LYNCH SYNDROME: IN YOUR FACE BUT LOST IN SPACE (MOUNTAIN)!

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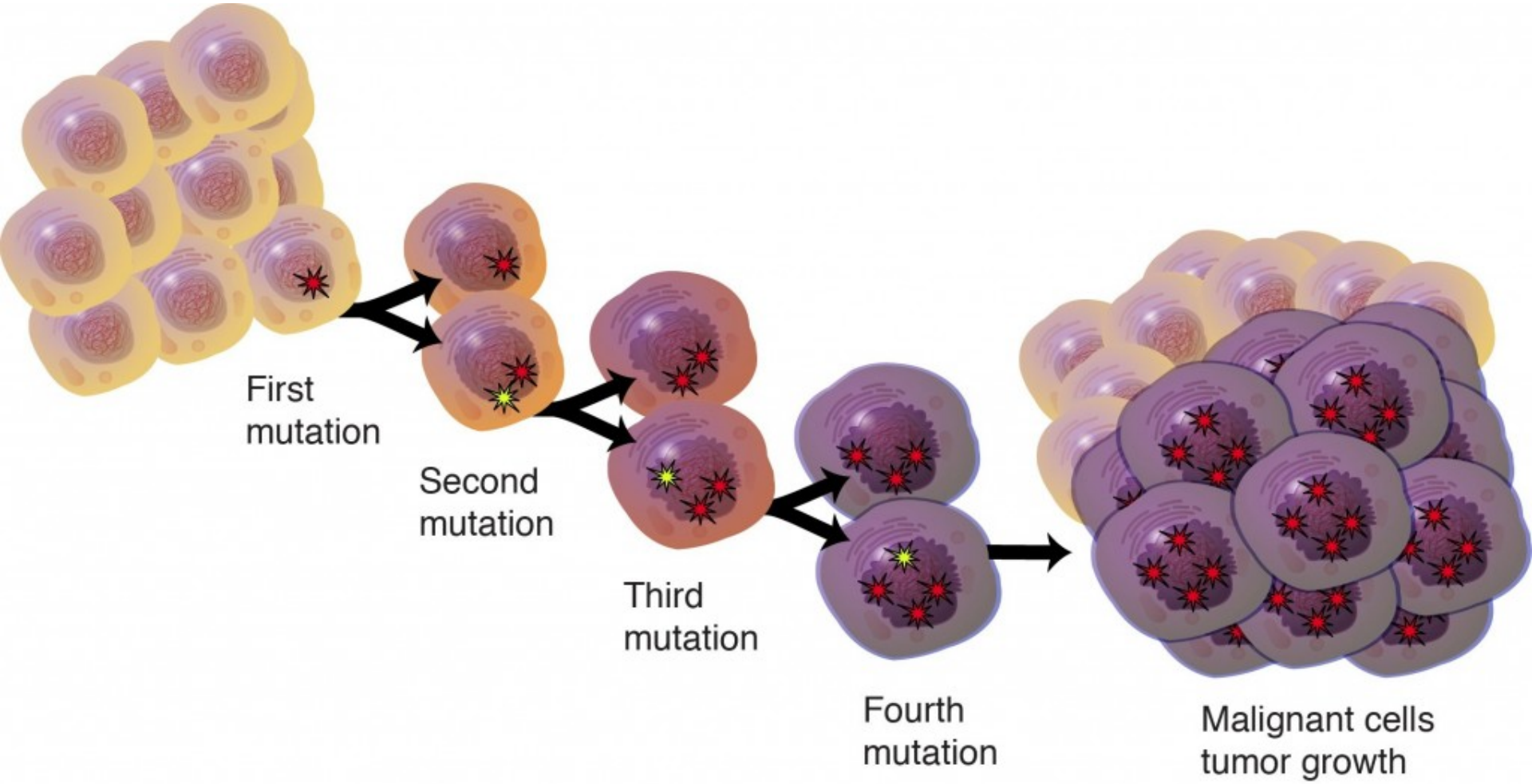
Objectives

