Cancer Genetics for Nurses

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CANCER IS A CLONAL DISORDER

- SOMATIC CELL OF ORIGIN
- PRIMARY ABNORMALITY
  PRIMARY GENETIC ALTERATION
- SECONDARY ABNORMALITY
  SECONDARY ALTERATION
- SUBSEQUENT ABNORMALITIES

- ACCUMULATION OF ABNORMALITIES

Biological Facts

- All cancers arise from genetic alterations
- Tumorigenesis is a multi-step process
- About 5% to 10% of cancer is hereditary
- Use of knowledge regarding its biology
  - predictive tests to identify genetic predisposition
  - diagnostic tests to detect cancer in its earliest stages
  - therapies that target gene abnormalities in cancer cells

BASIC CHARACTERISTICS

- **CANCER-RELATED GENE MUTATIONS**
- **ALTERATION IN CELL CYCLE CONTROL, GROWTH AND DIFFERENTIATION**
- **ABNORMAL CELL-CELL AND CELL-MATRIX INTERACTION**
- **DYSREGULATED APOPTOSIS**
- **TUMOR ANGIOGENESIS**

- **IMMORTALIZATION**
- **METASTATIC POTENTIAL**

Genes Associated With Cancer Predisposition

Oncogenes

- Accelerates cell division
- Cancer arises when stuck in “on” mode

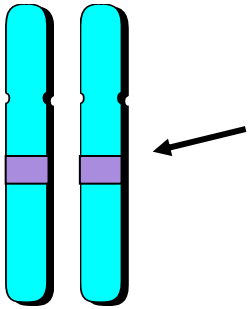
Tumor suppressor genes

- The cell’s brakes for tumor growth
- Cancer arises when both brakes fail

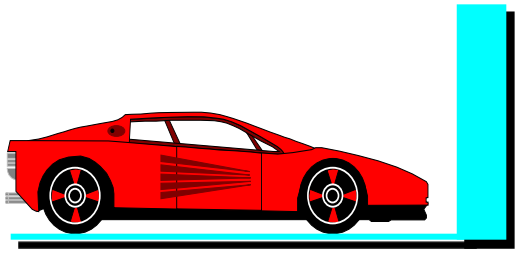
DNA damage-response genes

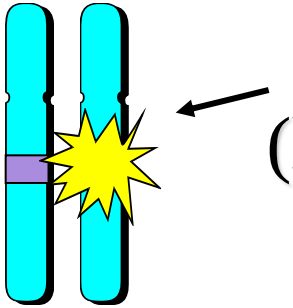
- The repair mechanics for DNA
- Cancer arises when both genes fail, speeding the accumulation of mutations in other critical genes

Oncogenes

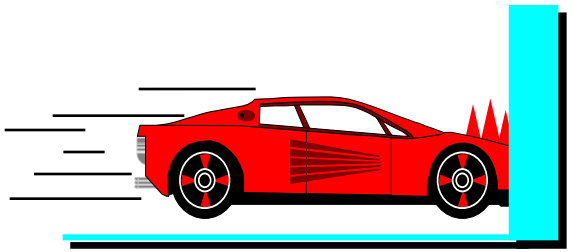


Normal genes (regulate cell growth)





1st mutation (leads to accelerated cell division)

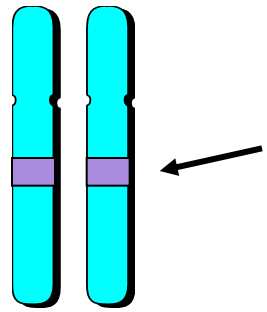


1 mutation sufficient for role in cancer development

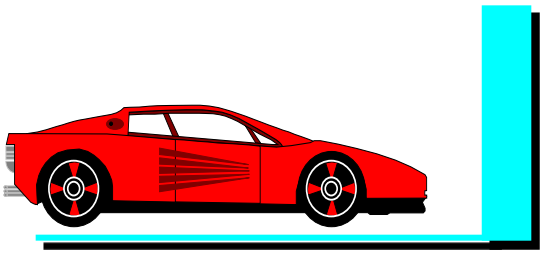
Cancers with oncogene defects

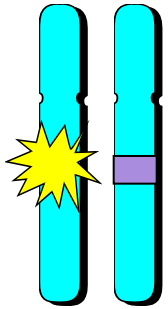
- Neuroblastoma
- Renal papillary carcinoma
- MEN2
- GIST
- Papillary thyroid carcinoma

Tumor Suppressor Genes

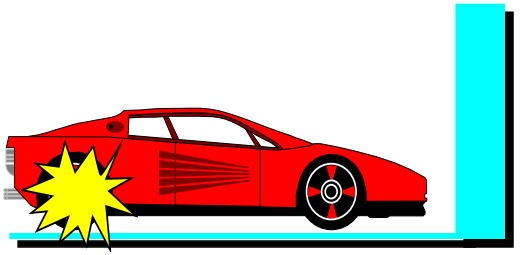


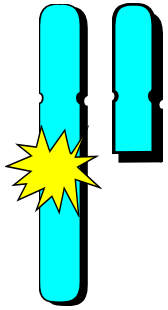
Normal genes
(prevent cancer)



