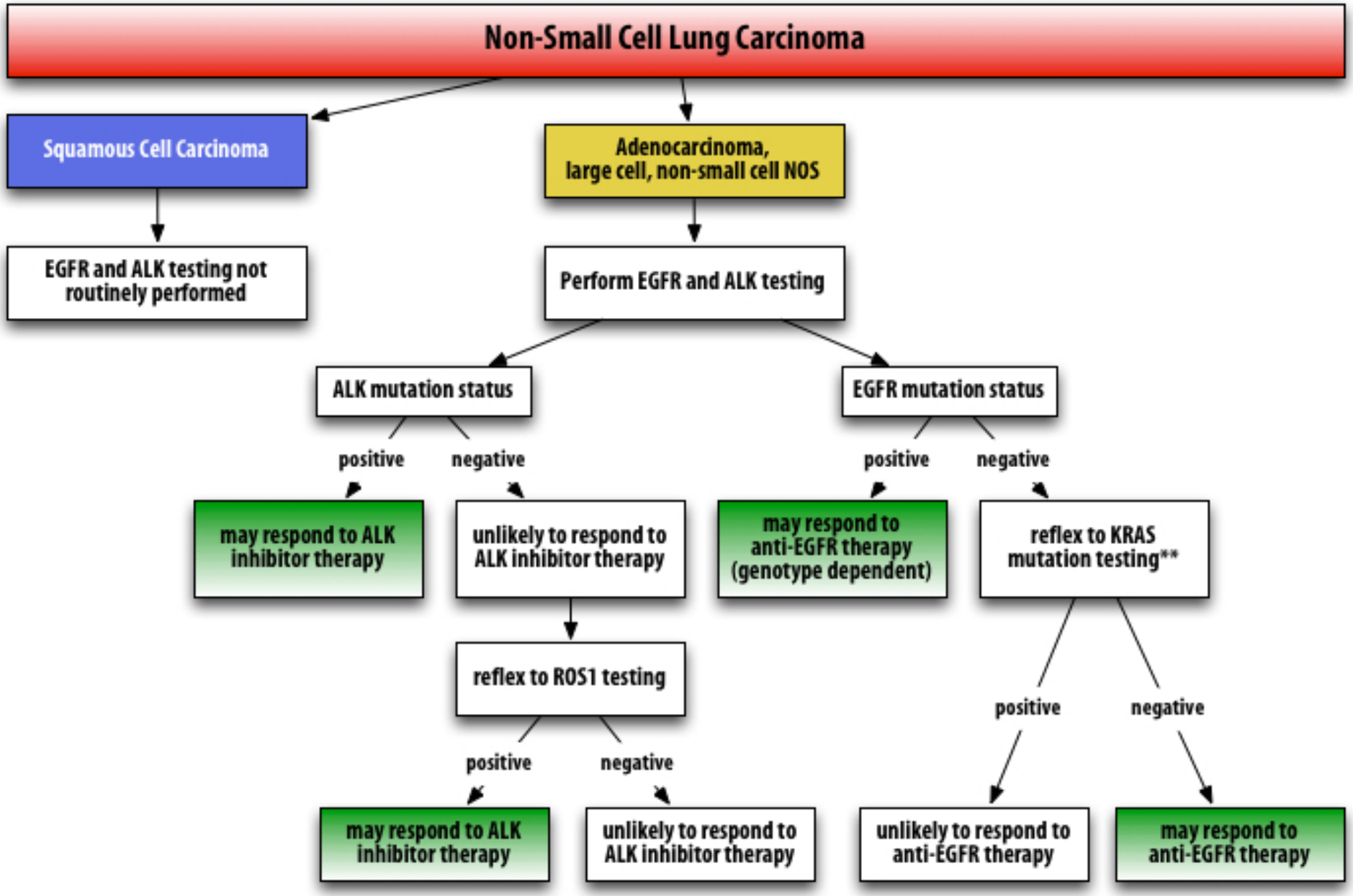
Trillions of dollars…

CANCER RESEARCH UK

LUNG CANCER


Lung Adenocarcinomas
Large Cell (10%)
Adenocarcinoma (70%)
Squamous Cell (20%)
NSCLC Heterogeneity
KRAS (30%)
Unknown (42%)
EGFR (15%)
EML4-ALK (5%)
BRAF (2%)
PIK3CA (1%)
MEK (1%)
HER2 (2%)
FGFR4 (2%)

NSCLC

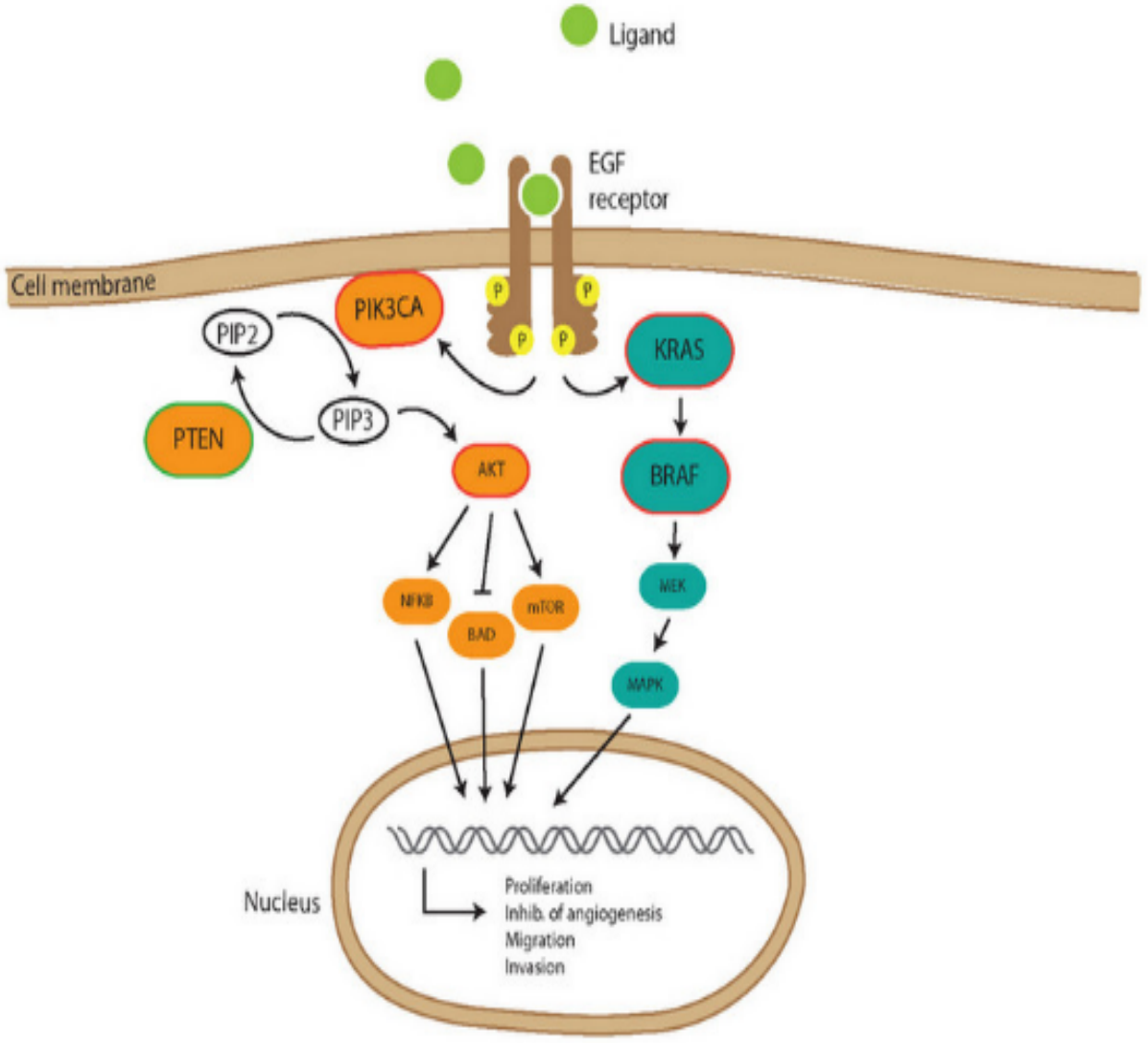

Non-Small Cell Lung Carcinoma
Squamous Cell Carcinoma
Adenocarcinoma, large cell, non-small cell NOS
EGFR and ALK testing not routinely performed
Perform EGFR and ALK testing
ALK mutation status
EGFR mutation status
positive
negative
positive
negative
may respond to ALK inhibitor therapy
unlikely to respond to ALK inhibitor therapy
may respond to anti-EGFR therapy (genotype dependent)
reflex to KRAS mutation testing**
reflex to ROS1 testing
positive
negative
positive
negative
may respond to ALK inhibitor therapy
unlikely to respond to ALK inhibitor therapy
unlikely to respond to anti-EGFR therapy
may respond to anti-EGFR therapy

LUNG CANCER (NSCLC)

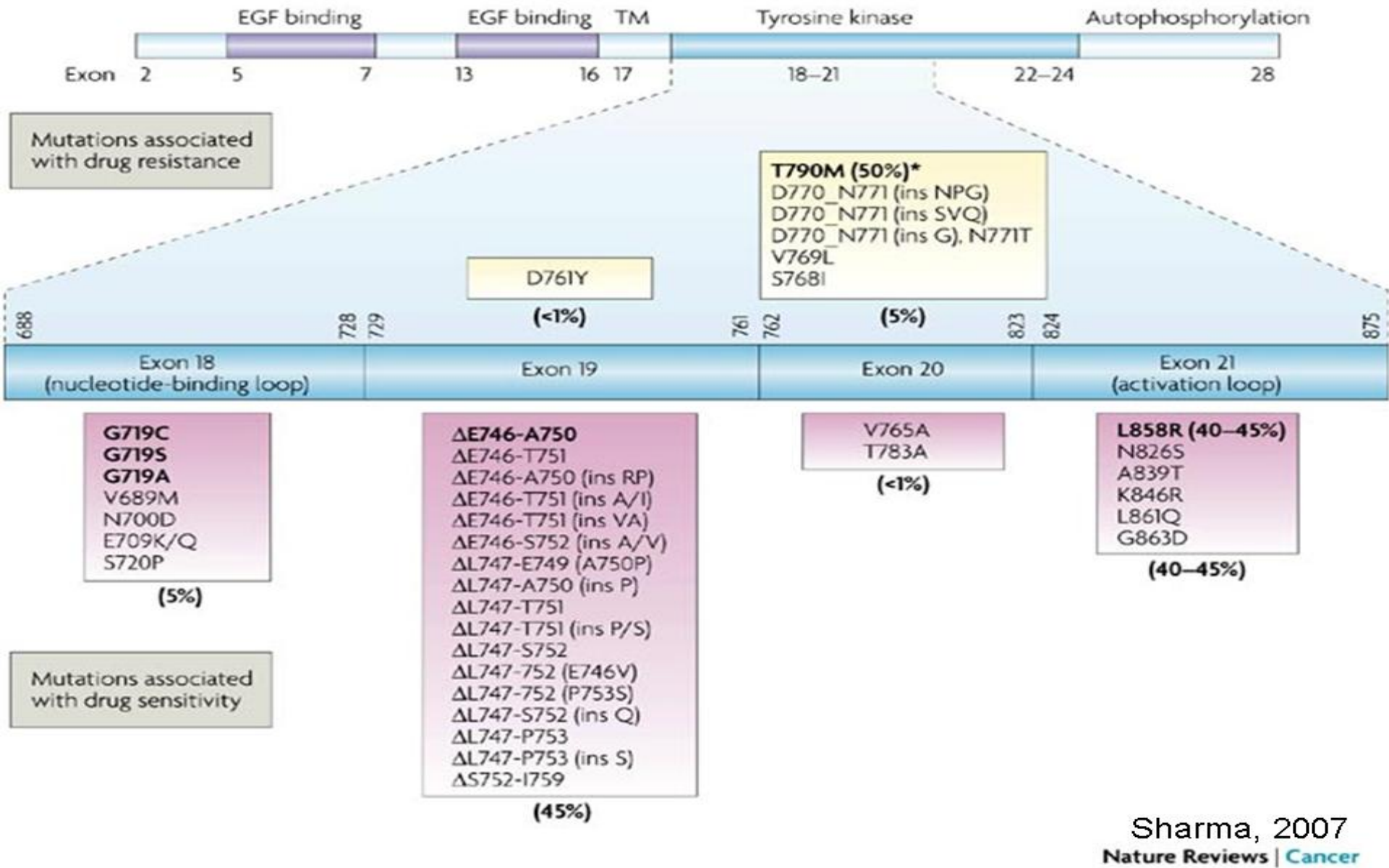
- EGFR Mutation
- KRAS Mutation
- ALK (FISH)
- ROS1 (FISH)
- ERBB2 (HER2), BRAF, DDR2, AKT1,HRAS, JAK2, KDR, MAP2K1, NOTCH1, NRAS, NTRK1, NTRK2, NTRK3, PIK3CA, PIK3R1, PIK3R2, PTEN, PTPRD, CDKN2A, TP53 (NGS) / ALK, RET, MET, FGFR1 (FISH) / ERCC1, TS, RRM1…

EGFR

- Also called HER1 or erbB-1
- 15% of NSCLC (Asia 22-62%)
- Women, non-smokers (eski dönemler uygulama)
- mutations in EGFR= sensitivity to EGFR TKIs
- exon 19 deletions, L858R point mutation in exon 21
- erlotinib, gefitinib, afatinib
- T790M mutation, amplification of the MET oncogene associated with resistance
- NSCLC>SCLC associated with resistance