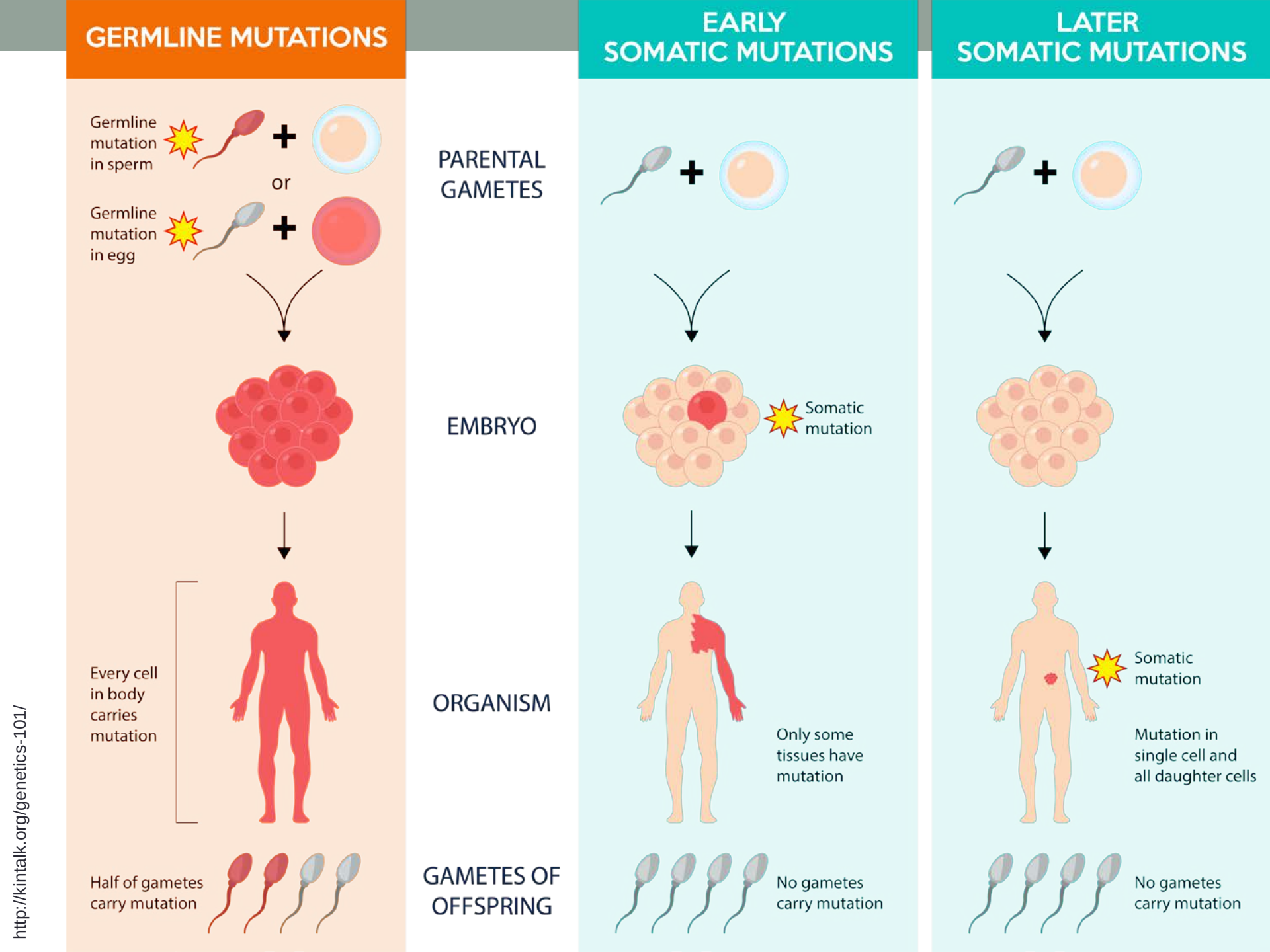
- Review basic features of Lynch syndrome
- Recognize patients/families with possible Lynch syndrome
- Understand basics of genetic testing for Lynch syndrome
- Let no Lynch patient slip through the cracks!