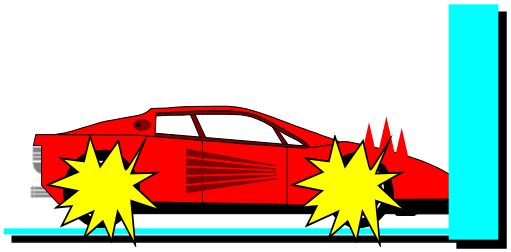


1st mutation
(susceptible carrier)

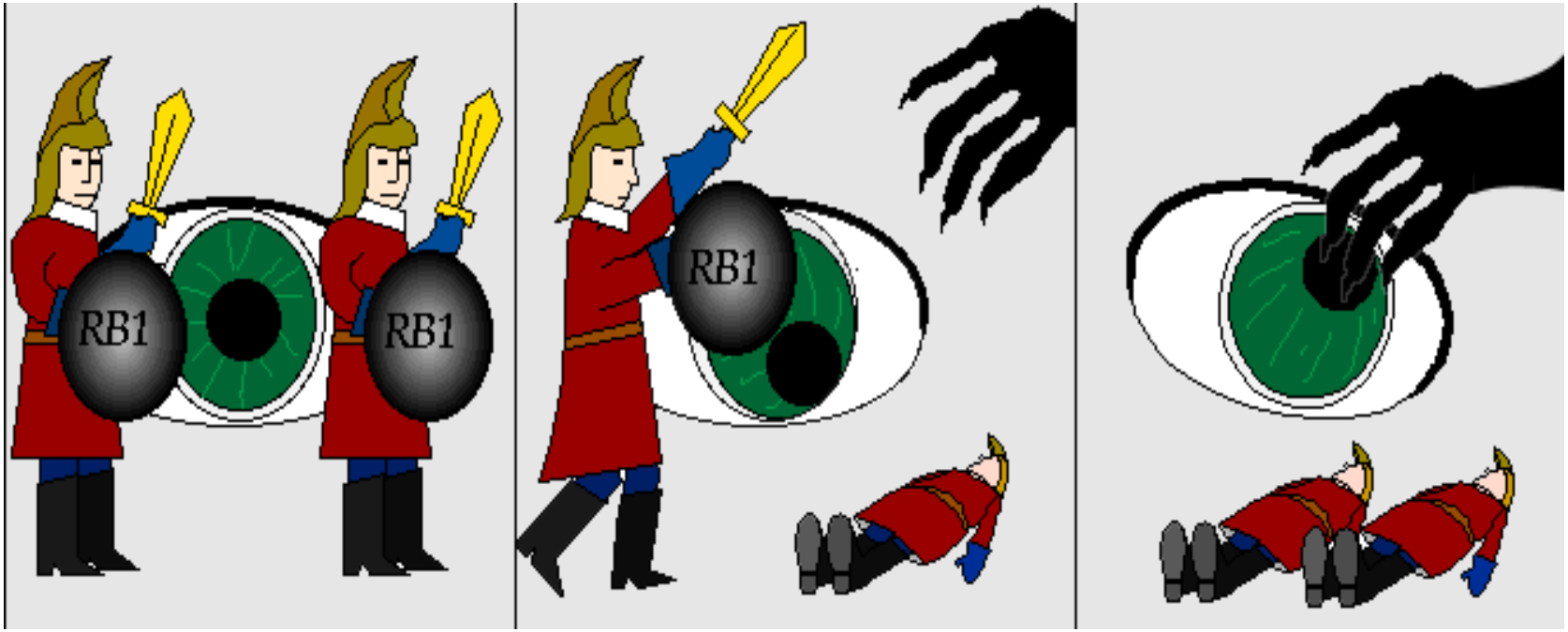




2nd mutation or loss
(leads to cancer)