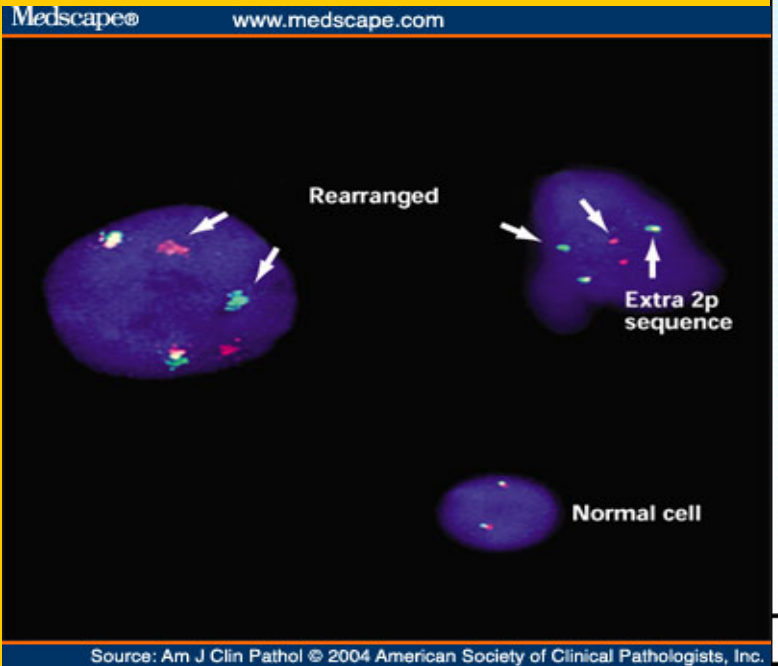
EGFR

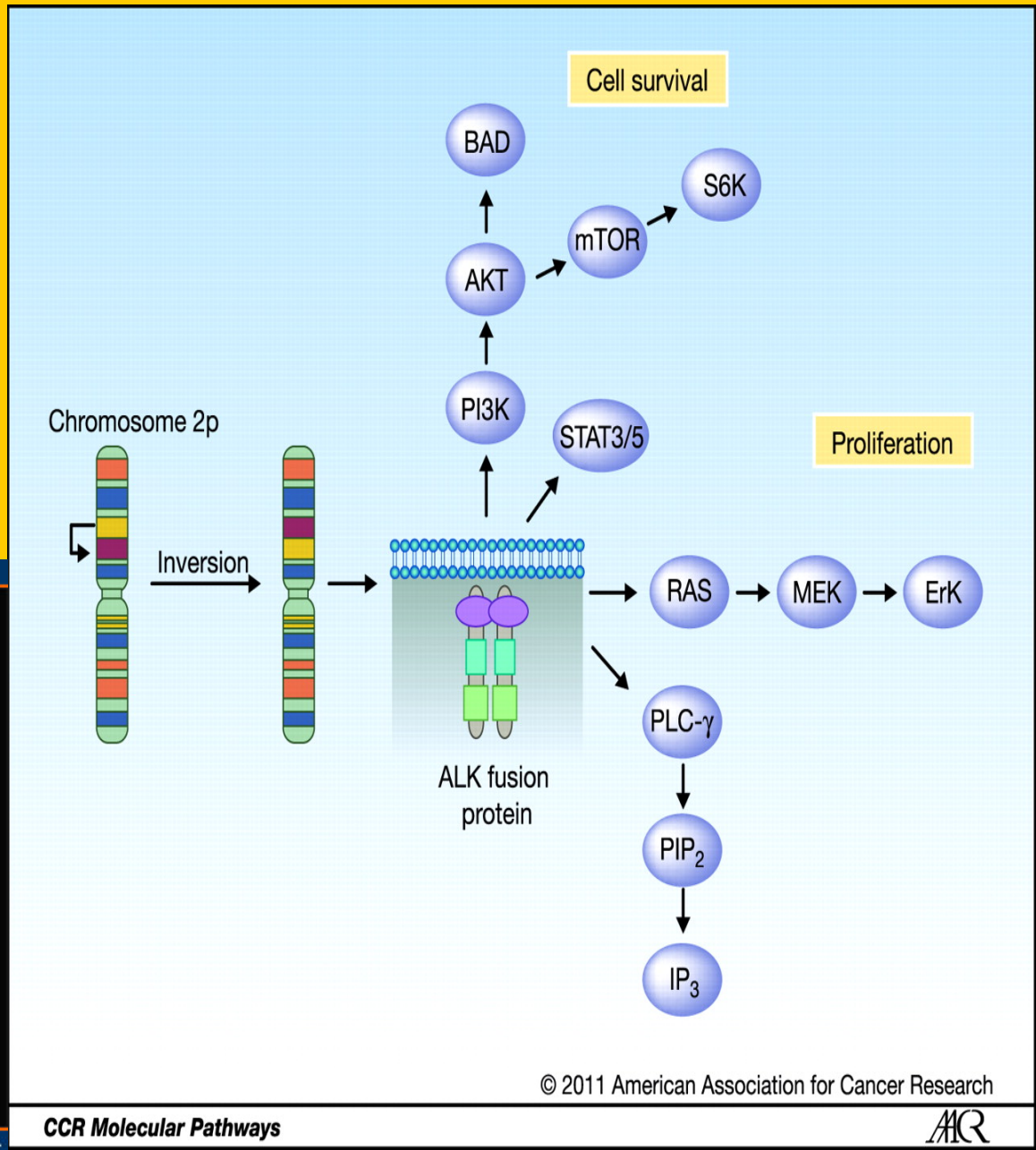


Sharma, 2007
Nature Reviews | Cancer

ALK

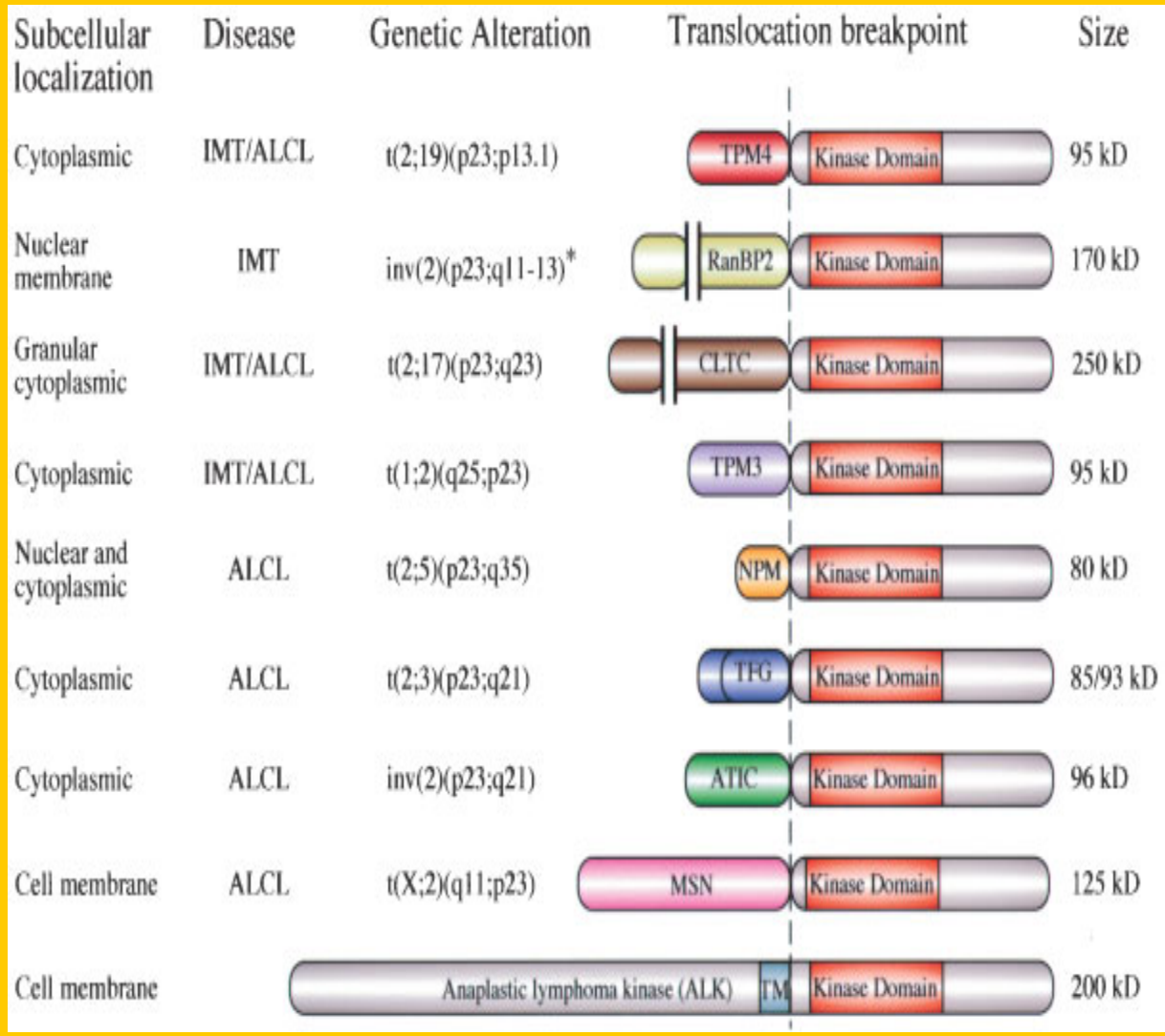
- EML4-ALK (Inv(2)(p21p23))
- The gold standard assay for diagnosing ALK-positive NSCLC is FISH (also IHC and RT-PCR)
- Associated with never smoking history, younger age and adenocarcinoma with signet ring or acinar histology
- ALK gene arrangements X EGFR or KRAS mutations
- EGFR phenotype + EGFR negative > ALK
- ALK tyrosine kinase inhibitors=Crizotinib, ceritinib





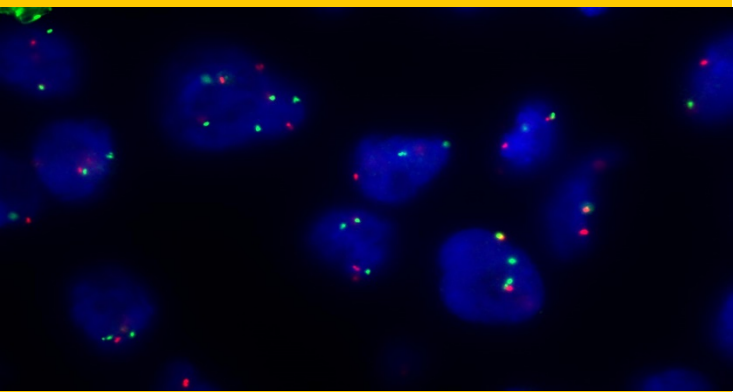
ALK (Anaplastic Lymphoma Receptor Tyrosine Kinase)

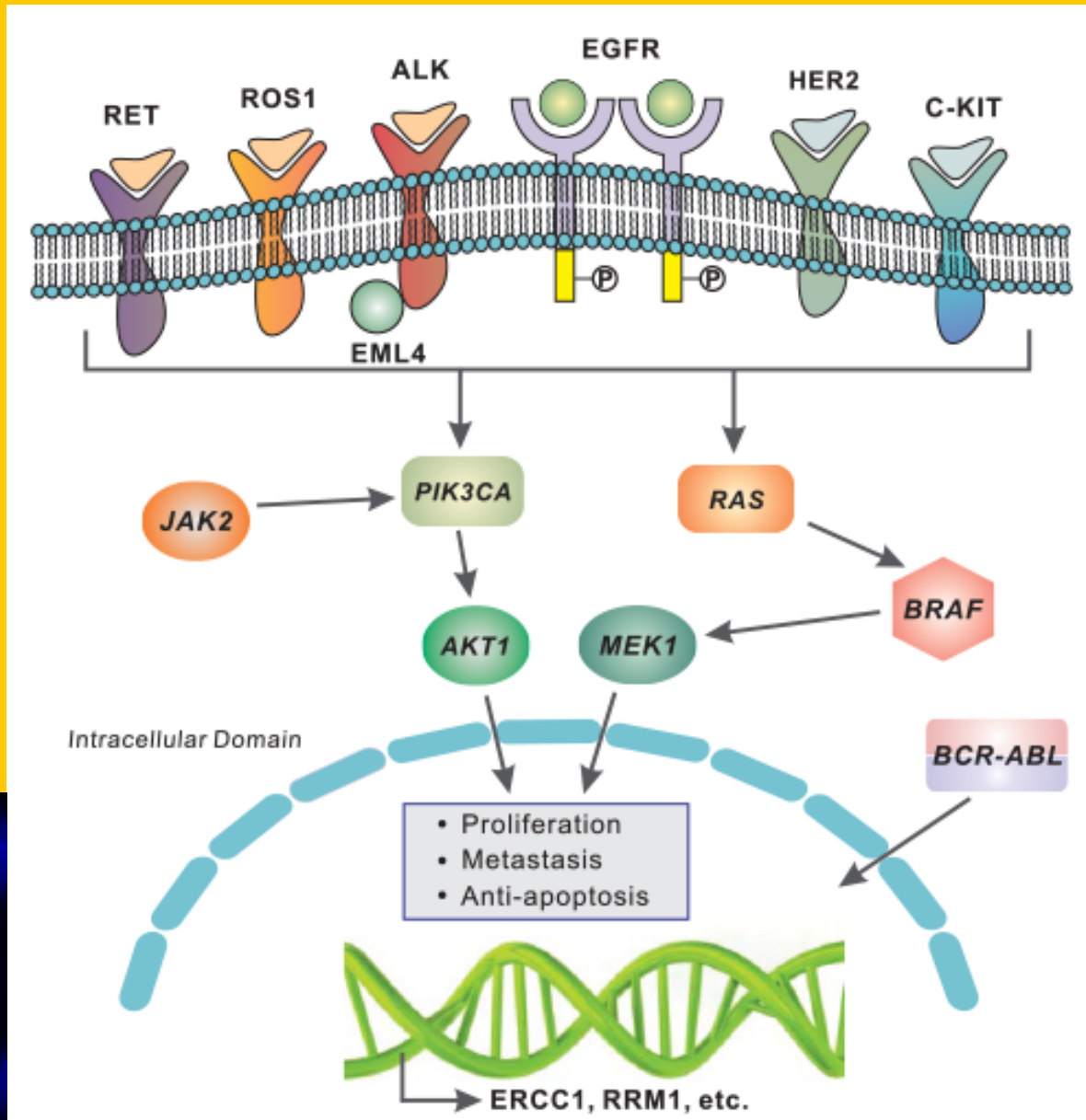
- **ALK fusions with nucleophosmin (nucleolar phosphoprotein B23, numatrin) (NPM1) have been detected in anaplastic large cell lymphomas**
- **ALK fusions with vinculin (VCL) in renal medullary cancer**
- **ALK fusions with tropomyosin 3 (TPM3) or tropomyosin 4 (TPM4) in inflammatory myofibroblastic tumors**
- **Missense mutations in neuroblastoma and anaplastic thyroid cancers.**



ROS

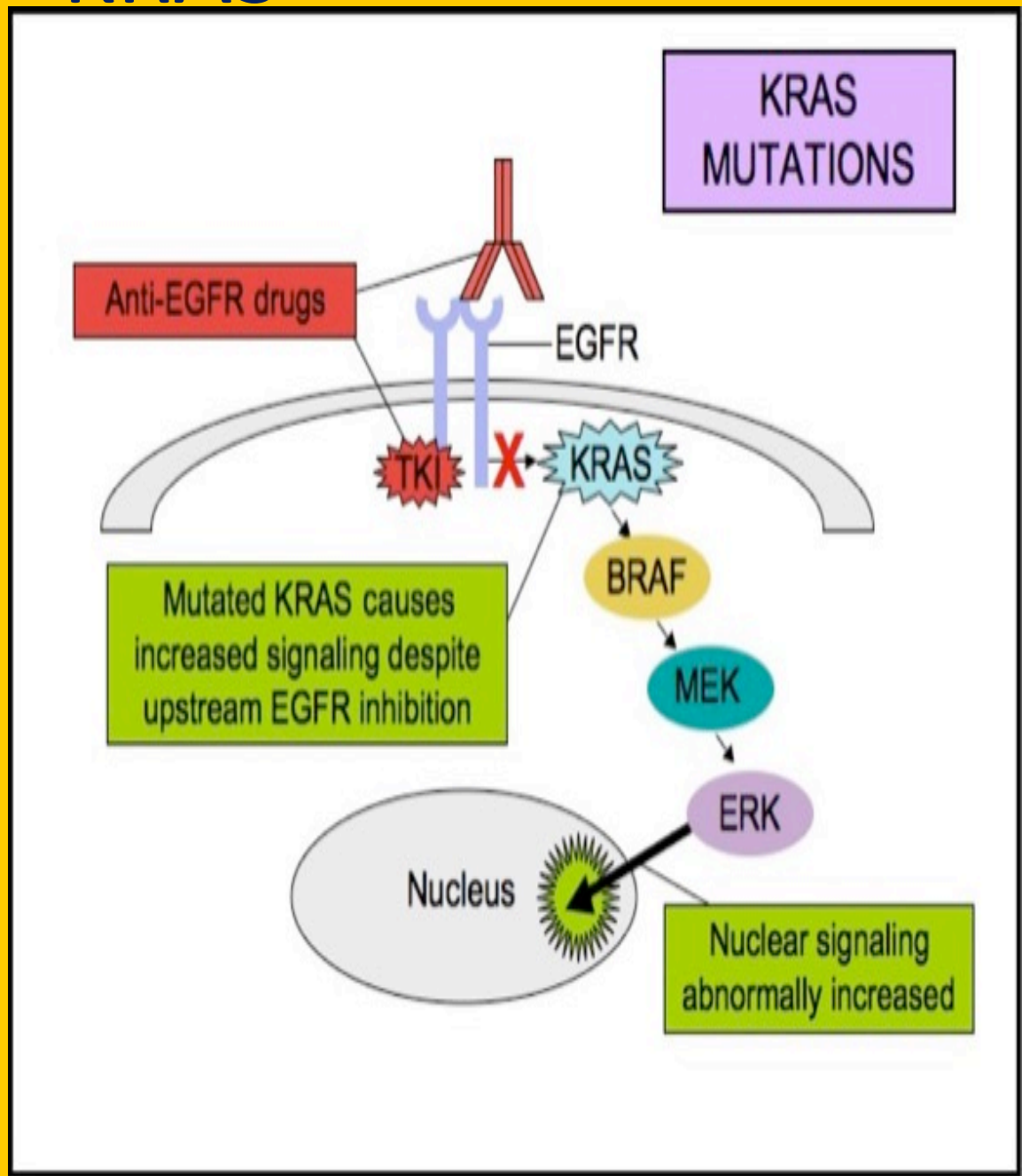
- ROS1 is a receptor tyrosine kinase of the insulin receptor family
- 1-2% NSCLC
- Adenocarcinoma histology, younger patients, and never-smokers
- FISH
- Crizotinib





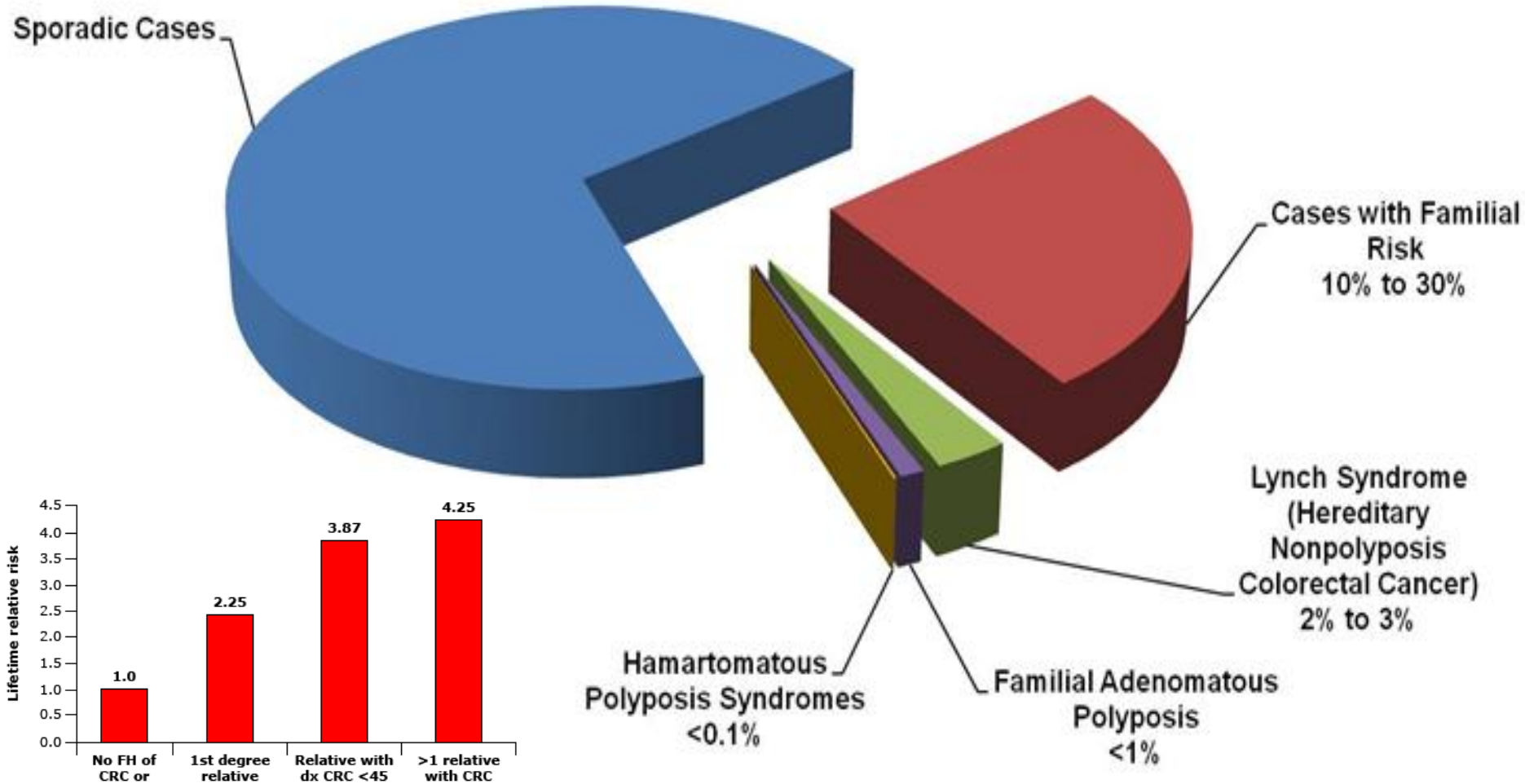
KRAS

- Smokers
- Worse prognosis
- Codon 13 mutation appeared predictive of worse survival from adjuvant chemotherapy
- MEK inhibition with selumetinib, MEK inhibition with trametinib, mTOR inhibition (ridaforolimus)