All cancers occur due to

genetic mutations,

but most are not hereditary

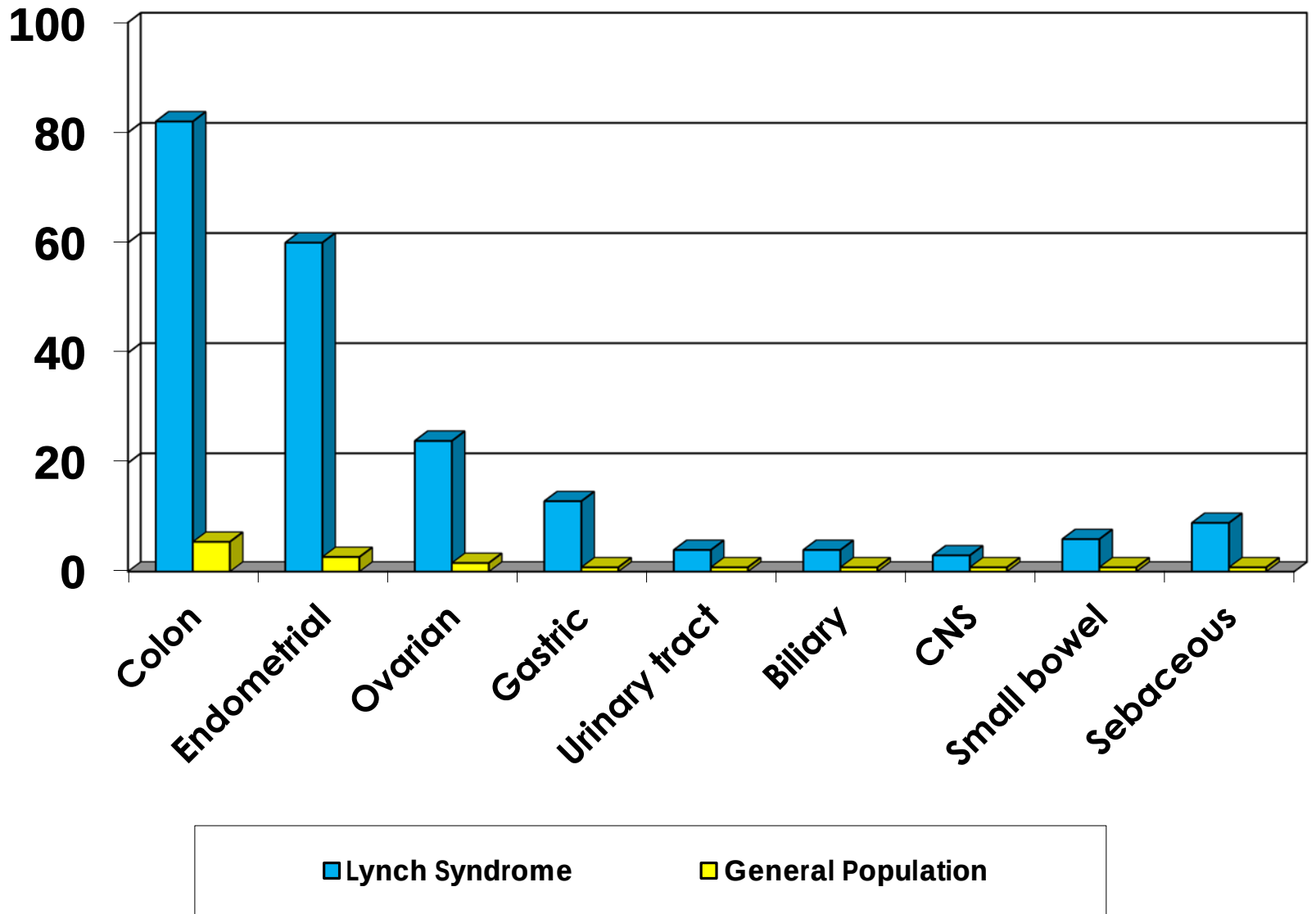

First mutation
Second mutation
Third mutation
Fourth mutation
Malignant cells tumor growth



Lynch syndrome/HNPCC

- Accounts for ~3% of CRC and 1-2% of endometrial cancer
- Lifetime cancer risks: 90% in men, 70% in women
- Early-onset (~44-61y) colorectal cancer (52-82%)
- Extra-colonic tumors
  - Uterine (25-60%)
  - Ovarian (4-12%)
  - Gastric (6-13%)
  - Urinary tract (1-4%)
  - Small bowel (3-6%)
  - Bile ducts (1-4%)
  - Sebaceous skin tumors (1-9%)
  - Brain tumors - usually glioma/glioblastoma (1-3%)

Lynch syndrome cancer risks



Lynch is a defect of mismatch repair

- Mismatch repair (MMR) pathway maintains genomic stability by correcting base-base mismatches and insertion/deletion mispairs generated during DNA replication and recombination