Knudson's "Two-Hit" Model for Retinoblastoma



Normal
2 intact copies

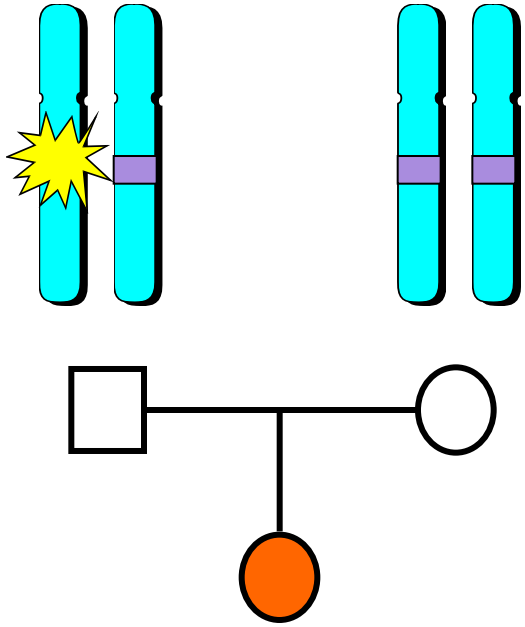
Predisposed
1 intact copy
1 mutation

Affected
Loss of both copies

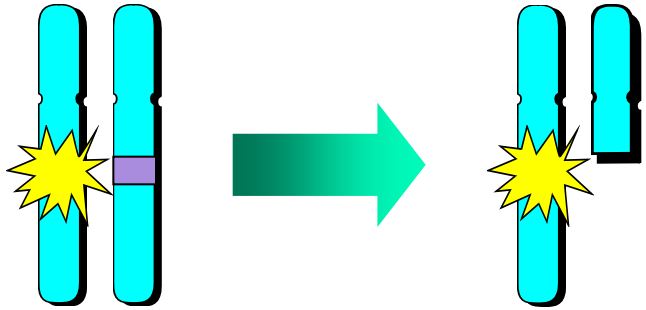
Modified from *Time,* Oct. 27, 1986

The Two-Hit Hypothesis

First hit



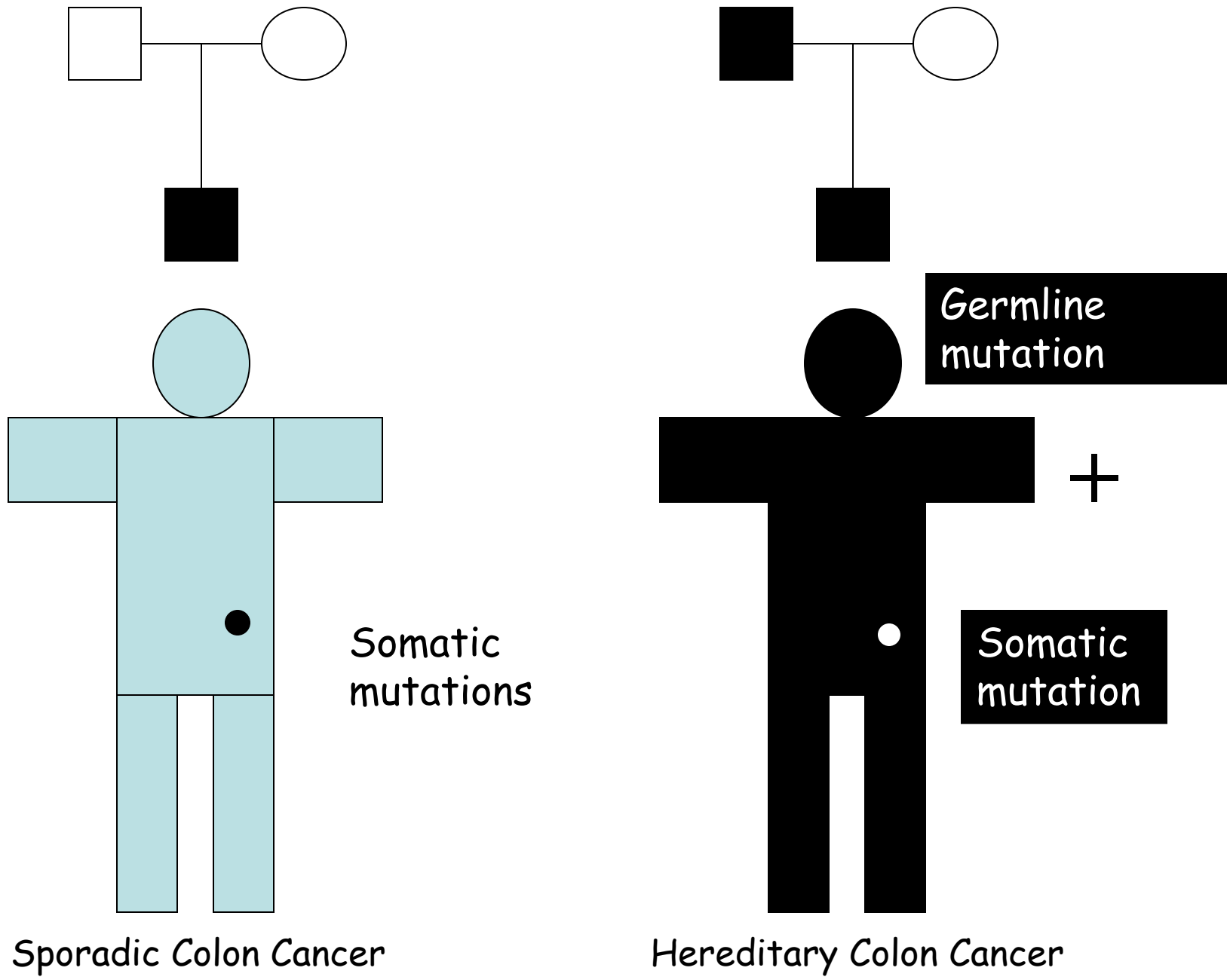
First hit in germline of child



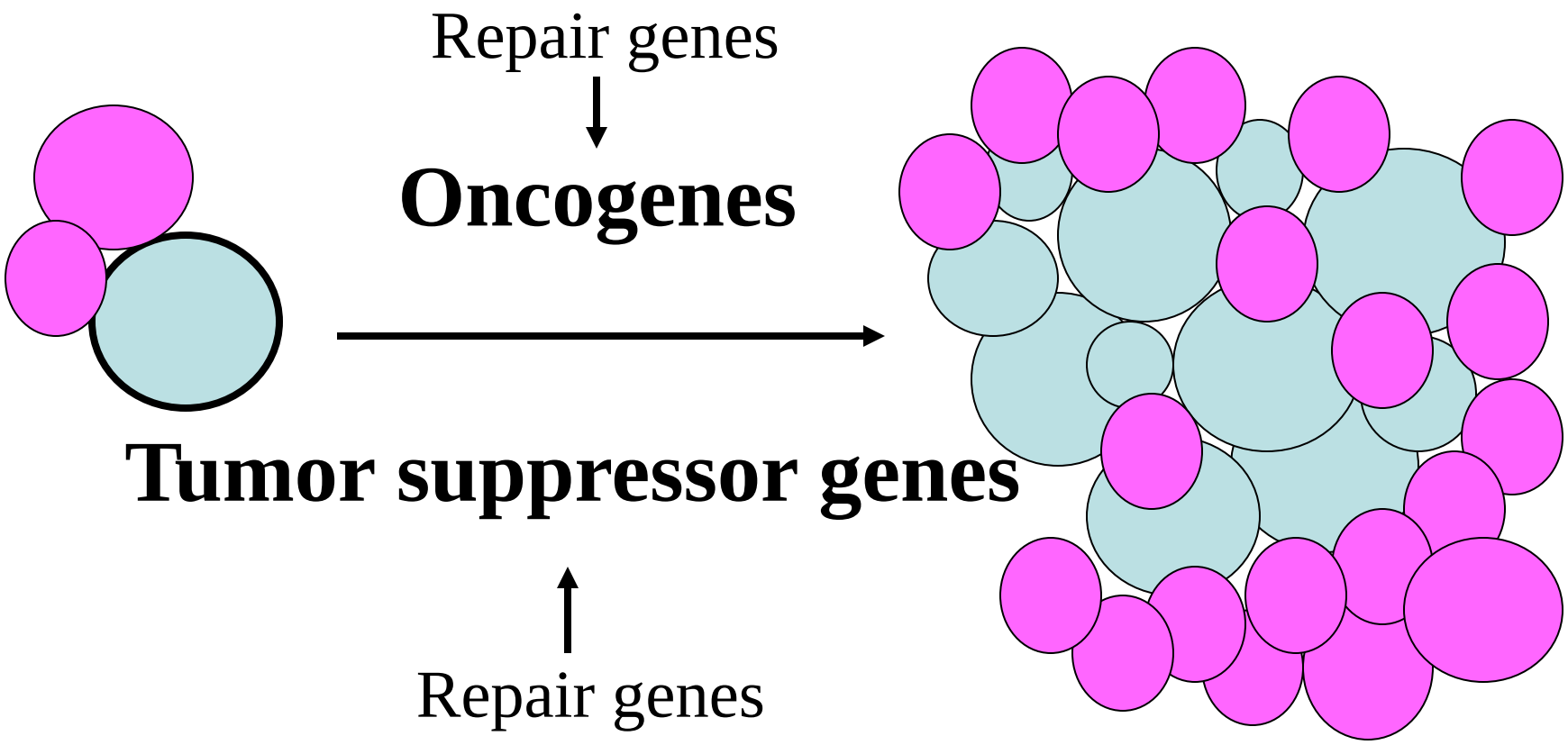
Second hit (tumor)

Cancers with Tumor Suppressor Gene defects

- FAP and variants
- LFS
- VHL
- NF1 and 2
- Familial melanoma
- Gorlin S.
- Cowden S.
- PJS
- Retinoblastoma
- Wilms tumor
- MEN1
- Clear cell renal carcinoma
- Hereditary breast / ovarian
- Prostate ca
- Diffuse gastric ca


Germline mutation
+
Somatic mutations
Somatic mutation
Sporadic Colon Cancer
Hereditary Colon Cancer

BEGINNING OF AN ABNORMAL CLONE



CELL CYCLE CONTROL

- **G0 TO M PHASE**
- **CYCLIN DEPENDENT KINASE PROTEINS**
- **PREVENT CELL WITH DAMAGED DNA FROM UNDERGOING DIVISION**
- **ALLOW TIME FOR DNA REPAIR**
- **SHUTTLE UNREPARABLE CELLS TO APOPTOSIS**
- **ABNORMALITIES RESULT IN UNCONTROLED GROWTH**

ABNORMAL DIFFERENTIATION

- **STEM CELL vs TERMINALLY DIFF. CELL**
- **TRANSCRIPTION FACTORS**
- **TRANSCRIPTION FACTOR RECEPTORS**

- **EGF and EGFR**
- **FGF and FGFR**
- **PDGF, VEGF, NGF**

- **POTENT ANTI-TUMOR DRUG TARGETS**

Chemical Oncogenesis

- Multi-step
- Initiation→Promotion→Progression
- Classes of carcinogen
    - genotoxic
        - clastogenic
        - mutagenic
    - mitogenic
    - cytotoxic
    - others