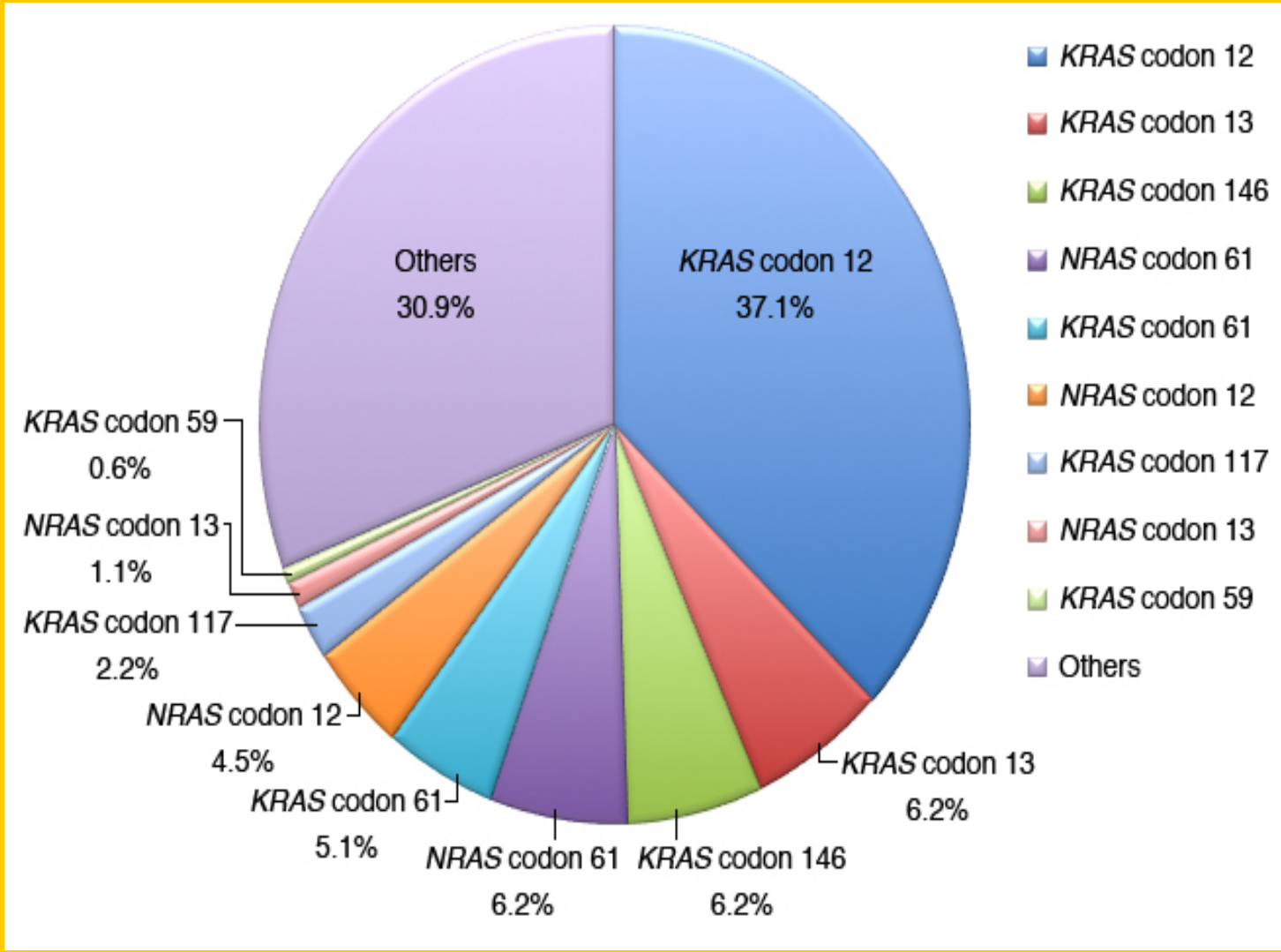
COLON CANCER

Colon Cancer Cases Arising in Various Family Risk Settings

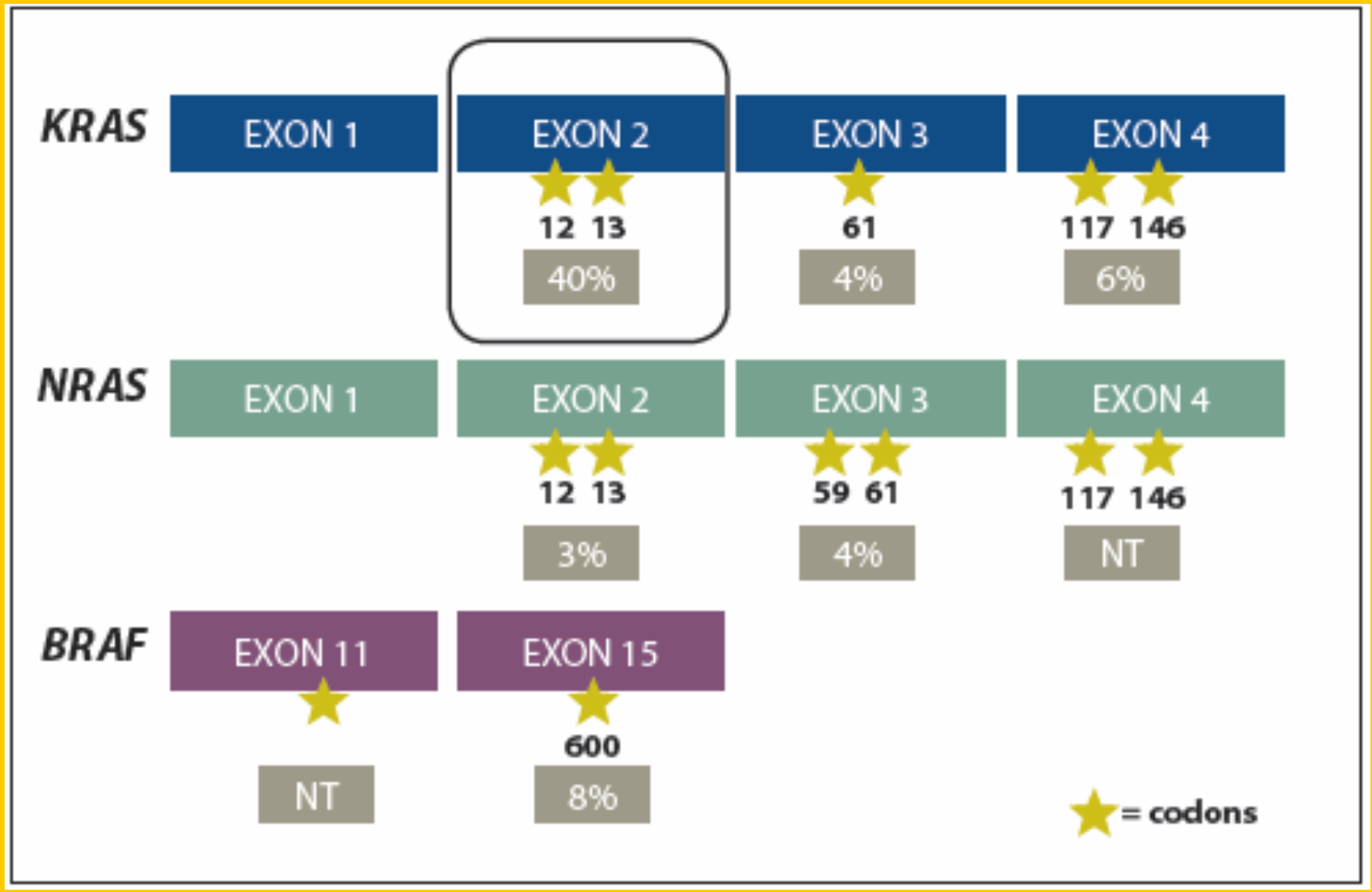


COLON CANCER

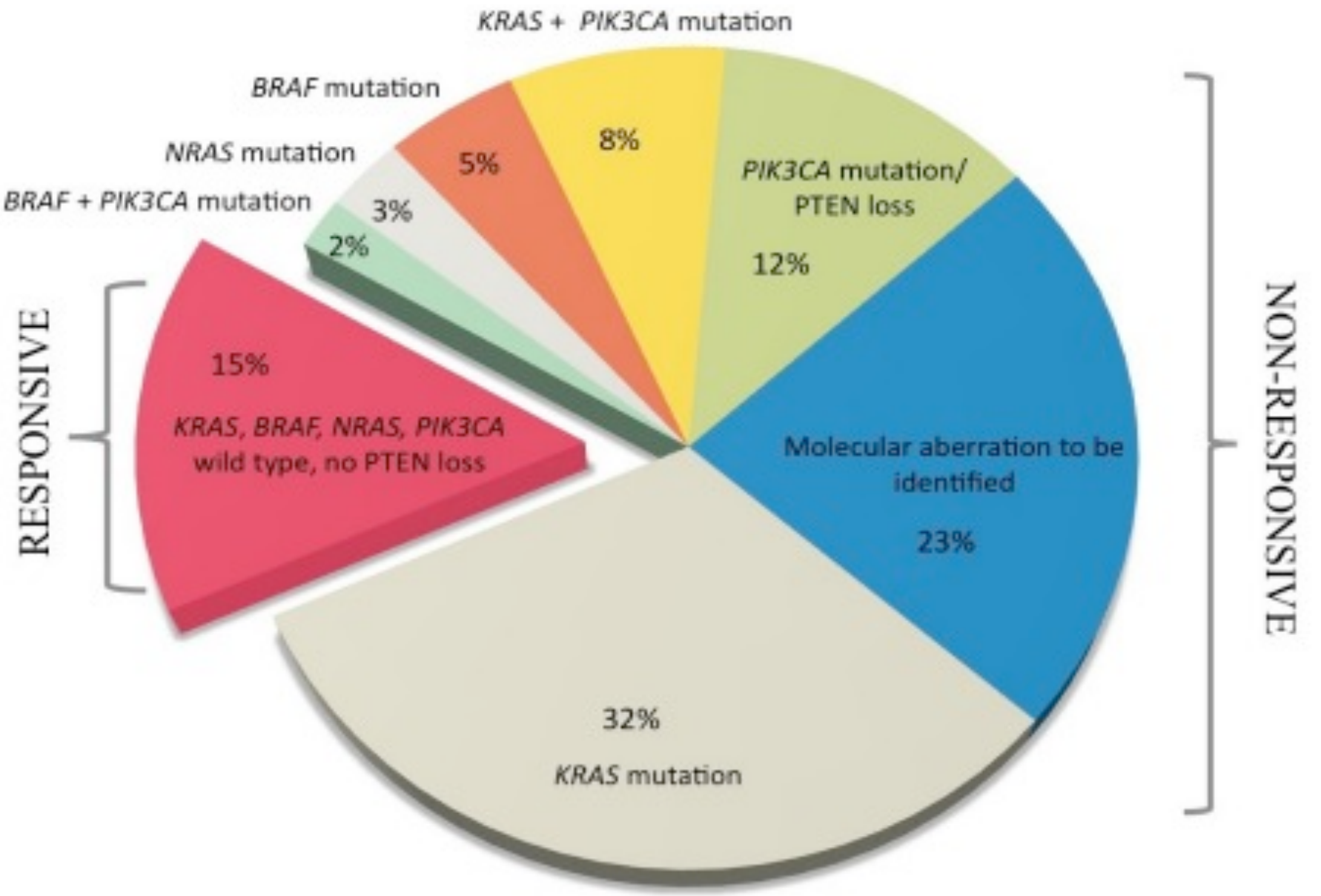
- KRAS Mutation
- NRAS Mutation
- BRAF Mutation
- MSI
- EGFR Expression, PI3K, TS, ERCC1, UGT1A1, VEGFR2, MET (FISH)



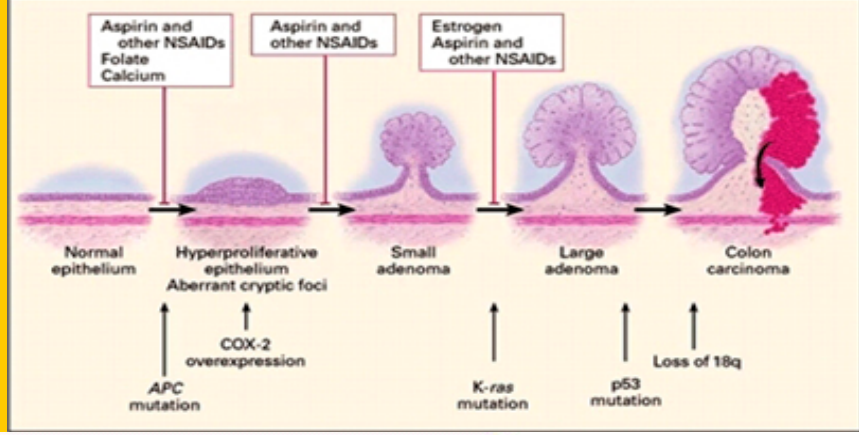
COLON CANCER



COLON CANCER



Colon Carcinogenesis



Pathways to tumorigenesis in colorectal cancer

Classic pathway

Germline mutation pathway

Serrated/methylated pathway

Adenoma-to-carcinoma (APC, KRAS,P53)

Lynch syndrome (MLH1, MSH2, MSH6, PMS2)

MLH1 methylation CIMP-high (BRAF)

Deficient mismatch repair

Colorectal cancer

Microsatellite instability colorectal cancer

What is Microsatellite Instability (MSI)?

Microsatellites are repetitive segments of DNA
The same number of repeats are present in every cell

Normal microsatellite with 2 repeats

Microsatellite Instability:
The number of microsatellite repeats differs between normal cells/tissue and tumour cells/tissue

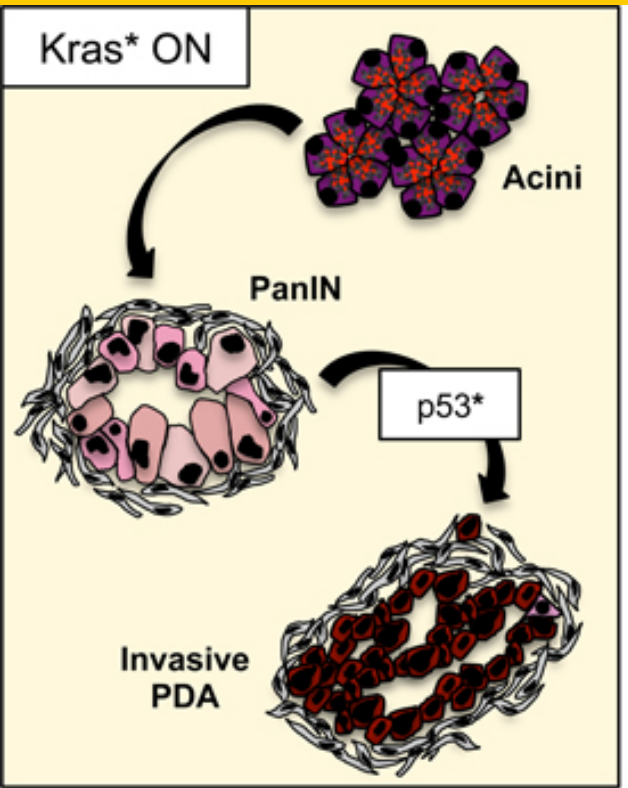
Normal tissue 2 repeats

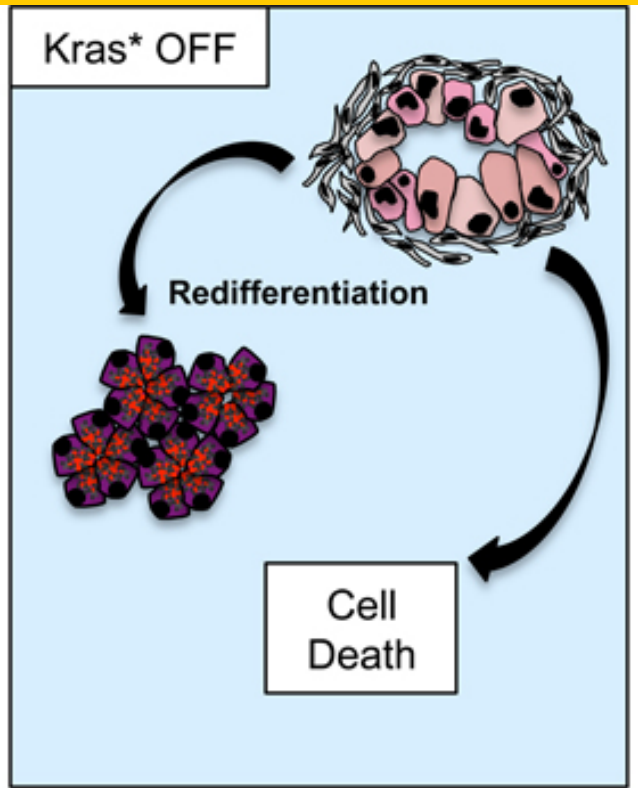
Tumour tissue with MSI variable repeat size 5 & 3

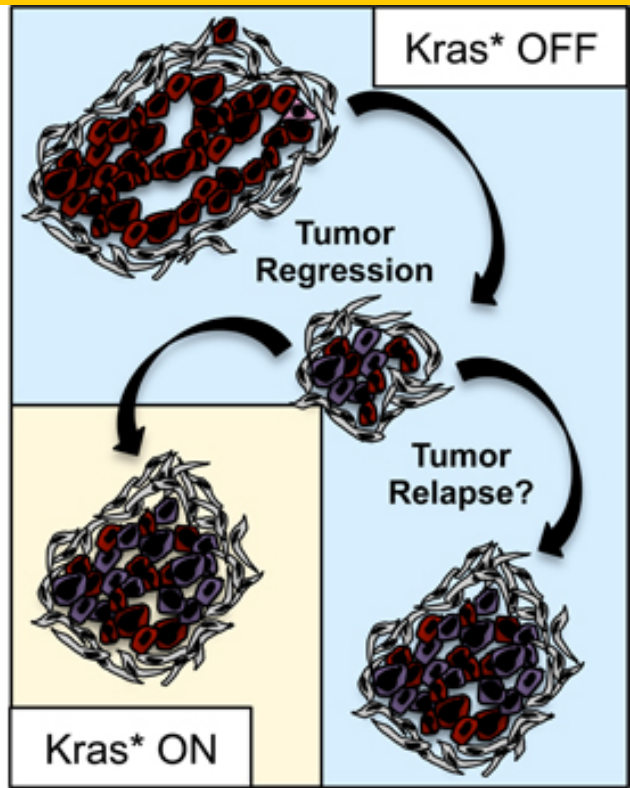
MSI is a pathology finding specific to Lynch syndrome colon tumours