- Germline heterozygous mutations in MMR genes cause Lynch syndrome
  - *MLH1* and *MSH2*: ~90% of Lynch
  - *MSH6*: 7-10%
  - *PMS2*: <5%
  - **EPCAM* deletions can also cause Lynch by methylating *MSH2*: ~1-3% of Lynch

When to suspect Lynch

- Colorectal or endometrial cancer and:
  - Colorectal or endometrial cancer diagnosed before 50
  - Synchronous or metachronous Lynch-related cancers
  - Tumor tissue with evidence of MSI by PCR or histology
  - Tumor tissue IHC with loss of MMR expression
  - At least one first-degree relative with any Lynch-related cancer diagnosed before 50
  - At least two first-degree relatives with any Lynch-related cancers regardless of age of cancer diagnosis

Constitutional Mismatch Repair Deficiency

- Related to Lynch but not the same!
- Caused by biallelic mutations in an MMR gene
- IHC shows complete loss of one protein *even in normal tissues*
- Significant risk for childhood cancers
  - Colon or small bowel cancer often prior to teenage years
  - >10 polyps is common (and different from Lynch)
  - CNS tumors
  - Blood cancers
- Café-au-lait macules (can mimic Neurofibromatosis)

Testing for Lynch syndrome

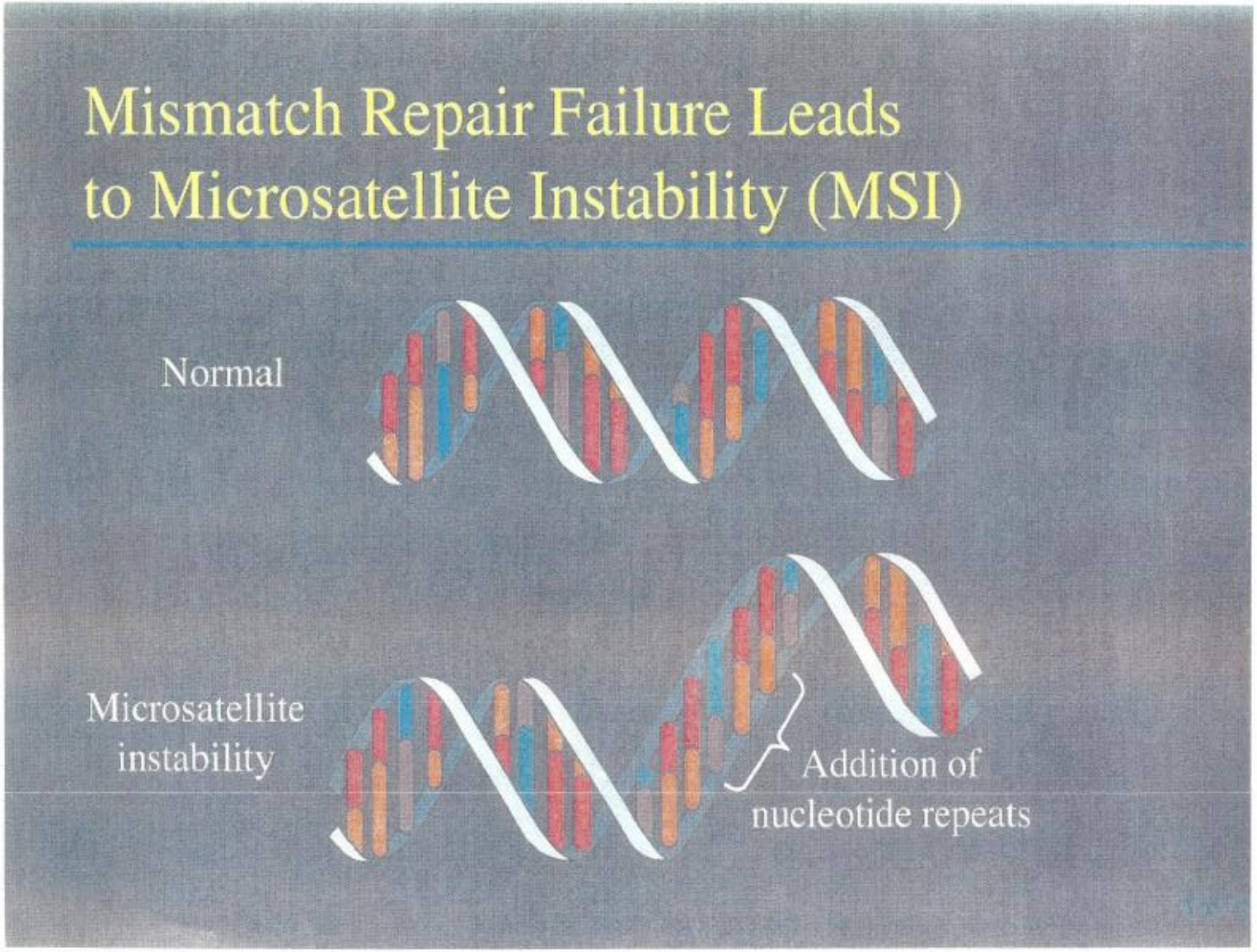
- Screening via MMR assessment on tumor tissue
  - MSI PCR and/or IHC (not the same thing!)
  - Bethesda guidelines vs Universal screening
- Germline DNA testing on blood or saliva
  - Single gene (based on IHC results) vs multi-gene panel
- Somatic DNA testing on tumor tissue
  - Should ideally be paired with germline
  - **Never a substitution** for germline testing