Chemical Oncogenesis

- Alkylating agent – leukemia
- Arsenic – skin cancer
- Vinyl chloride – angiosarcoma
- Nitrosamine – CA stomach
- Asbestos – mesothelioma
- Tamoxifen – endometrial cancer

Hereditary Cancer

- 5-10%
- Mendelian inheritance
- Mostly tumor suppressor gene defect
- Two-hit hypothesis with germline mutation
- Inherited predisposition
- Preventable, Surveillance necessary

Common hereditary cancers

- Breast
- Ovary
- Colon
- Endometrium
- Thyroid

Uncommon hereditary cancer

- Retinoblastoma
- Cerebellar hemangioblastoma
- Pheochromocytoma
- Diffuse gastric cancer
- Wilms’ tumor
- Hepatoblastoma

Common non hereditary cancer

- Liver and bile duct cancer
- Lung cancer
- Head and Neck cancer
- Leukemia
- Lymphoma
- Germ cell tumor
- Sarcoma

Familial vs. Hereditary Cancers

- Sporadic = without family history
- Familial = clustering within a family due to shared genetic and/or environmental risk factor(s)
- Hereditary = transmitted within a family due to inheritance of mutated gene(s)

Cancer with DNA repair abnormalities

- Hereditary Non-Polyposis Colorectal Cancer (HNPCC)
- Xeroderma pigmentosum
- Chromosome breakage syndromes :Ataxia telangiectasia, Fanconi pancytopenia, Bloom syndrome, Nijmegen breakage syndrome

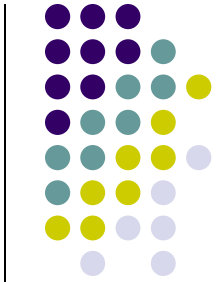
Managing Hereditary Cancer

- Detailed pedigree construction
- Clinical and pathologic diagnosis in proband
- Determination of potential testing
- Pre-test genetic counseling
- Psychological evaluation
- DNA-based testing
- Post-test genetic counseling
- Determination of potential prevention

Cancer with identifiable molecular defects

- FAP
- HNPCC
- Hereditary breast/ ovarian cancers
- Retinoblastoma
- LFS
- VHL
- Chromosome breakage S.
- NF1 and 2
- Cowden S.
- MEN 1 and 2
- Wilms tumor

5 Step approach to suspected cases

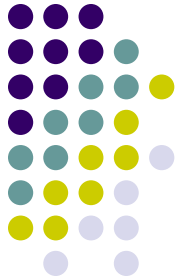


- F Family history gathering
- R Risk estimation
- C Counseling, Care, and Cancer genetic test in proband
- P Prophylactic measures
- T Testing of family members pre-symptomatically

FRCPT

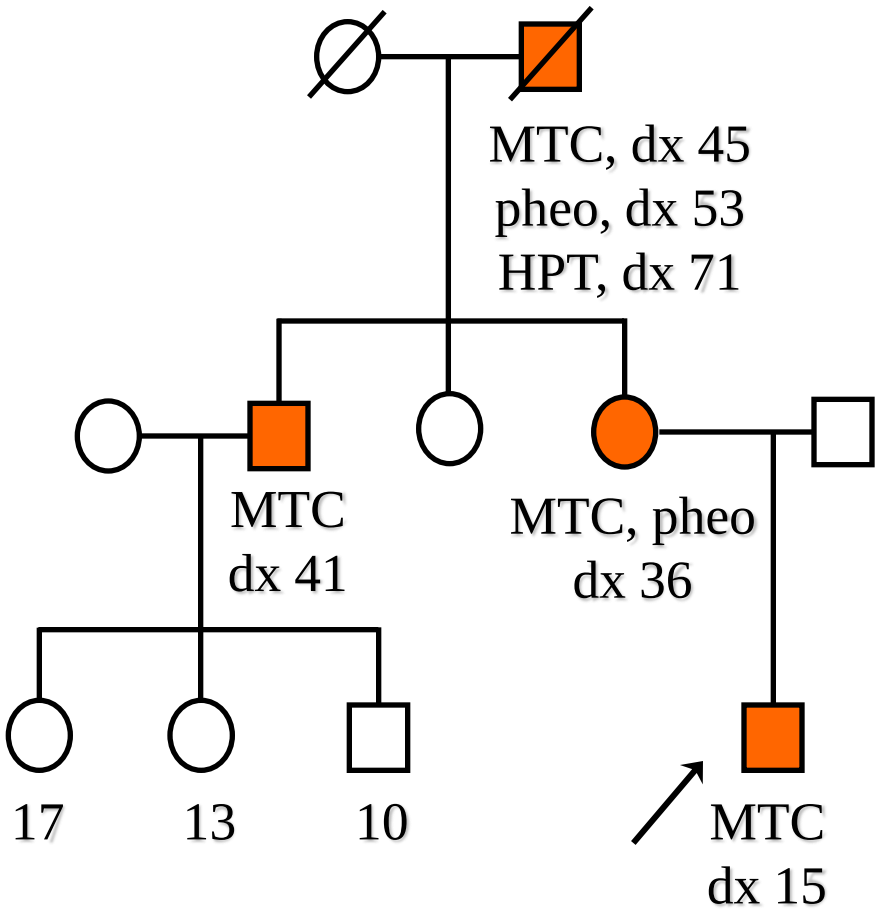
Taking family history

F



- 3 generations if possible
- Include everyone involved- not only the affected
- Designate each cancer within individuals
- Pedigree record is much more practical and simpler to follow than text recording