KRAS

- v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
- Codon 12 is the most frequently mutated KRAS site
- Pancreatic>colorectal>biliary tract>lung>small intestine>endometrium>ovary

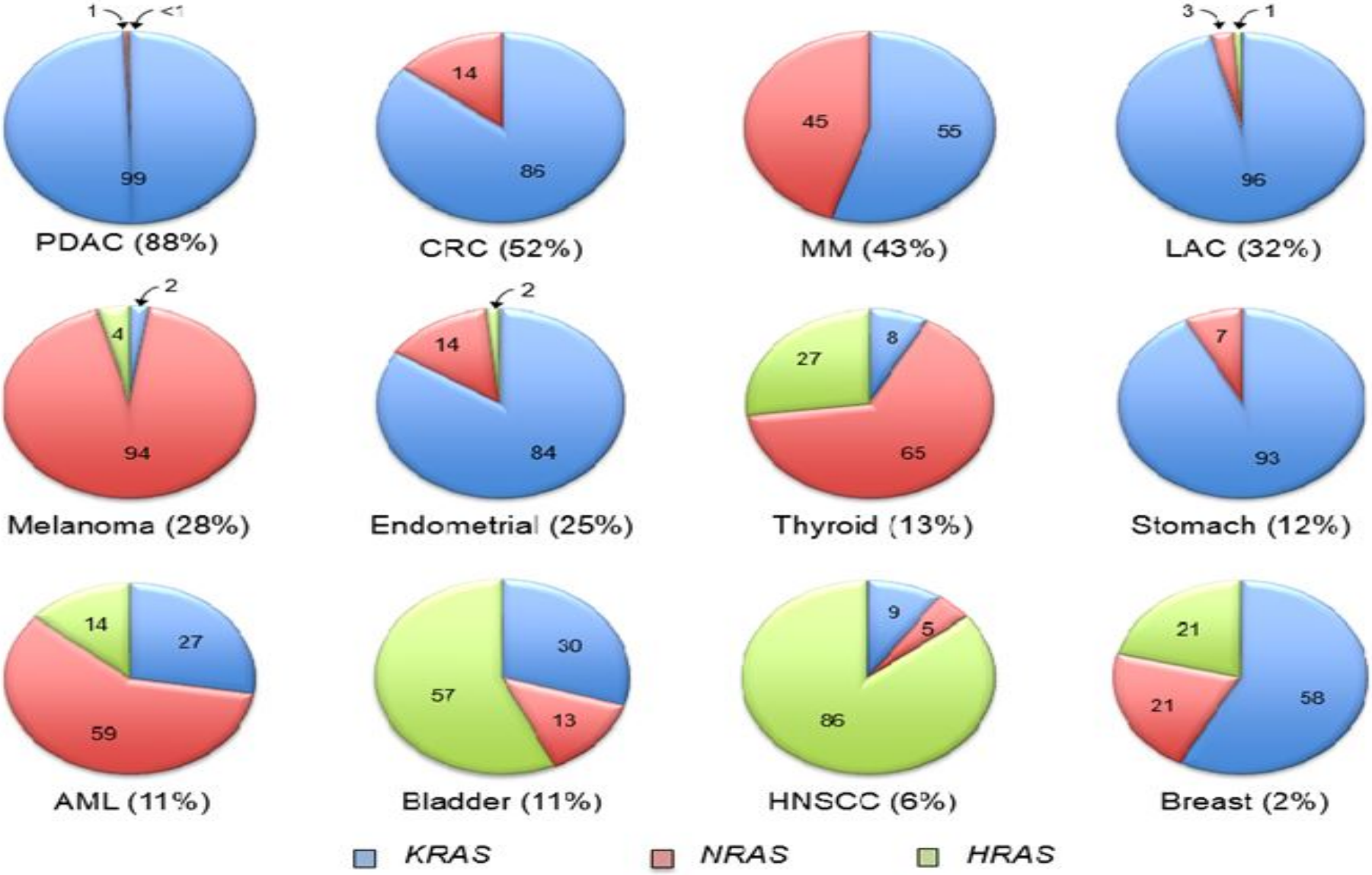






NRAS

- 3% of colorectal cancer, 6% of thyroid cancer, 10–25% of melanomas
- Codon 61 mutations



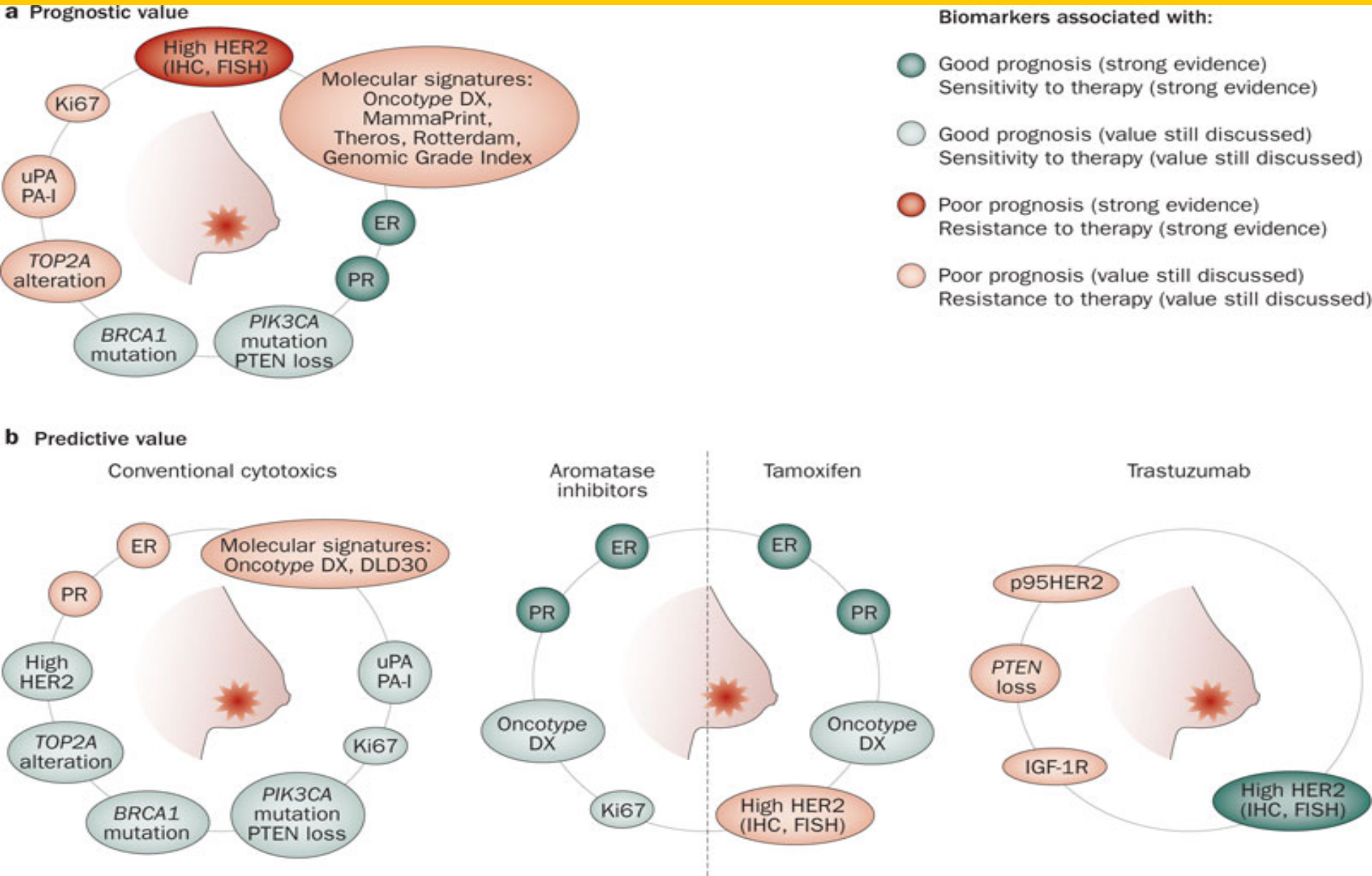
BREAST CANCER

- Estrogen receptor (ER)
- Progesterone Receptor (PR)
- HER2 (ERBB2) (FISH)

Major genes associated with breast and ovarian cancer

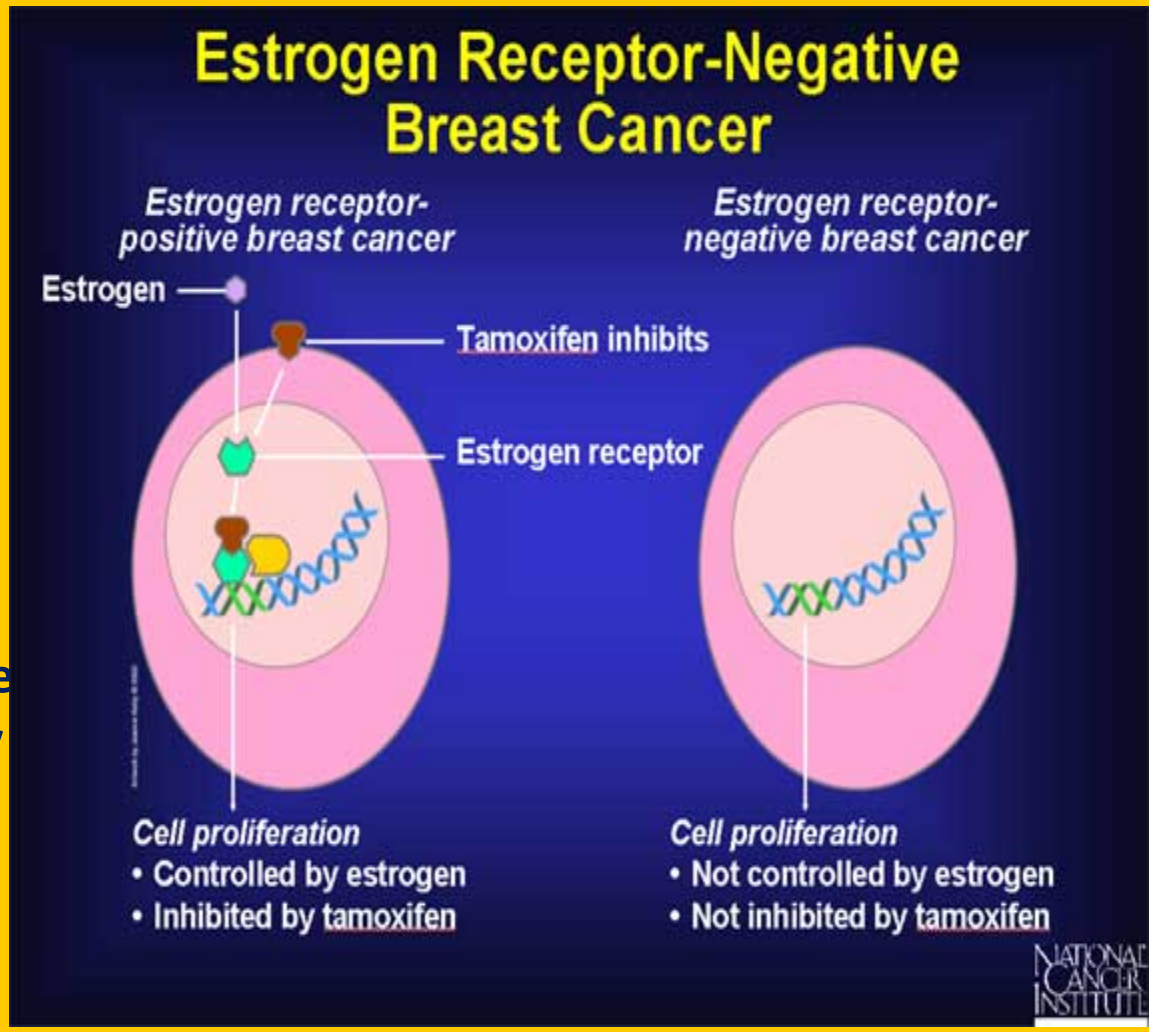
Gene	Associated syndrome	Major associated abnormalities
BRCA1	Hereditary breast cancer and ovarian cancer	Breast, ovarian, fallopian tube, male breast, pancreas, prostate cancers
BRCA2	Hereditary breast cancer and ovarian cancer	Breast, ovarian, fallopian tube, male breast, pancreas, prostate cancers
TP53	Li-Fraumeni	Breast cancer, soft tissue and bone sarcomas, leukemia, brain cancer, adrenocortical cancer, choroid plexus cancer, bronchoalveolar lung cancer
PTEN	Cowden/PTEN hamartoma	Hamartomas, papillomas of the lips and mucous membranes, acral skin keratoses, trichillemmomas of skin, macrocephaly, breast cancer, endometrial cancer, non-medullary thyroid cancer, colon cancer, renal cell cancer
CDH1	Hereditary diffuse gastric cancer	Lobular breast cancer, diffuse gastric cancer
STK11	Peutz-Jeghers	Hamartomatous gastrointestinal tract polyps; characteristic mucocutaneous pigmentation; cancers of the breast, small bowel, stomach, colorectal, pancreas, lung, endometrium and ovary; sex cord tumor
Mismatch repair genes (*MSH2, MLH1, MSH6, PMS2*) *EPCAM* gene	Lynch (hereditary nonpolyposis colon cancer)	Colon, endometrial, ovarian, stomach cancers

BREAST CANCER

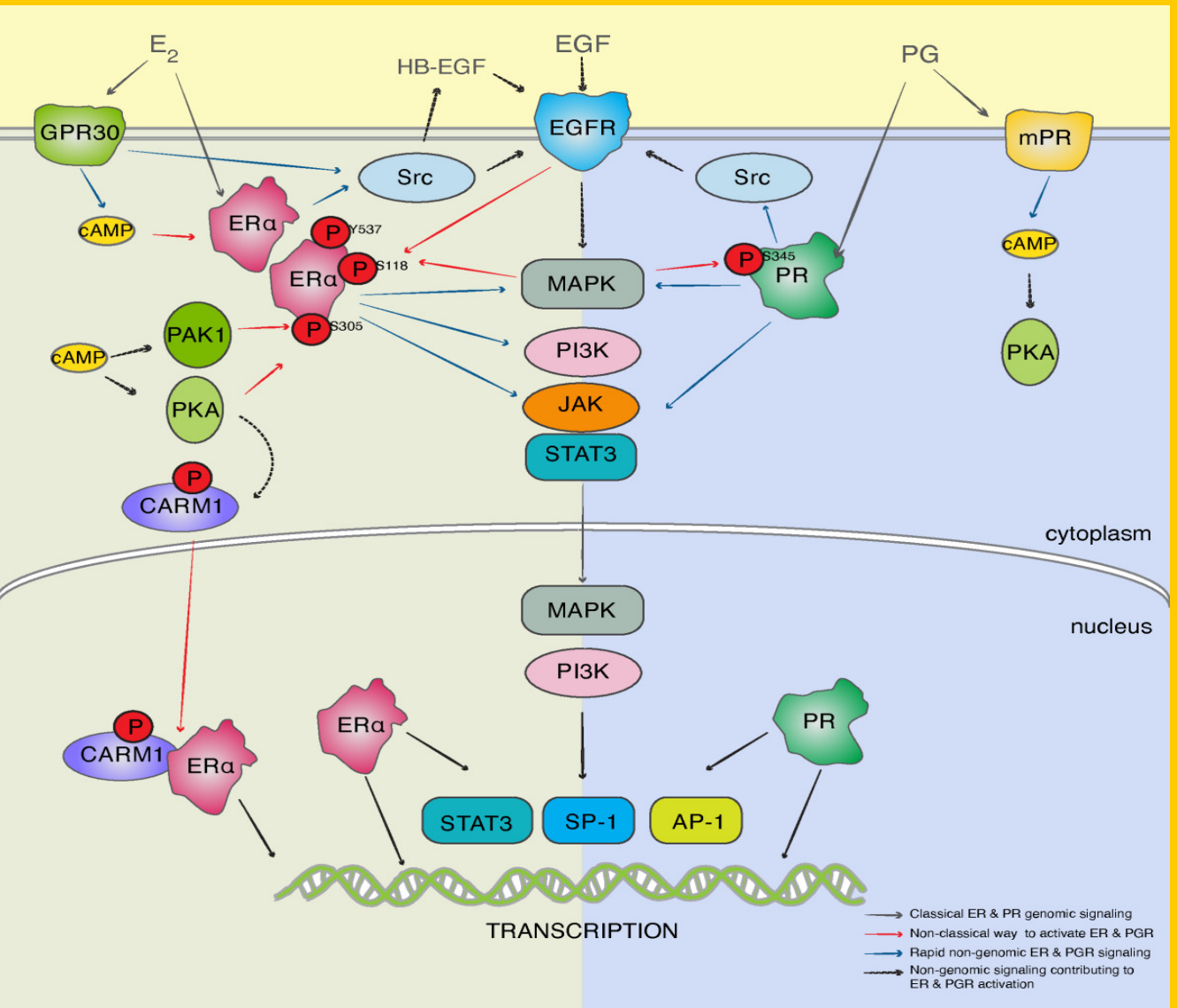


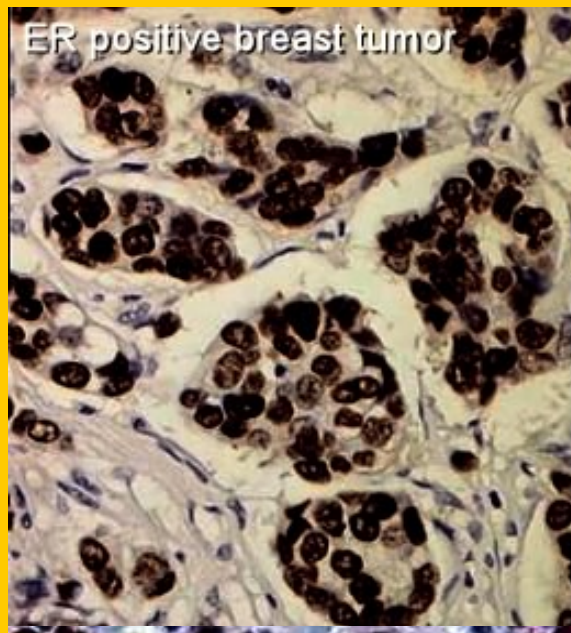
ER/ PR

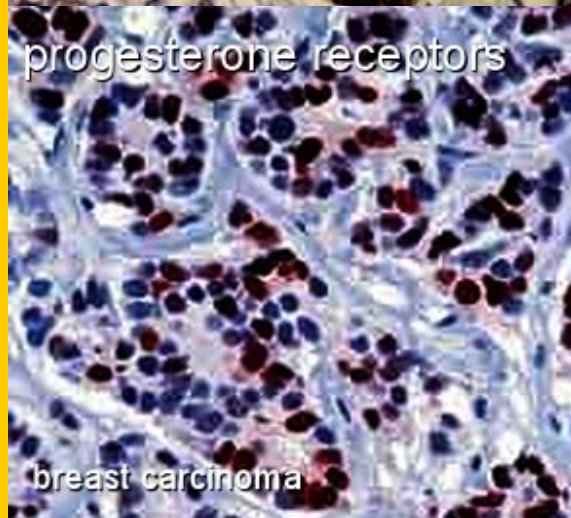
- The nuclear hormone receptor superfamily (also membrane)
- ER 75%, PR 65% of breast cancers
- ERs and PRs are both overexpressed in malignant breast tissue
- ER-alpha, ER-beta…PR-A, PR-B
- PR status is heavily dependent on ER
- ER-positive, PR-negative disease have a more aggressive
- Should be performed routinely in all invasive breast cancers
- Selective ER modulators (SERMs) and selective ER downregulators (SERDs)



