Updates on Genetic Testing for Hereditary Cancer Syndromes and Red Flags for Referrals

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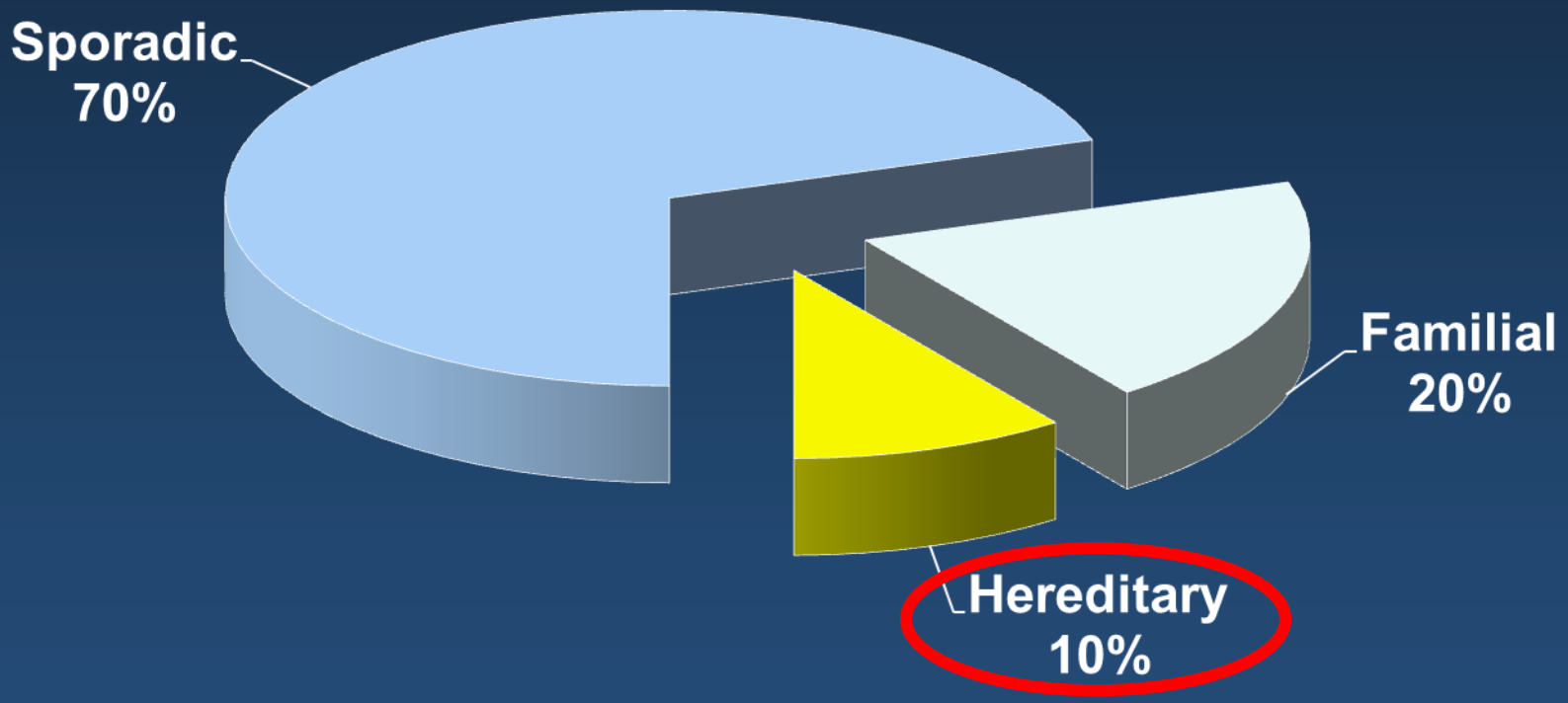
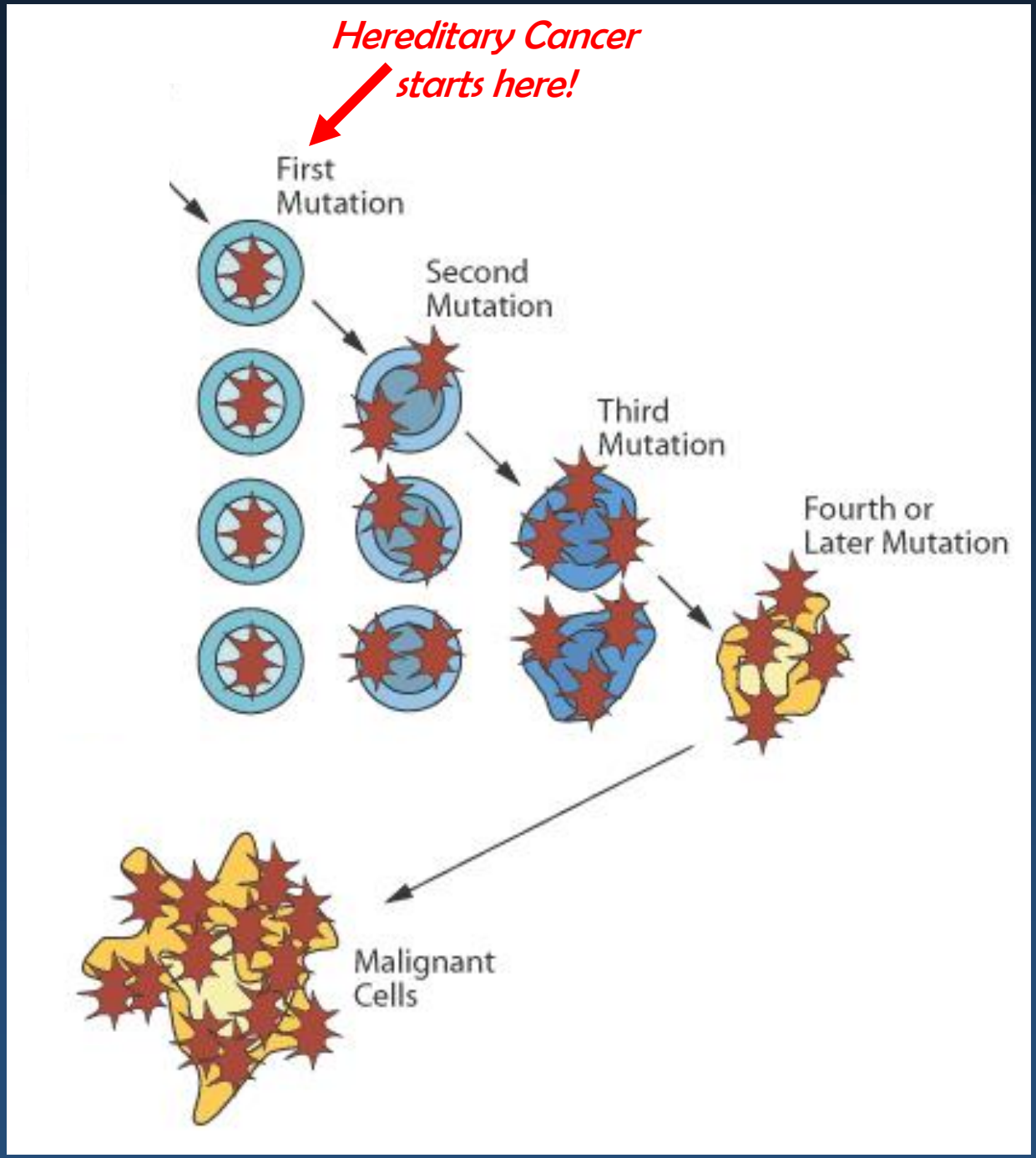
Objectives