Tumor screening via IHC and MSI

- IHC assesses for presence/absence of MMR proteins
  - Negative stain means the protein is absent – suggests a mutation
  - Positive stain means the protein is present – argues against a mutation

- MSI PCR assesses how well MMR proteins are functioning
  - **Beware! Presence of MSI does not absolutely mean Lynch**
  - ~15% of all CRCs are MSI-H but only 3-5% are due to Lynch
    - Remaining 10-12% are sporadic with an average age of dx of 70
      - 70% of these have *MLH1* promoter methylation due to **somatic** *BRAF* V600E mutation
        - Will show loss of MLH1 and PMS2 on IHC

Mismatch Repair Failure Leads to Microsatellite Instability (MSI)



Single gene vs. panel testing

- Single gene
  - Sanger (or Next-Gen) sequencing
  - Looks for mutations in one gene
  - Higher cost per gene

- Multi-gene panel
  - Next-Gen sequencing – may include deletion/duplication
  - Looks for mutations in several genes simultaneously
  - Lower cost per gene
  - Increased likelihood for variants of unclear significance or pathogenic mutations in genes with unclear management guidelines

How many people have Lynch syndrome?

3-5% of patients with CRC

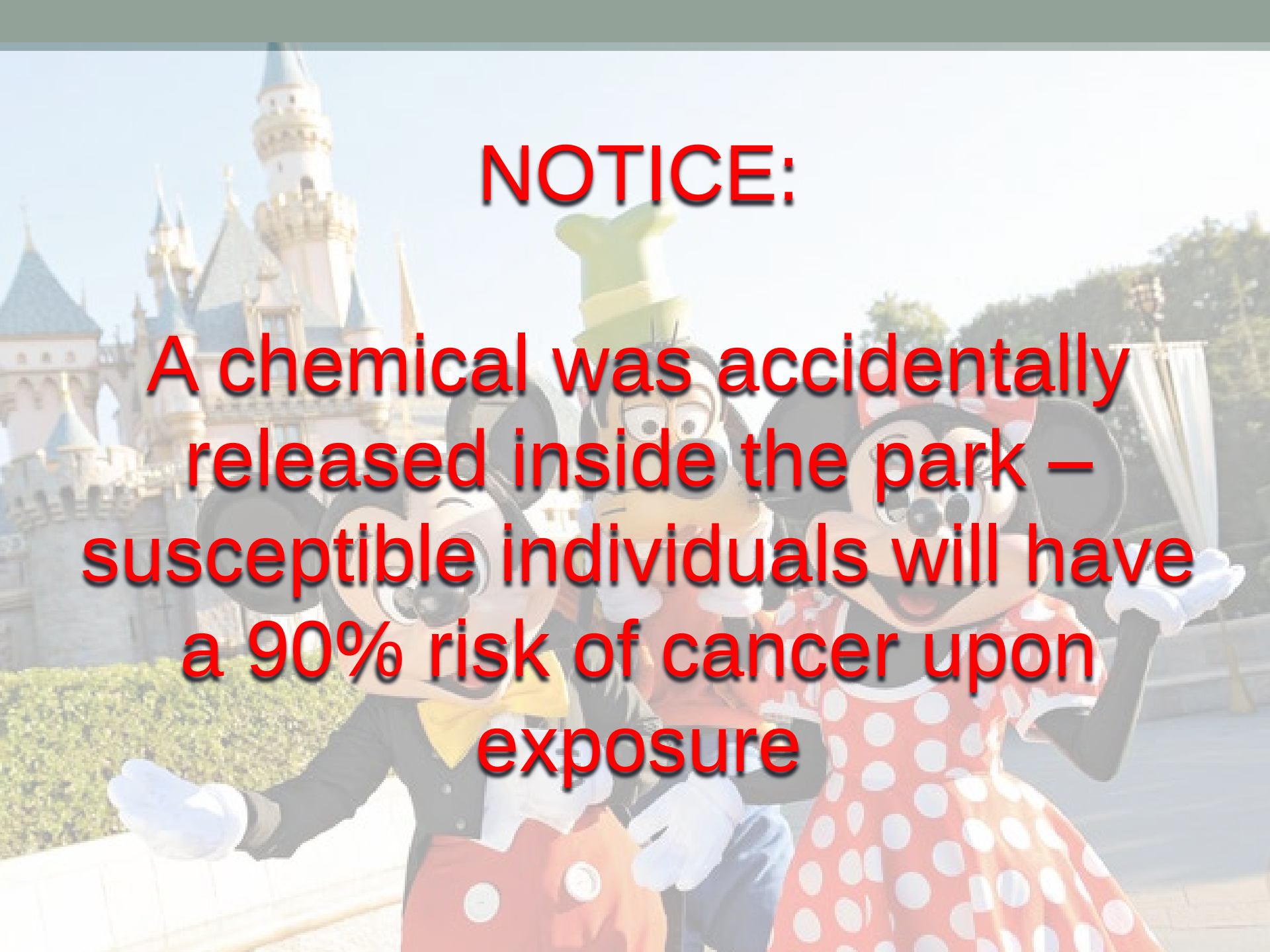
2-3% of women with uterine cancer

1 in 400 Americans: ~814,000 people

Can we find everyone with Lynch?

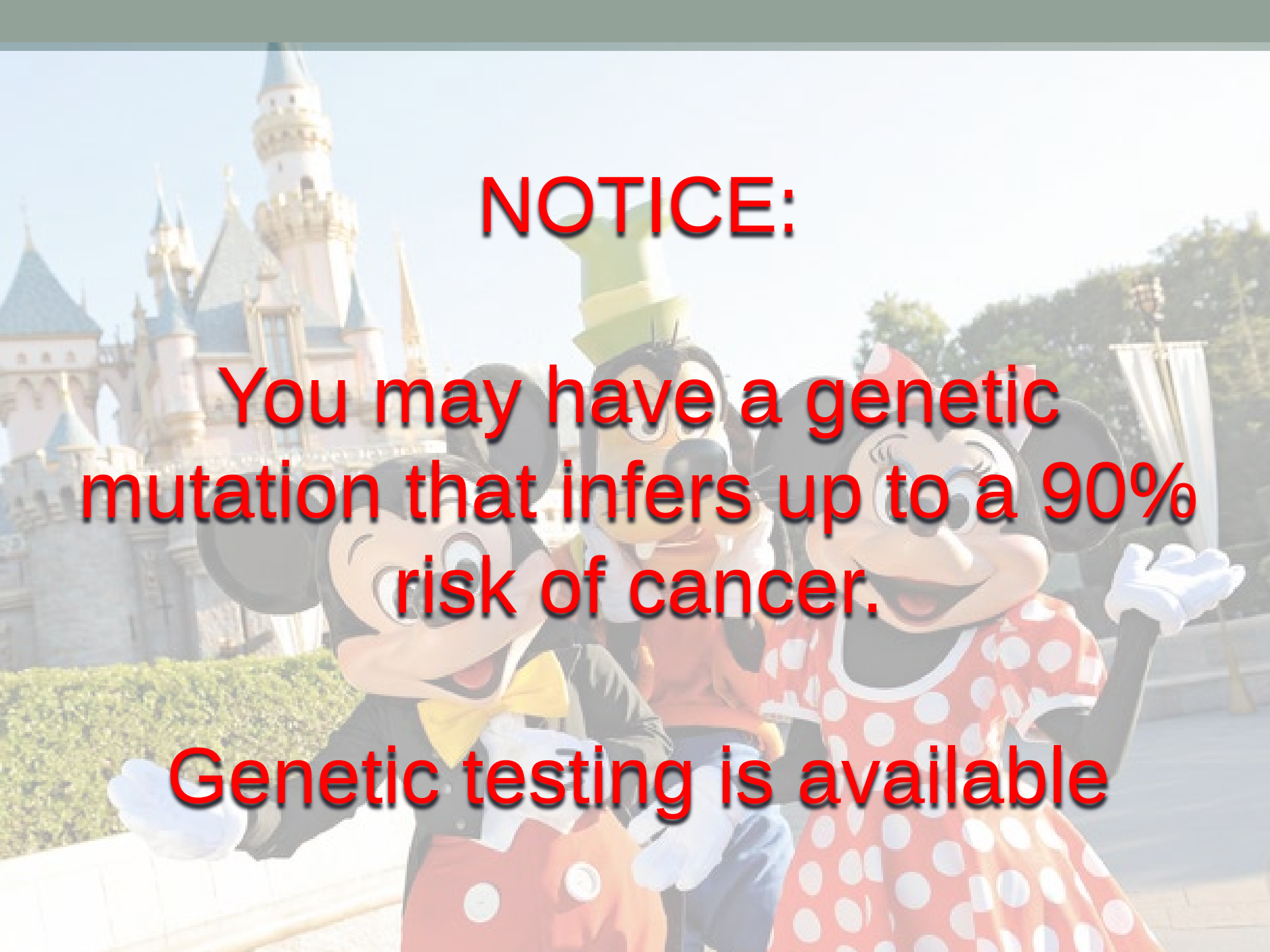
- Where do we start?
  - Time of cancer diagnosis is too late!
  - Family history screening by primary care?
  - Population based screening?