ER/ PR


E2
HB-EGF
EGF
PG
GPR30
EGFR
Src
Src
mPR
cAMP
ERα
P Y537
ERα
P S118
P S345
PR
cAMP
MAPK
PAK1
P S305
cAMP
PI3K
PKA
JAK
PKA
STAT3
P
CARM1
cytoplasm
MAPK
nucleus
PI3K
P
CARM1
ERα
ERα
PR
STAT3
SP-1
AP-1
TRANSCRIPTION
Classical ER & PR genomic signaling
Non-classical way to activate ER & PGR
Rapid non-genomic ER & PGR signaling
Non-genomic signaling contributing to ER & PGR activation


ER positive breast tumor

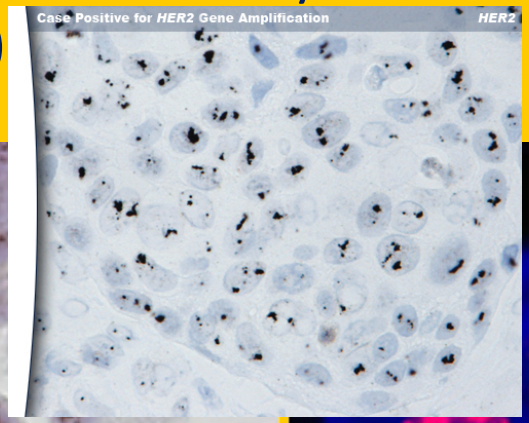

progesterone receptors
breast carcinoma

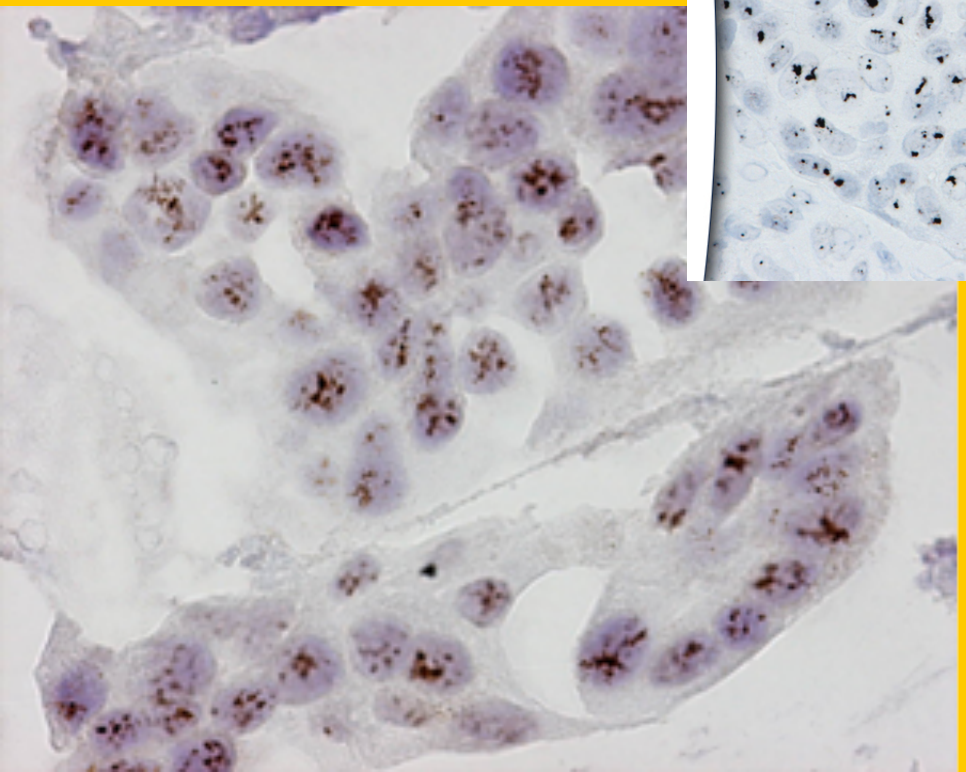
ER/ PR

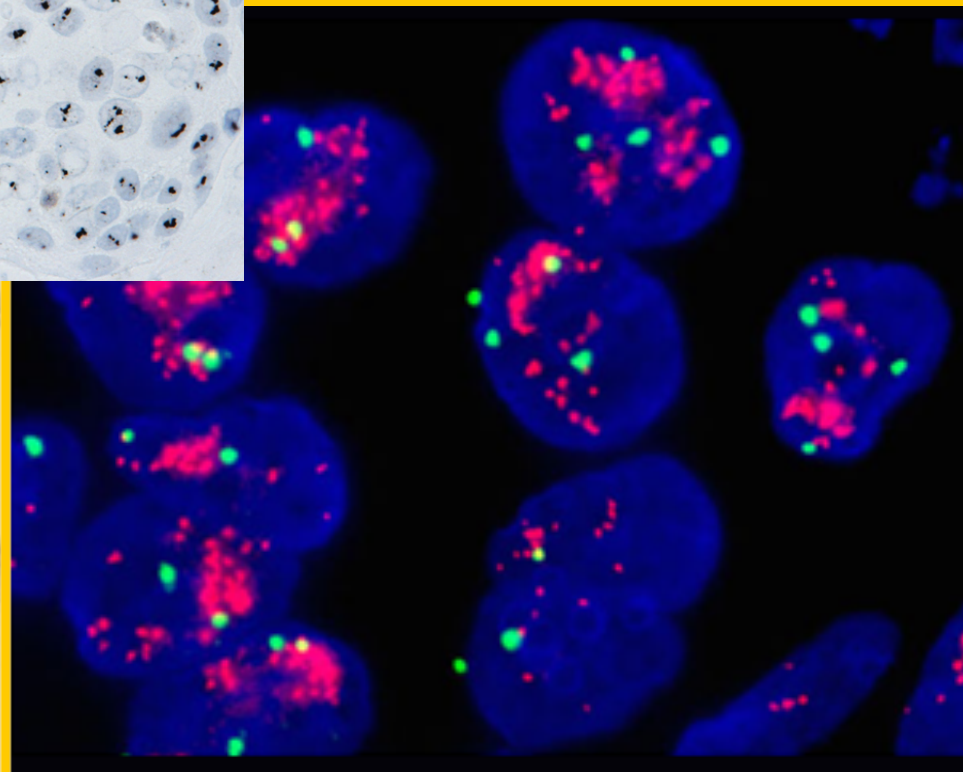
- %1 positive=treatment
- ER-positive tumors are more likely to be histologically well differentiated, to have a lower fraction of dividing cells, and to be diploid
- Also less likely to be associated with mutations, loss, or amplification of breast cancer-related genes such as p53, HER2, or HER1 (EGFR)
- Metastases in bone, soft tissue, or the reproductive/genital tracts
- IHC, measurement of ER messenger RNA by either northern blot analysis or reverse transcriptase polymerase chain reaction (RT-PCR)

HER2 (ERBB2)

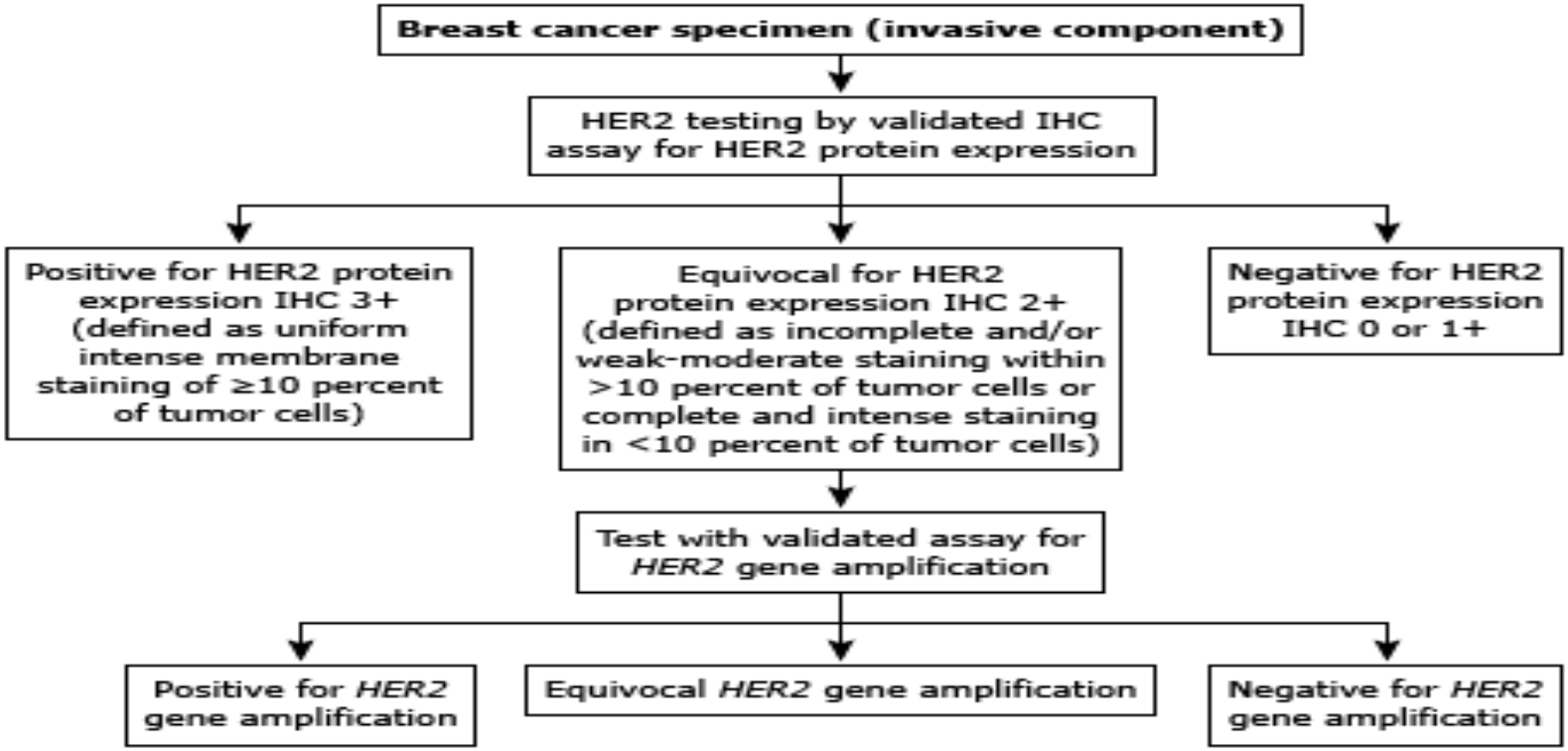
- Human epidermal growth factor receptor 2 oncogene
- Amplification of HER2 or overexpression of its protein product is observed in 18 to 20 percent of human breast cancers.
- FISH-amplified [ratio of HER2 to CEP17 (chromosome 17 centromere) of >2.2] or average HER2 gene copy number>6 signals/nucleus (?1.8-2.2)
- Silver (SISH) or chromogenic in-situ hybridization (CISH)
- Trastuzumab (Herceptin)







Algorithm for IHC in assessment of HER2 status



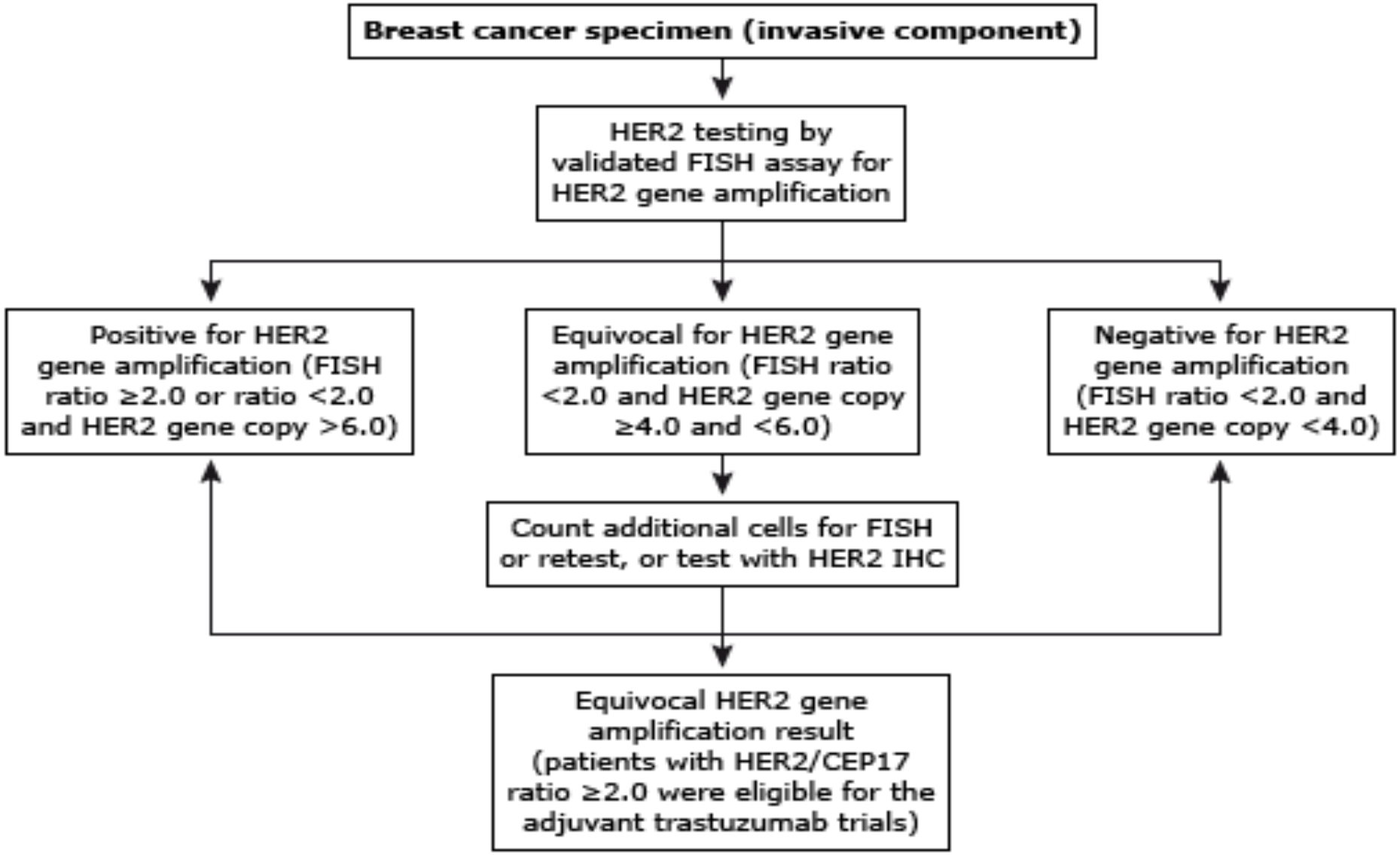
HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry.