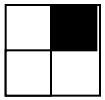
MEN 2A Family



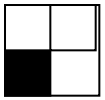
Affected

MTC = medullary thyroid Ca
pheo = pheochromocytoma
HPT = hyperparathyroidism

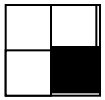
colon

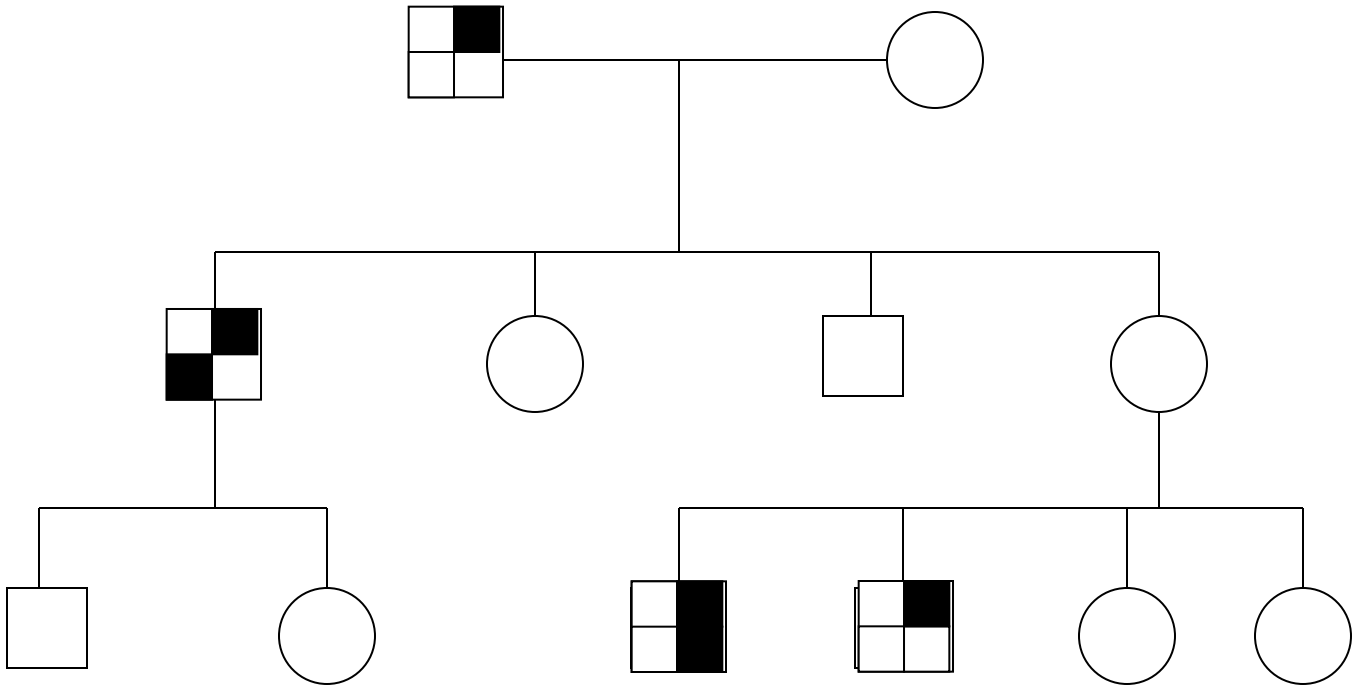


urinary



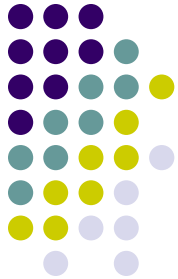
prostate





Risk estimation

R

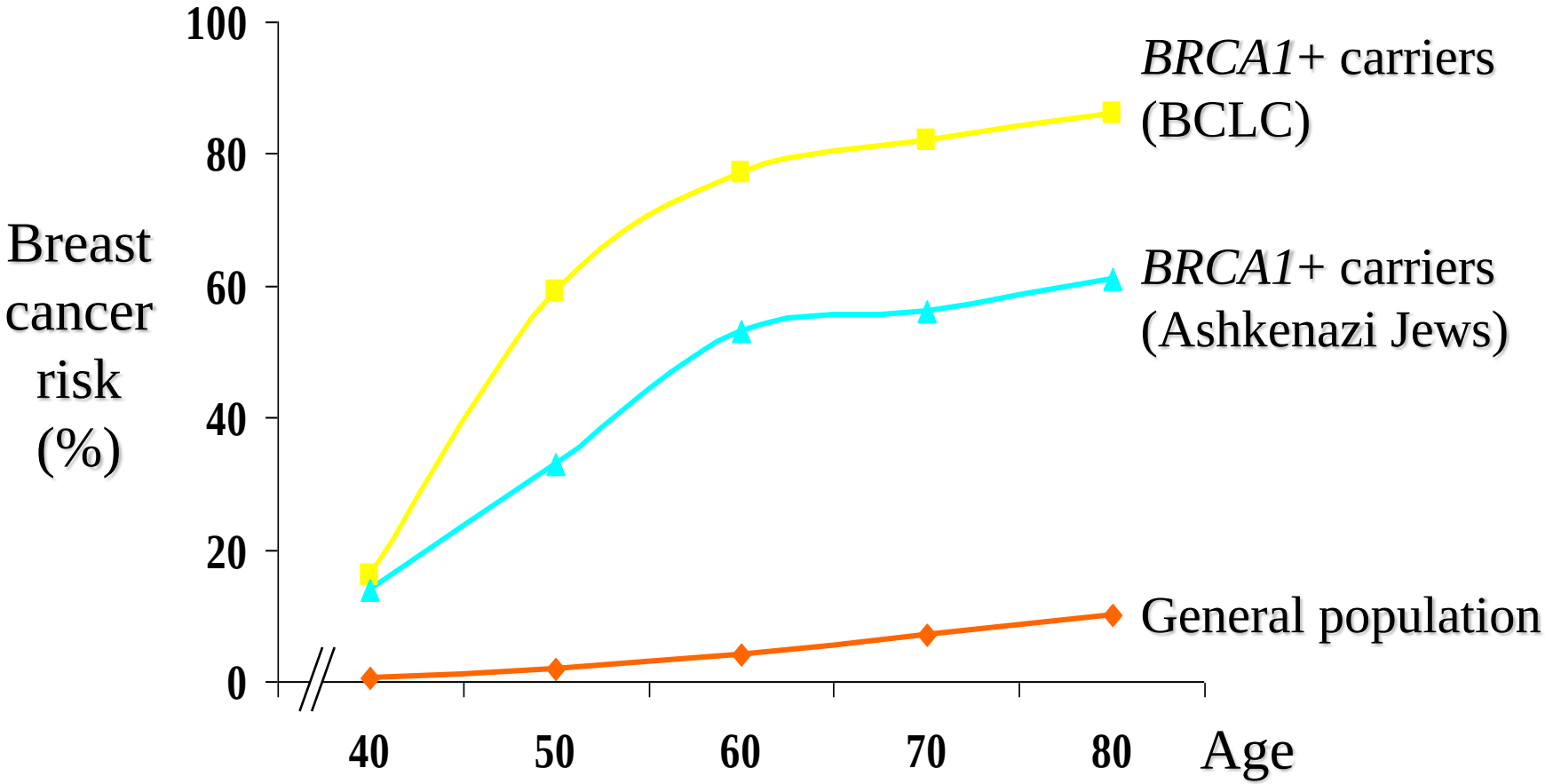


- The goal is to answer “How likely this is a hereditary cancer ?” if so then “How much is a cancer risk ?”
- Based upon
  1. family history
  2. personal history
  3. tissue type
  4. other features of syndrome
  5. known mutation status
- Risk can be accurately predicted or roughly estimated

When to suspect hereditary cancer

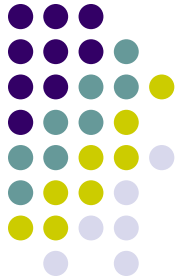
- In a patient
  - multiple primary
  - bilateral
  - young age at Dx
  - rare histology
  - other related tumor
  - associated congenital defects
  - associated precursor
  - associated karyotypic abnormality
- In a family
  - >=2 FDR with similar cancer
  - >=2 FDR with related cancer
  - >=3 any R with similar ncer
  - R with feature of a syndrome