- Does everyone want to be found?



NOTICE:

A chemical was accidentally released inside the park – susceptible individuals will have a 90% risk of cancer upon exposure



NOTICE:

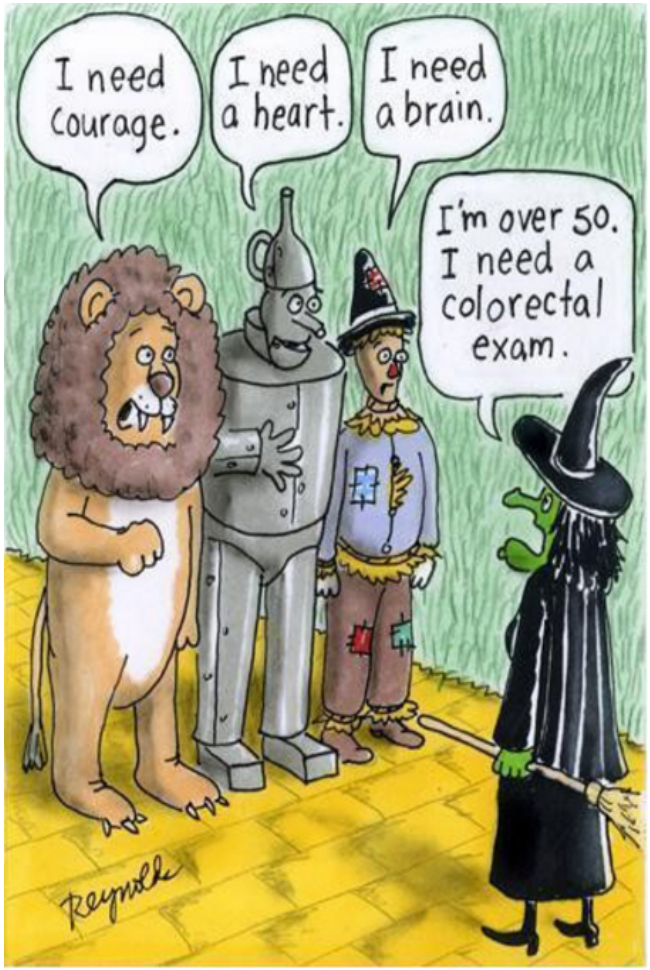
You may have a genetic mutation that infers up to a 90% risk of cancer.

Genetic testing is available

Do they want to be found?

- Regular screening of unaffected individuals with Lynch syndrome reduces risk of CRC by 56% and death by 65% but a significant portion of at-risk individuals decline testing
- Lack of understanding
- Lack of trust in medical field and/or genetic testing
- Concerns over
  - Discrimination by insurance, employers, etc
  - Fear of cancer
  - Guilt of passing it to children

Thank you!



American Cancer Society®

For more information on the different ways you can be tested, call 1.800.227.2345 or visit www.cancer.org/NYNJ.