Revised with information from:

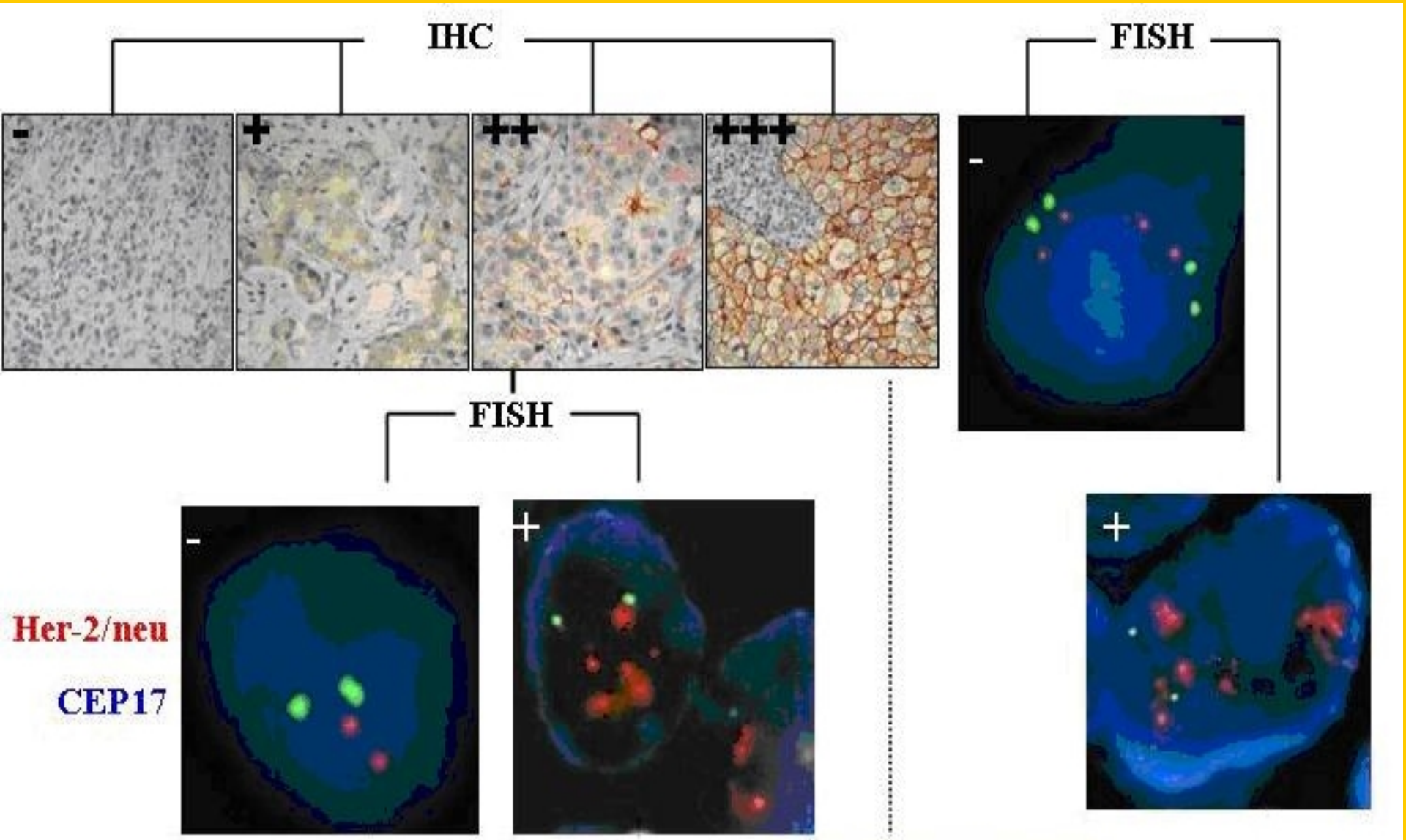
1. *Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. J Clin Oncol 2013. DOI: JCO.2013.50.9984.*

Modified from: Wolff AC, Hammond EH, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Onc 2007; 25:118. Copyright © 2007 American Society of Clinical Oncology.

HER2

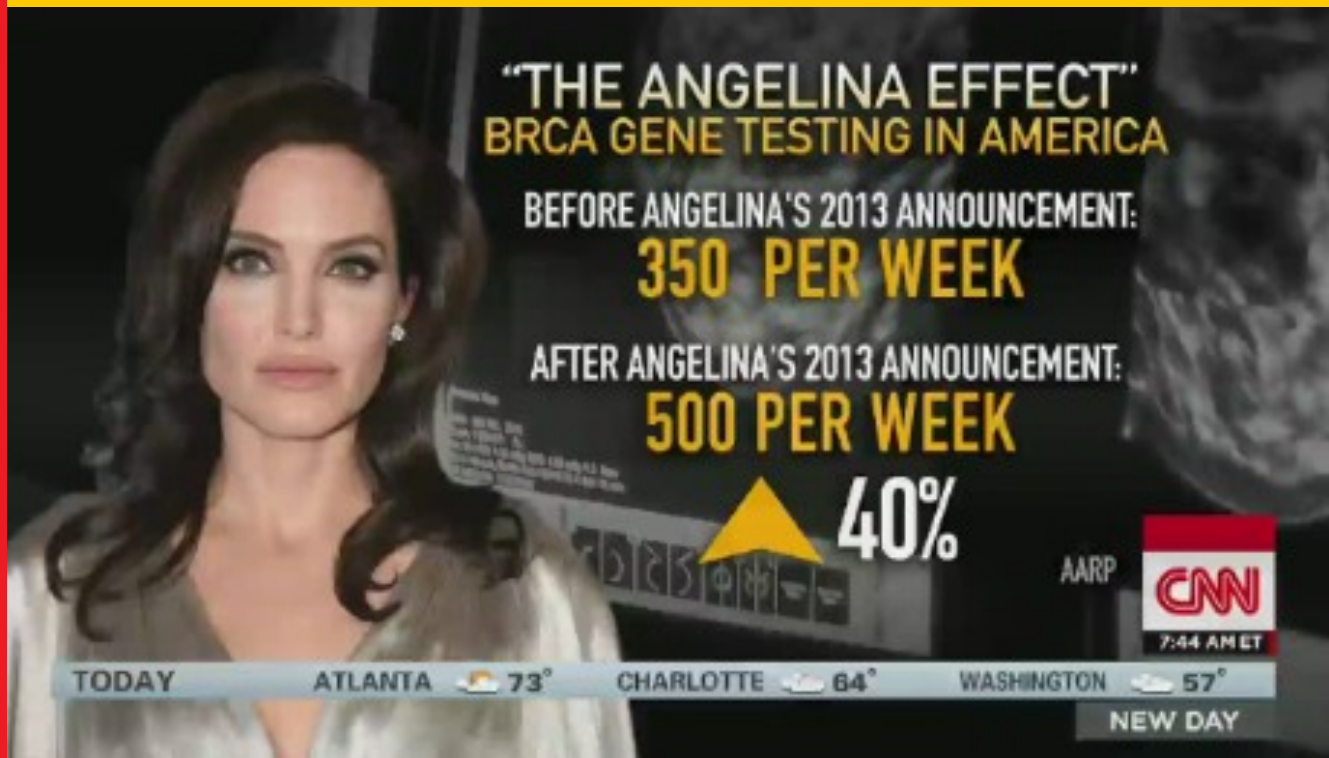

Breast cancer specimen (invasive component)
HER2 testing by validated FISH assay for HER2 gene amplification
Positive for HER2 gene amplification (FISH ratio ≥2.0 or ratio <2.0 and HER2 gene copy >6.0)
Equivocal for HER2 gene amplification (FISH ratio <2.0 and HER2 gene copy ≥4.0 and <6.0)
Negative for HER2 gene amplification (FISH ratio <2.0 and HER2 gene copy <4.0)
Count additional cells for FISH or retest, or test with HER2 IHC
Equivocal HER2 gene amplification result (patients with HER2/CEP17 ratio ≥2.0 were eligible for the adjuvant trastuzumab trials)

HER2



BRCA 1/2

- BRCA1, through interaction with a number of genes including BARD1, BRCA2, CHK1, and RAD51, is involved in double-strand break repair, cell cycle checkpoint activation, which allows cells time to repair damage before progressing to mitosis, and DNA damage response activation .
- BRCA2 binds and regulates the strand invasion recombinase, RAD51, which is required for homologous recombination of double-strand DNA breaks.
- *BRCA1* or *BRCA2* mutation in the general population of is approximately 0.25 percent
- *BRCA1* and *BRCA2* mutations are inherited as autosomal dominant, highly penetrant, germline mutations



National Comprehensive Cancer Network criteria for consideration of BRCA1/2 genetic testing

A. Individual from a family with a known deleterious BRCA1/BRCA2 mutation*[•Δ]

B. Personal history of breast cancer[◊] plus one or more of the following:

- Diagnosed age ≤45 years
- Diagnosed age ≤50 years with ≥1 first-, second-, or third-degree blood relative (on the same side of the family) with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer at any age, or with a limited family history[Δ]
- Two breast primaries[§] when first breast cancer diagnosis occurred ≤50 years
- Diagnosed ≤60 years with a triple negative breast cancer
- Diagnosed ≤50 years with a limited family history[Δ]
- Diagnosed at any age with ≥1 first-, second-, or third-degree blood relative (on the same side of the family) diagnosed with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer ≤50 years
- Diagnosed at any age with ≥2 first-, second-, or third-degree blood relatives (on the same side of the family) with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
- Diagnosed at any age with ≥2 first-, second-, or third-degree blood relatives (on the same side of the family) with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age
- First-, second-, or third-degree male blood relative (on the same side of the family) with breast cancer
- For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish), no additional family history may be required[¥]

C. Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer

D. Personal history of male breast cancer

E. Personal history of pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age with ≥2 first-, second-, or third-degree blood relatives (on the same side of the family) with breast and/or ovarian cancer and/or pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age

F. Family history only[‡]:

- First- or second-degree blood relative meeting any of the above criteria
- Third-degree blood relative with breast cancer[◊] and/or ovarian/fallopian tube/primary peritoneal cancer with ≥2 first-, second-, or third-degree blood relatives (on the same side of the family) with breast cancer (at least one breast cancer ≤50 years) and/or ovarian/fallopian tube/primary peritoneal cancer

Society of Gynecology Oncology criteria for *BRCA* mutation testing

Women affected with:
▪ High-grade epithelial ovarian/tubal/peritoneal cancer
▪ Breast cancer ≤45 years
▪ Breast cancer with close relative¶ with breast cancer ≤50 years or close relative¶ with epithelial ovarian/tubal/peritoneal cancer at any age
▪ Breast cancer ≤50 years with a limited family historyΔ
▪ Breast cancer with ≥2 close relatives¶ with breast cancer at any age
▪ Breast cancer with ≥2 close relatives¶ with pancreatic cancer, aggressive prostate cancer (Gleason score ≥7)
▪ Two breast primaries, with the first diagnosed prior to age 50
▪ Triple negative breast cancer ≤60 years
▪ With breast cancer and Ashkenazi Jewish ancestry
▪ Pancreatic cancer with ≥2 close relatives¶ with breast, ovarian/tubal/peritoneal, pancreatic, or aggressive prostate cancer (Gleason score ≥7)
Women unaffected with cancer, but with:
▪ A first degree or several close relatives that meet one of the above criteria
▪ A close relative¶ carrying a known *BRCA1* or *BRCA2* mutation
▪ A close relative with male breast cancer

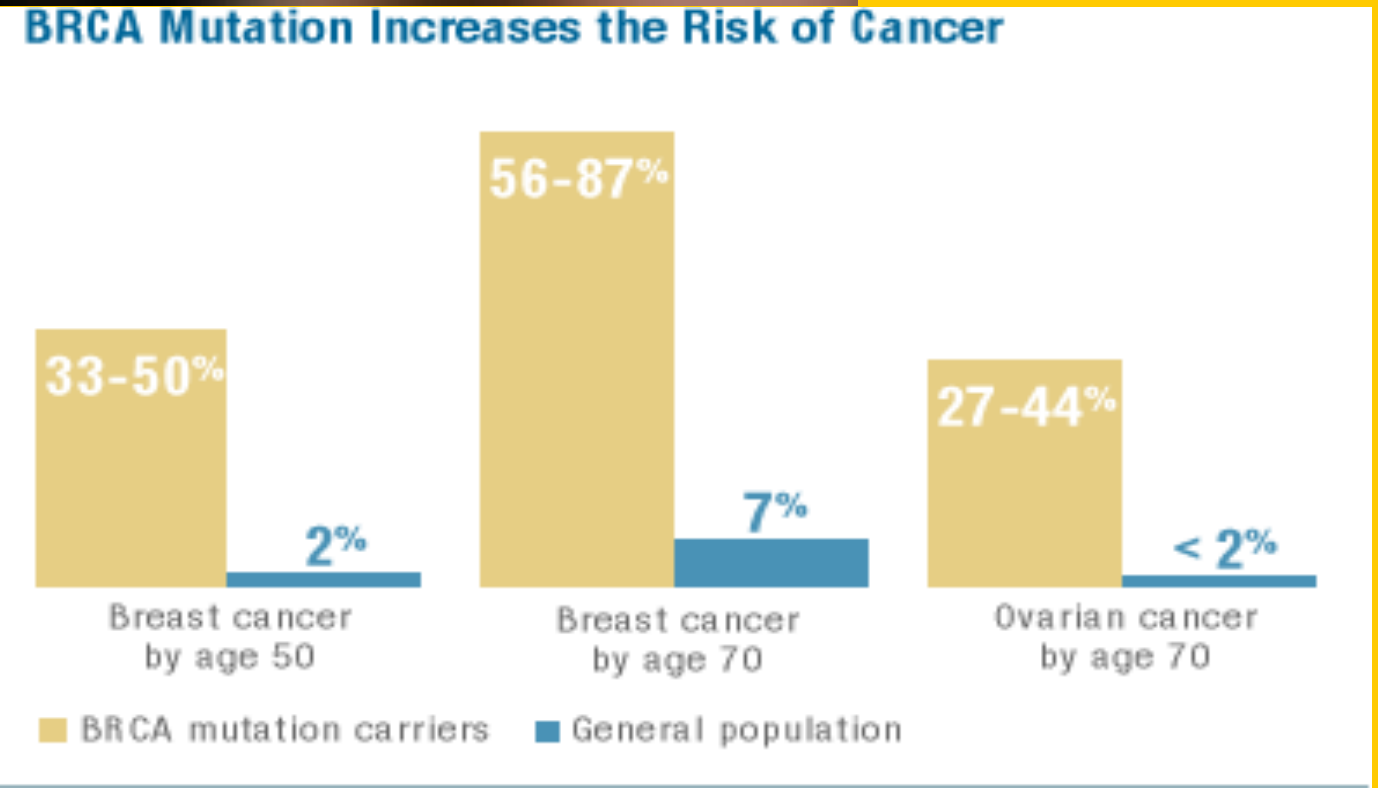
Patients with an increased likelihood of having an inherited predisposition to breast* and ovarian/tubal/peritoneal cancer who should receive genetic counseling and be offered genetic testing.

* Invasive and ductal carcinoma in situ breast cancers.
¶ Close relative is defined as a first degree (parent, sibling, offspring), second degree (grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling) or third degree (first cousin, great-grandparent or great-grandchild) relative.
Δ Limited family history includes fewer than 2 first- or second-degree female relatives of female relatives surviving beyond 45 years.

BRCA 1/2

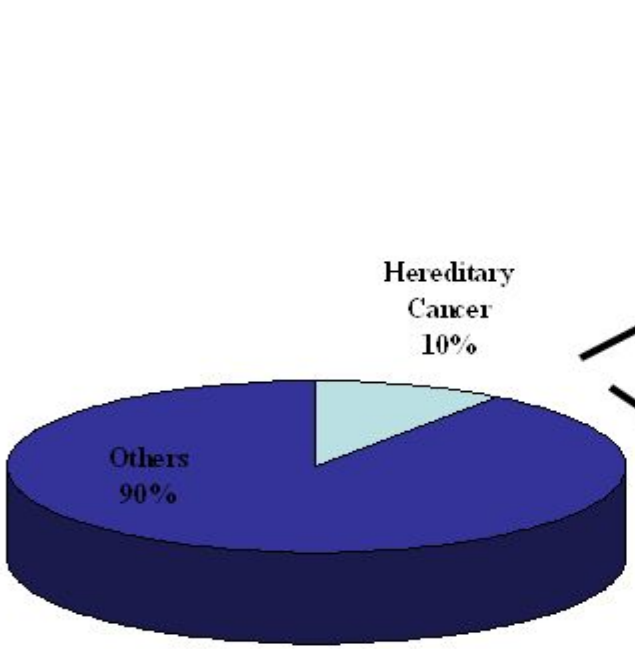
Male breast cancers: 0.1% in general population, BRCA1: 1%, BRCA2: 6%

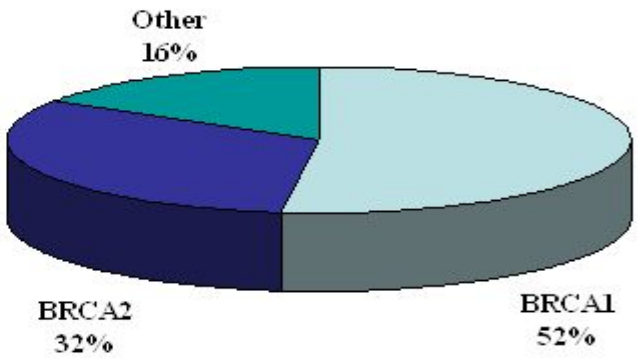
- Male BRCA2 mutation carriers have increased risk of prostate and pancreatic cancer cancer.