Comparing Breast Cancer Risk Estimates in BRCA Mutation Carriers



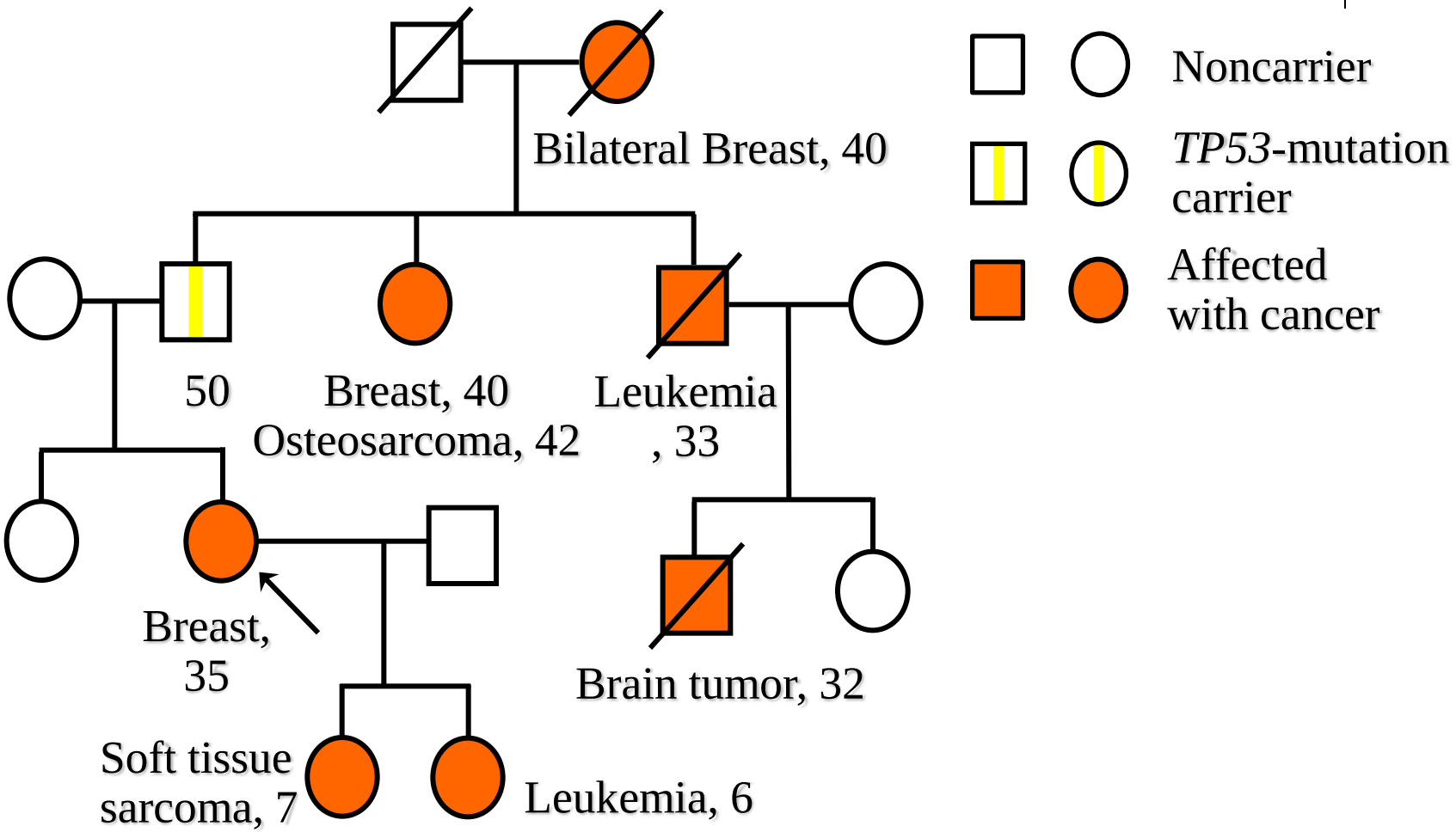
Easton DF et al. *Am J Hum Genet* 56:265, 1995
Struewing JP et al. *N Engl J Med* 336:1401, 1997

Cancer cluster and corresponding syndromes



- HNPCC : CRC, endometrial, urinary pelvis, GI tract, sebaceous gl CA, GBM, breast, sarcoma
- HBOC : breast, ovarian, prostate, pancreas
- LFS : breast, leukemia, sarcoma, brain
- HBCC : lobular breast, colon
- MEN 1 and 2
- VHL : cerebellar hemangioblastoma, hypernephroma, pheochromocytoma

Li-Fraumeni Syndrome



Counseling in Hereditary Cancer Care

- Issue of diagnosis (guilt, anger)
- Issue of at risk relatives (conflict, privacy)
- Issue of testing in children (autonomy)
- Issue of cancer surveillance (early cancer vs. precancerous detection)
- Issue of available prophylactic treatment

Ethical principles in counseling

- Beneficence
- Nonmaleficence
- Autonomy (non-directiveness)
- Confidentiality
- Voluntariness (informed consent)
- Justice

Example 1

- A family with following individual came for consultation
- Father with prostate Ca at 60
- 2 daughters with breast cancer in the 40s

Example 2

- Mother with CA ovary at 55
- Son with germ cell tumor at 20

Example 3

- 3 sisters with breast cancers at 60,62,and 58 among 10 siblings

Example 4

- 15 year old male with right sided cecal cancer without family history

Example 5

- 25 year old female with papillary thyroid cancer
- Two siblings with hyperthyroidism
- Mother with uterine myoma

Example 6

- 15 yr old with lymphoma
- Father with glioblastoma multiforme
- pUncle with lung cancer
- pAunt with rhabdomyosarcoma

Example 7

- 42 yr old with CA corpus
- Mother with abdominal pain LGIB and death at 40
- mAunt with pancreatic cancer

Example 8

- 46yo male with LGIB found to have polyposis by colonoscopy
- 3 sons are 15,9 and 6yo all well

Example 9

- Mother died of ascites and gut obstruction
- Daughter with breast cancer at 30
- 2 healthy daughters and 2 sons

Example 10

- Father died of CA nasopharynx
- Son with CA stomach at 45
- Grandson with leukemia at 12

Conclusion

- Familial cancer syndromes are not as common as sporadic cancer
- Subset of sporadic patients do have familial predisposition
- Recognition is frequently based on pedigree and /or clinical information
- Genetic counseling is necessary for patients and their families since testing and prevention may be available
- Familial cancer registry will be useful in the care of this group of patients