BRCA 1/2

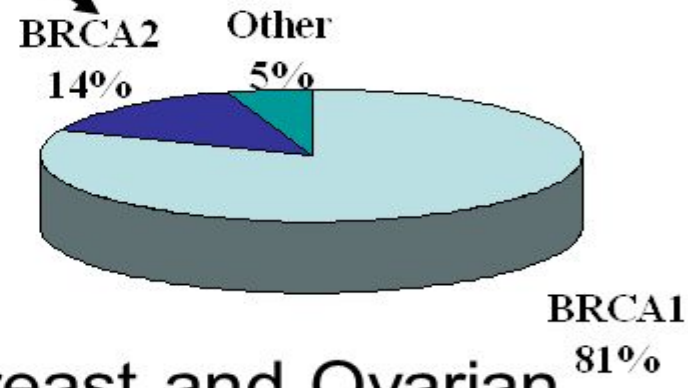
Contribution of BRCA1/2 to hereditary breast /ovarian cancer families:





Breast Cancer Families

Breast and ovarian cancers



Breast and Ovarian Cancer Families

King, Rowell, Love, 1993; Ford, Easton, Stratton, et al, 1998

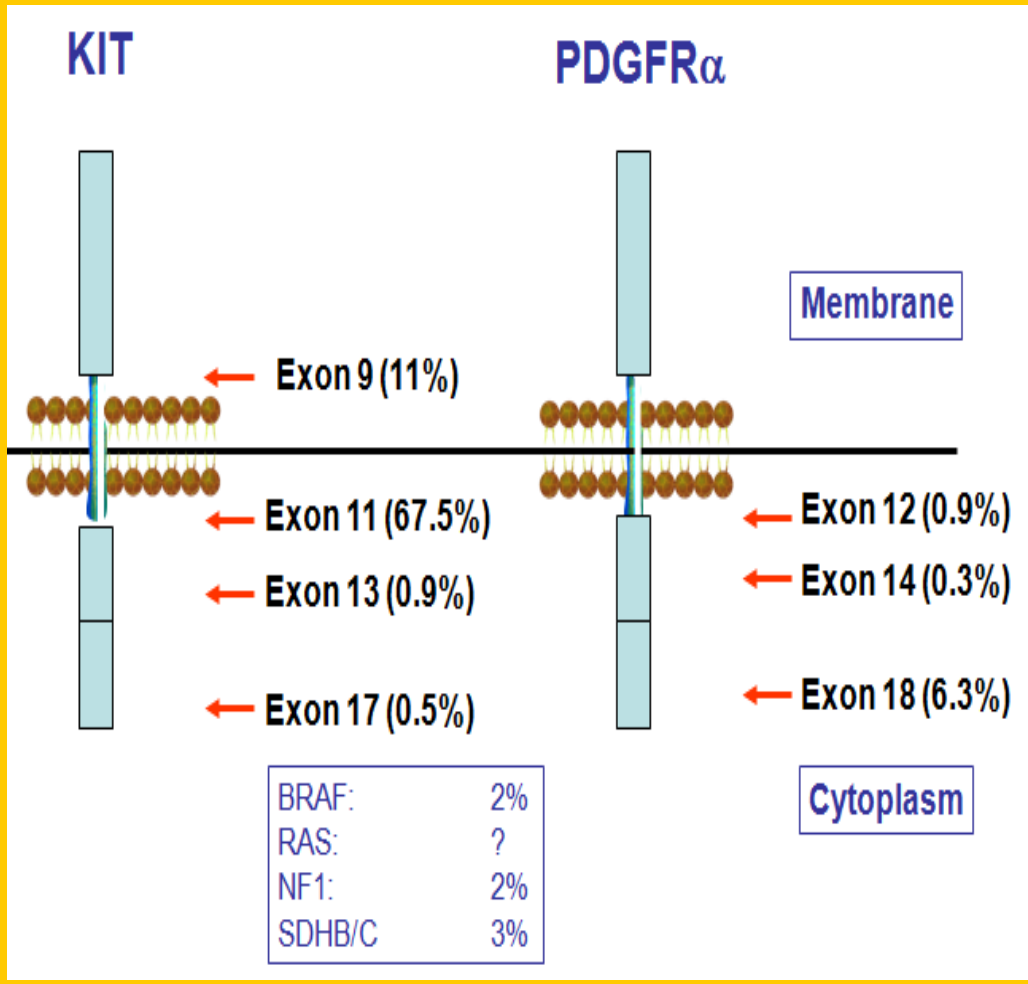
Table 1. Examples of Multigene Testing Panels for Breast Cancer.*

Company	Test	Website	Genes Included†
Ambry Genetics	BreastNext	www.ambrygen.com/tests/breastnext	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, TP53*
BreastHealth UK	BreastGene	www.breasthealthuk.com/screening-services/genetic-testing/breastgene	*ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, PALB2, PTEN, STK11, TP53*
Centogene	Breast Ovarian Cancer Panel	www.centogene.com/centogene/centogene-test-catalogue.php	*ATM, BARD1, BRIP1, CDH1, CHEK2, MEN1, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PMS1, PMS2, RAD50, RAD51C, RAD51D, XRCC2*
Emory Genetics Laboratory	High Risk Breast Cancer Panel	http://geneticslab.emory.edu/tests/MM201	*PTEN, STK11, TP53*
Fulgent Diagnostics	Breast Ovarian Cancer NGS Panel	http://fulgentdiagnostics.com/test/breast-ovarian-cancer-ngs-panel/	*APC, ATM, ATR, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, CTNNB1, EPCAM, FANCC, HOXB13, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PALLD, PMS2, PTEN, RAD50, RAD51, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL, XRCC2, XRCC3*
GeneDx	OncoGeneDx	www.genedx.com/test-catalog/available-tests/breastovarian-cancer-panel	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53, XRCC2*
Illumina	TruSight Cancer	www.illumina.com/clinical/translational_genomics/panels/kits.html	94 Genes plus 287 SNPs reported to be associated with risk of breast cancer
Invitae	Hereditary Breast Cancer, High-Risk Panel	www.invitae.com/en/physician/panel-detail/PNL0009/	*BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, TP53*
Myriad Genetics†	myRisk	www.myriad.com/products-services/hereditary-cancers/myrisk-hereditary-cancer/	*ATM, BARD1, BRCA2, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, RAD51C,* STK11, *TP53*
CD Genomics	Genetic Testing for the Cancer Susceptibility	www.cd-genomics.com/Genetic-Testing-for-the-Cancer-Susceptibility.html	Not specified
University of Washington†	BROCA – Cancer Risk Panel	http://web.labmed.washington.edu/tests/genetics/BROCA	*AKT1, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FAM175A, GEN1, MRE11A, MUTYH, NBN, PALB2, PIK3CA, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53, XRCC2*

* SNP denotes single-nucleotide polymorphism.
† For Myriad Genetics and the University of Washington, only genes for which breast-cancer risk is given as an indication are listed. For a complete list, see Table S1 in the Supplementary Appendix. In several cases, the panels include additional genes, and several companies also offer larger panels. Thus, even if the primary purpose of the test is prediction of the risk of breast cancer, results will often be available (and need to be interpreted) for a larger set of genes than those listed here.

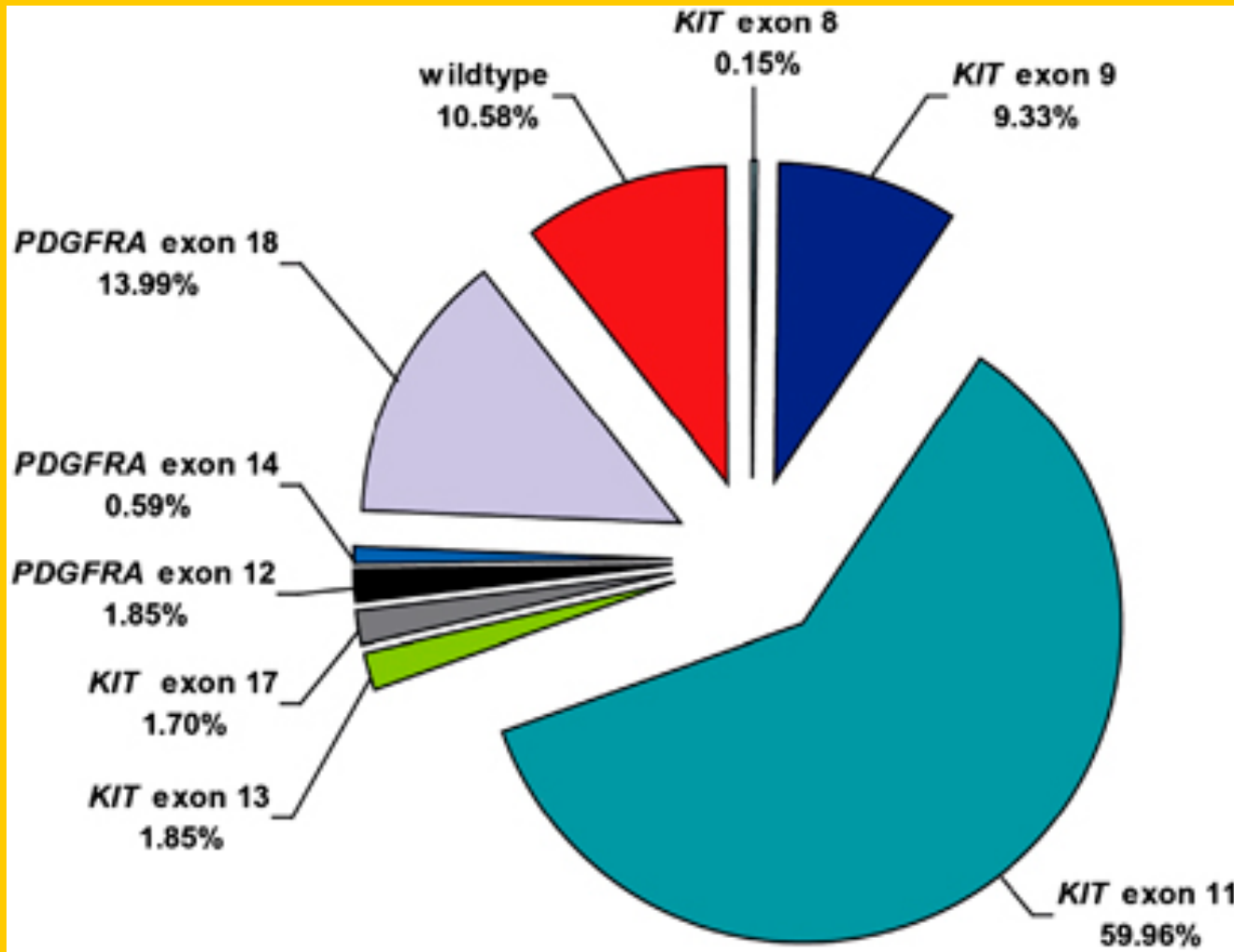
Gastrointestinal Stromal Tumors(GIST)

- The most common mesenchymal neoplasms
- Most often located in the stomach and proximal small intestine (Spindle cell type 70%, Epithelioid type 20%, Mixed type 10%)
- 1% of GI cancers
- 85 percent of pediatric GISTs lack mutations in KIT or PDGFRA (Carney-Stratakis syndrome, Carney triad)
- The majority of GISTs (≥90 percent) are positive for KIT expression, others PDGFRA



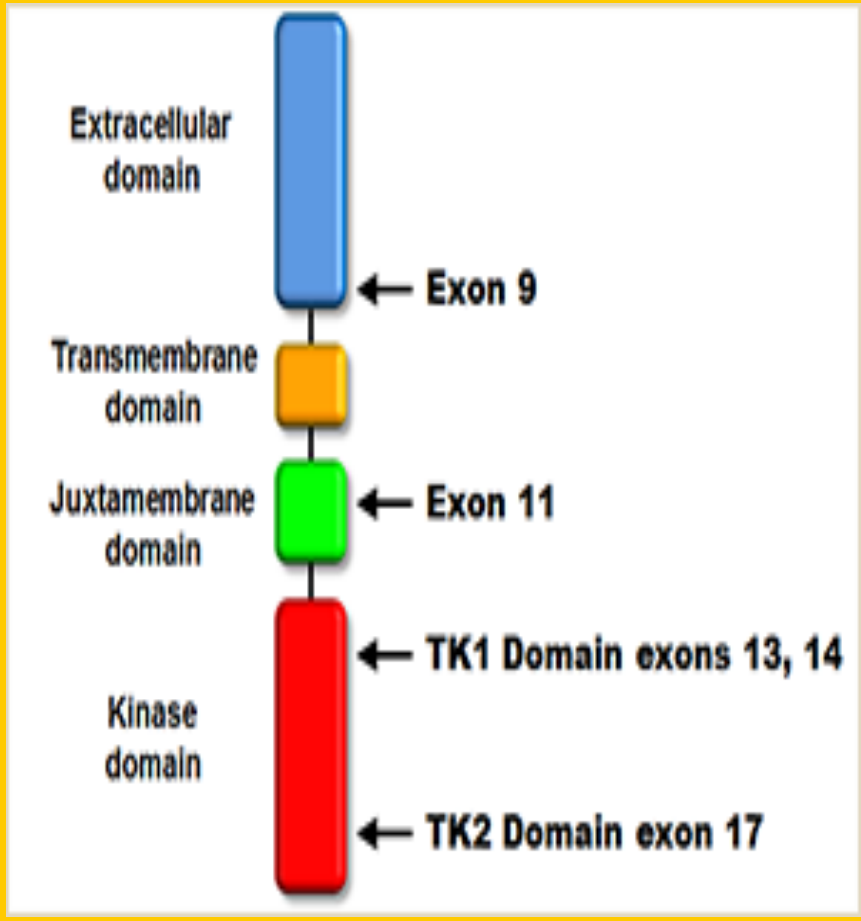
GIST

- cKIT
- PDGFRA
- SDH
- HER2(FISH)
- ERCC1



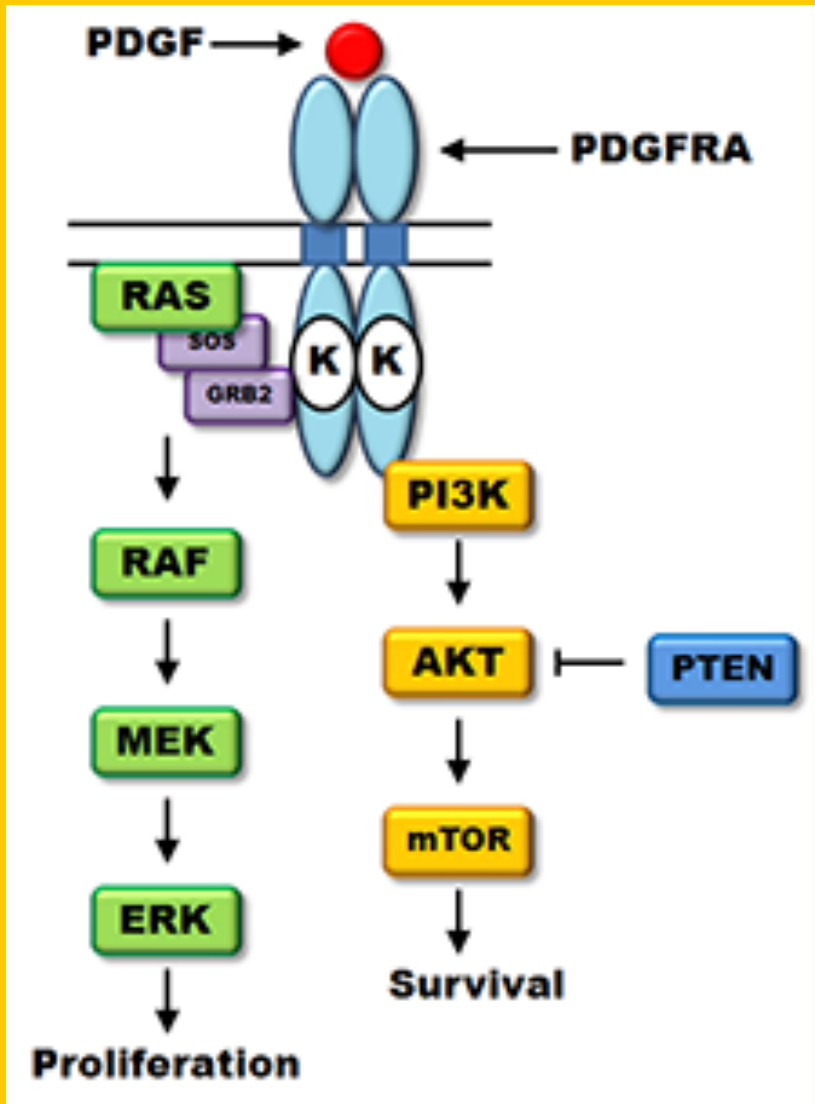
KIT

- 95 percent of GISTs arising in adults overexpress KIT
- 80 percent of GISTs have KIT gene mutations that lead to constitutive activation of the KIT receptor
- The mechanism of KIT overexpression in cases without an identifiable mutation in KIT is unclear
- Imatinib
- Patients with exon 11 mutations are more likely to respond, exon 9 mutations are aggressive

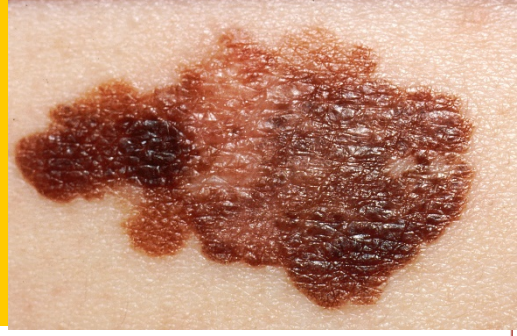


PDGFRA

- KIT-negative tumors are more likely to have PDGFRA mutations.
- Some PDGFRA mutations are characterized by relative insensitivity to imatinib (D842V), although others confer sensitivity to this agent.
- GIST that are wild-type for both KIT and PDGFRA have mutations in a subunit of the enzyme succinate dehydrogenase (SDH)



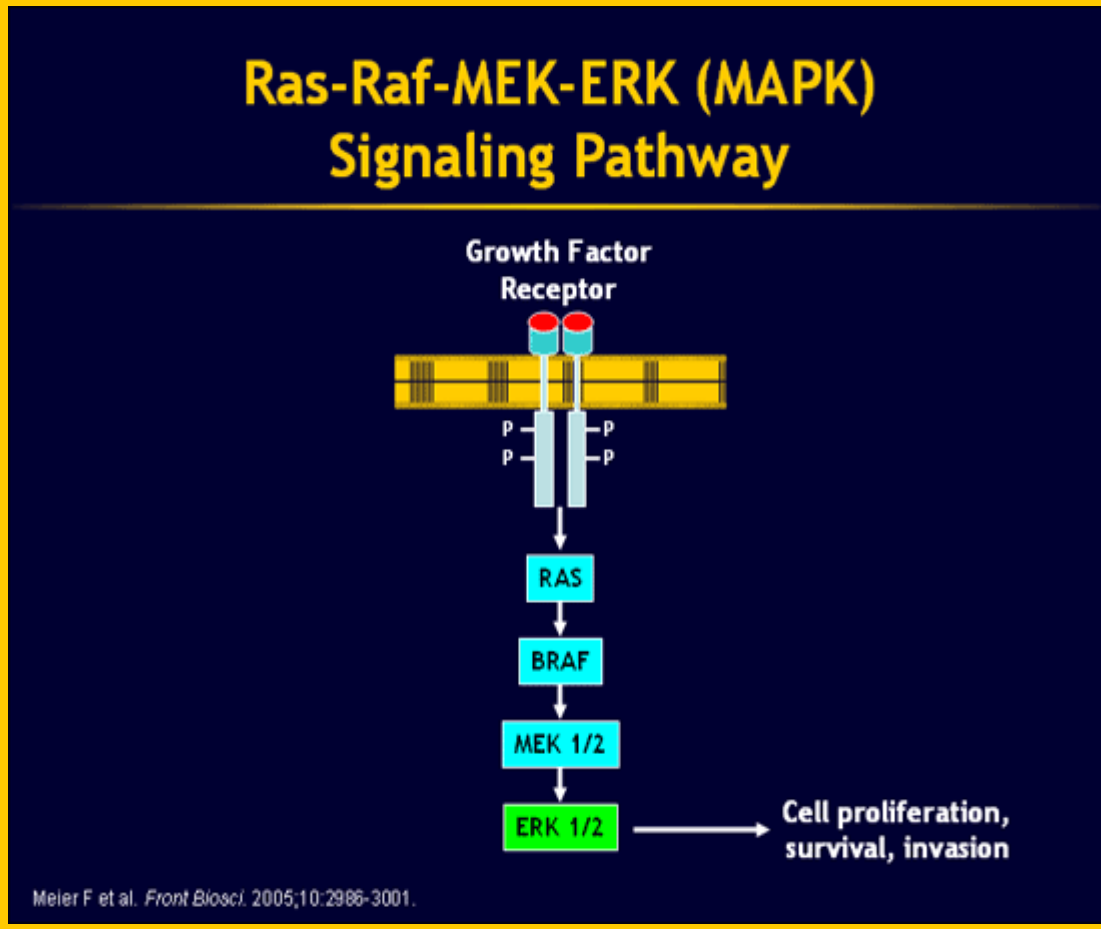
MELANOMA (CDKN2A)



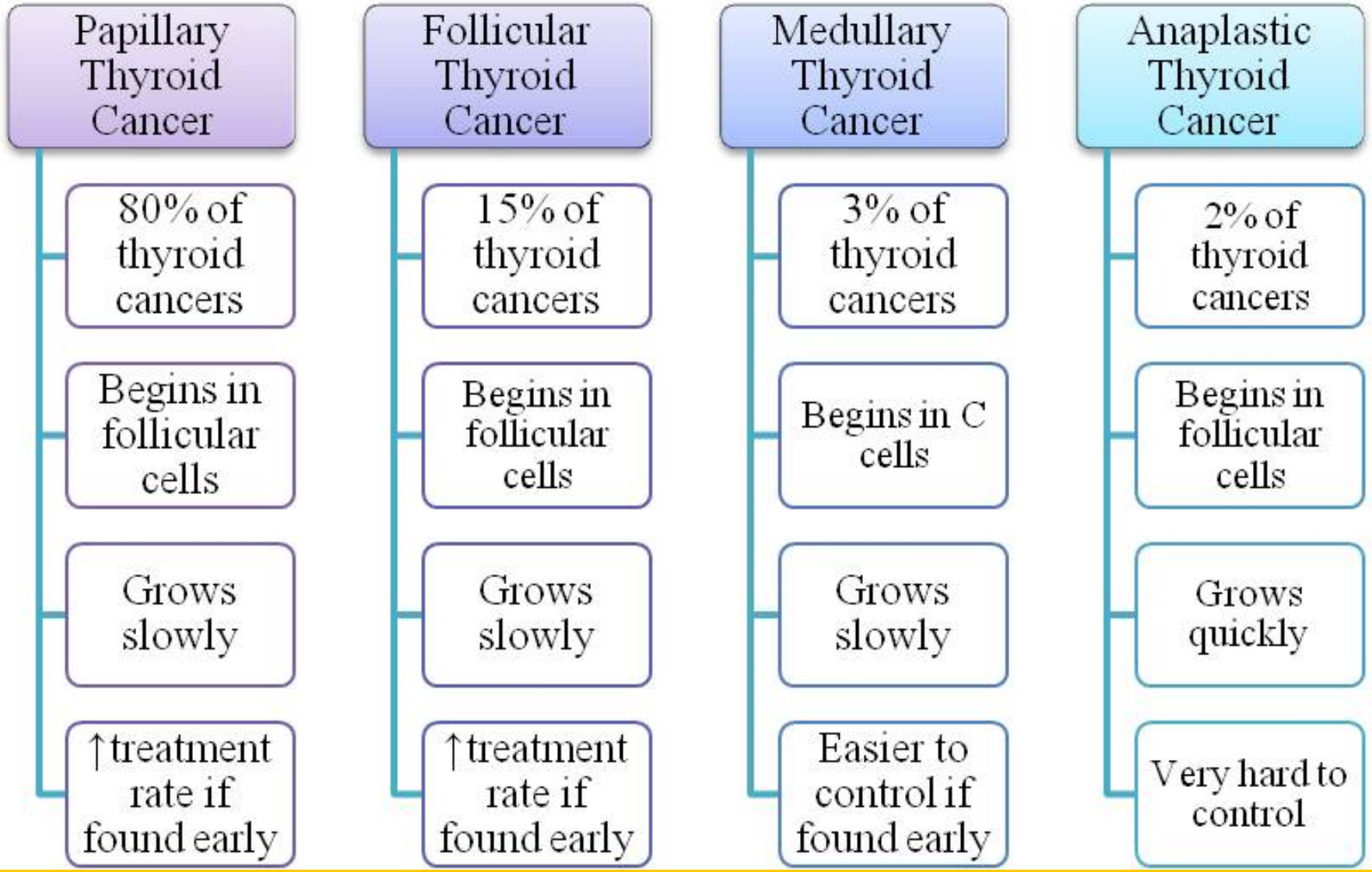
Oncogene	Incidence (%)	Type of melanoma	Comment
BRAF	40–50	Cutaneous	Found most frequently in sites where sun damage is intermittent and not chronic
NRAS	15–30	Cutaneous	NRAS mutations are mutually exclusive of BRAF mutations
c-KIT	5–10	Acral and mucosal	Found more frequently in chronic sun damaged skin
GNAQ and GNA11	80	Uveal (almost exclusively)	Uveal melanomas are very rare

BRAF

- v-raf murine sarcoma viral oncogene homolog B1
- 90% of the mutations V600E
- anti-BRAF agents (vemurafenib and dabrafenib)
- The MEK inhibitor trametinib (V600E/K)

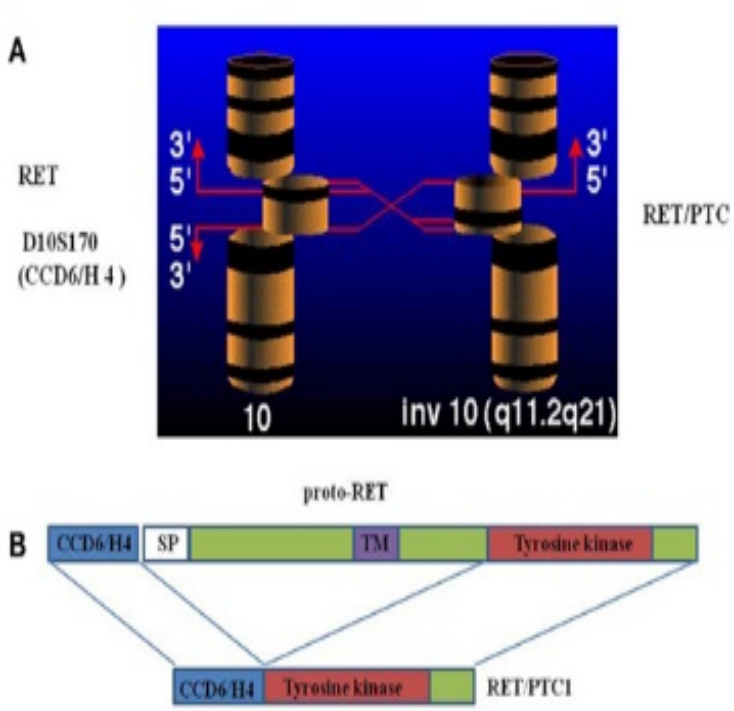


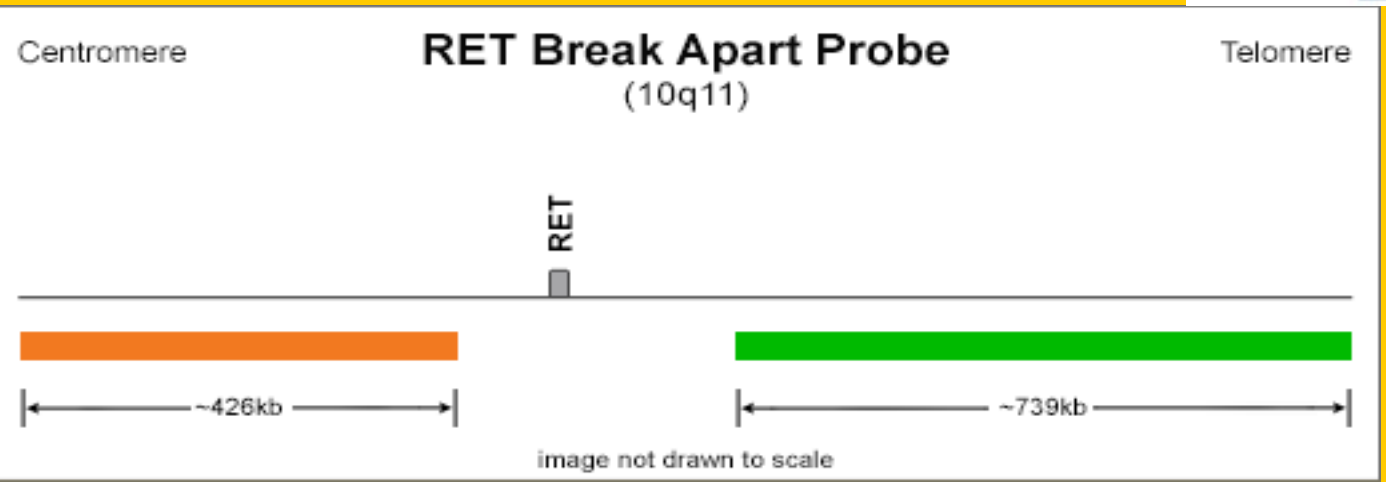
THYROID CANCER



THYROID CANCER

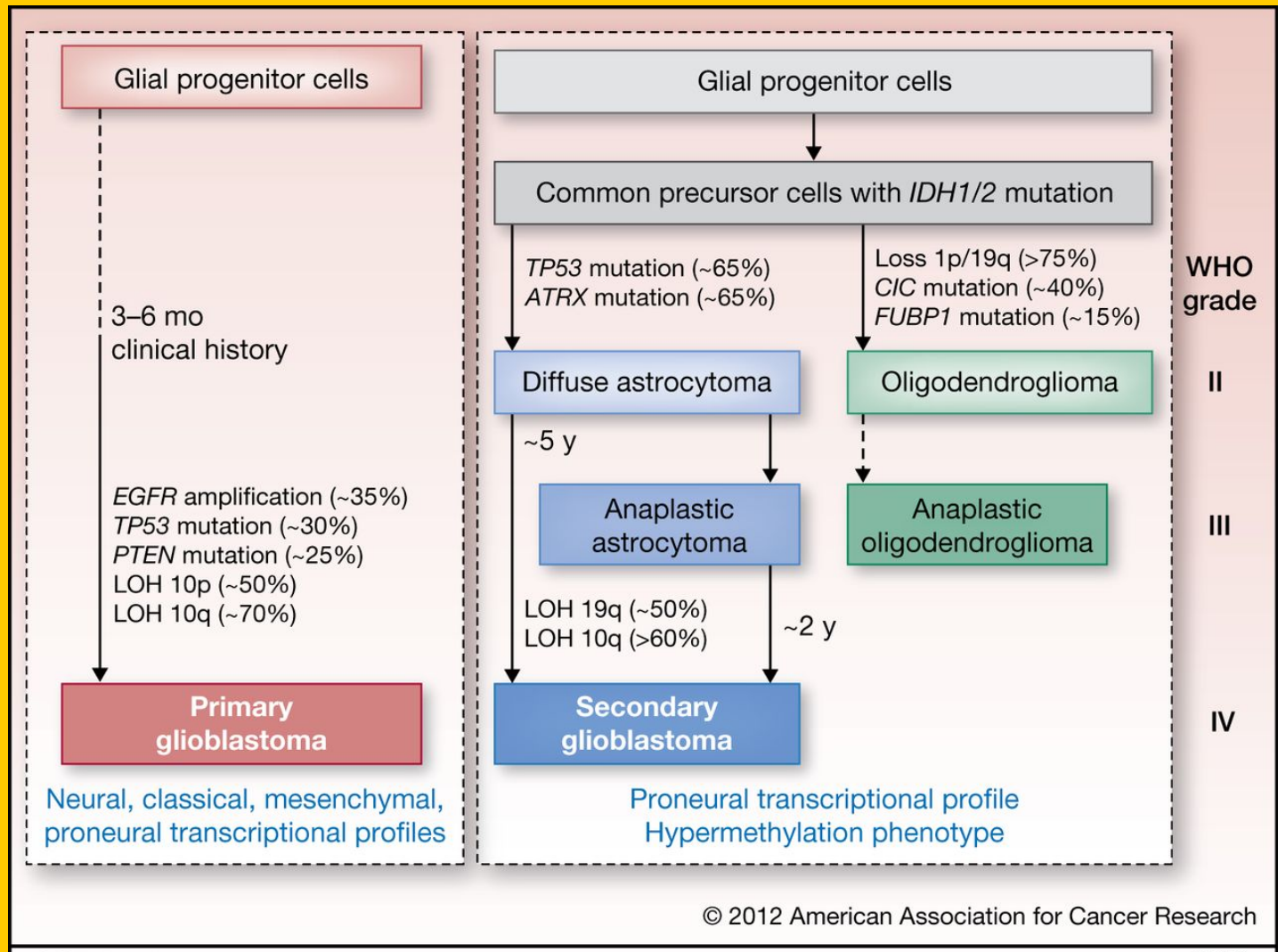
- BRAF
- RET (FISH)
- KRAS
- NRAS
- RET inhibitors: Cabozantinib, Vandetanib, Ponatinib, Sunitinib, Sorafenib



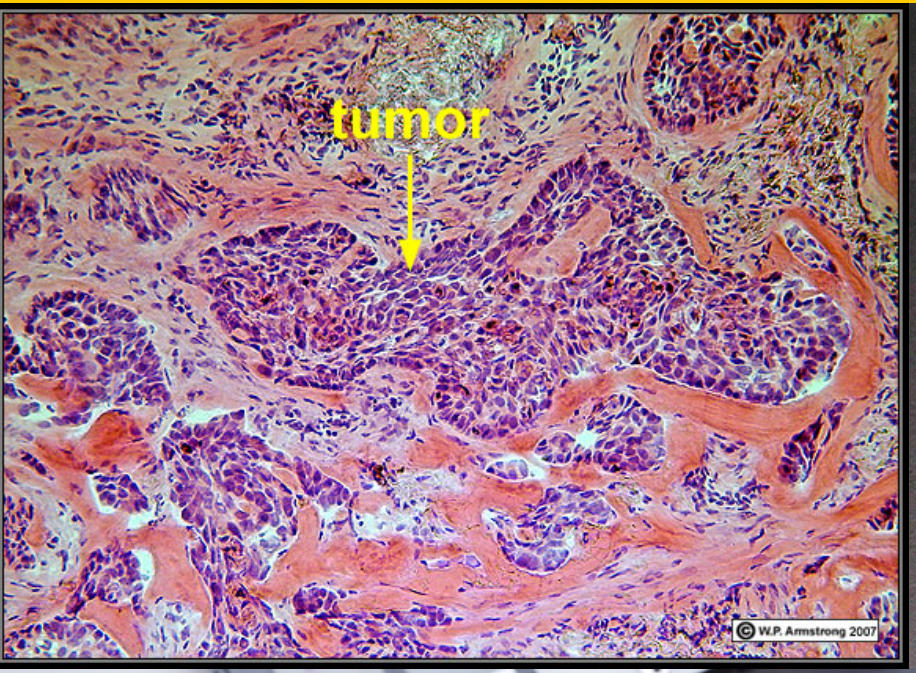


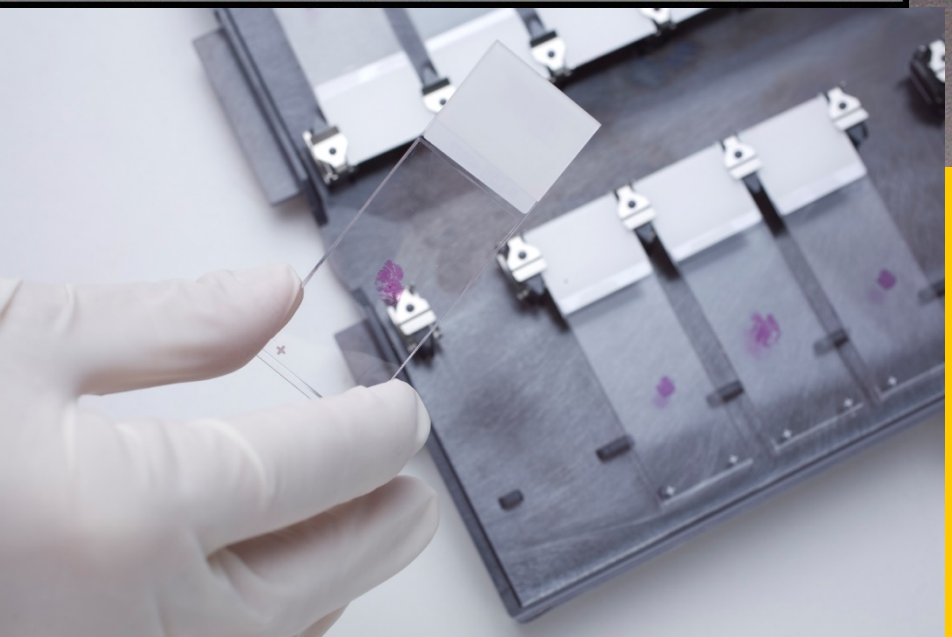
BRAIN CANCER

- IDH1/IDH2 (X AG-221)
- MGMT
- EGFRvIII
- 1p/19q



PATHOLOGY





False negative!!!

QIAGEN Actionable Insights Tumor Panel

Overlapping Genes

EGFR
PIK3CA
KIT
ALK
KRAS
BRAF
ERBB2
PDGFRA

Others

NRAS
ERBB3
ESR1
RAF1

ILLUMINA TrueSight Tumor 15

- **EGFR**
- **PIK3CA**
- **KIT**
- **KRAS**
- **BRAF**
- **ERBB2**
- **PDGFRA**
- **NRAS**
- **AKT1**
- **FOXL2**
- **GNA11**
- **GNAQ**
- **MET**
- **RET**
- **TP53**

DRUG COMPANIES and GENETICISTS

- ALK
- KRAS
- NRAS…

THANKS…


GENETİK HASTALIKLARI
Kuduz Riskli Temaslarda Profilaksi