- Review features and updates of hereditary cancer syndromes
- Discuss the role of genetic counseling, advances in genetic testing
  - Benefits and limitations
- Review red flags for referrals

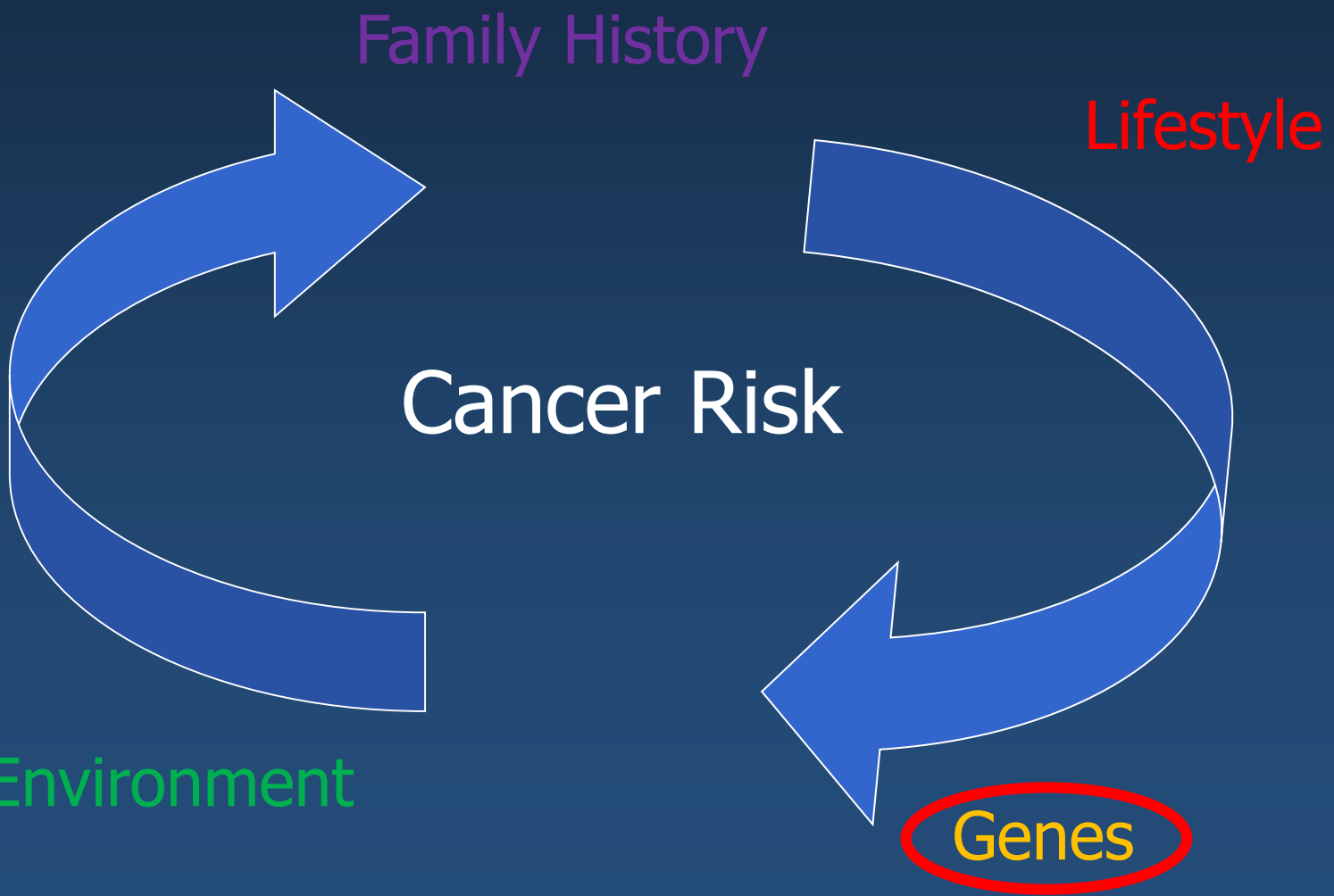
The World of Genetic Testing for Hereditary Cancer in 2018

5-10% of *ALL* Cancer is Inherited




Hereditary Cancer
starts here!
First
Mutation
Second
Mutation
Third
Mutation
Fourth or
Later Mutation
Malignant
Cells

Most Hereditary Cancer Syndromes are *NOT* associated with 100% Cancer Risk



Genetic Testing - Why Know??????

Benefits of Genetic Testing

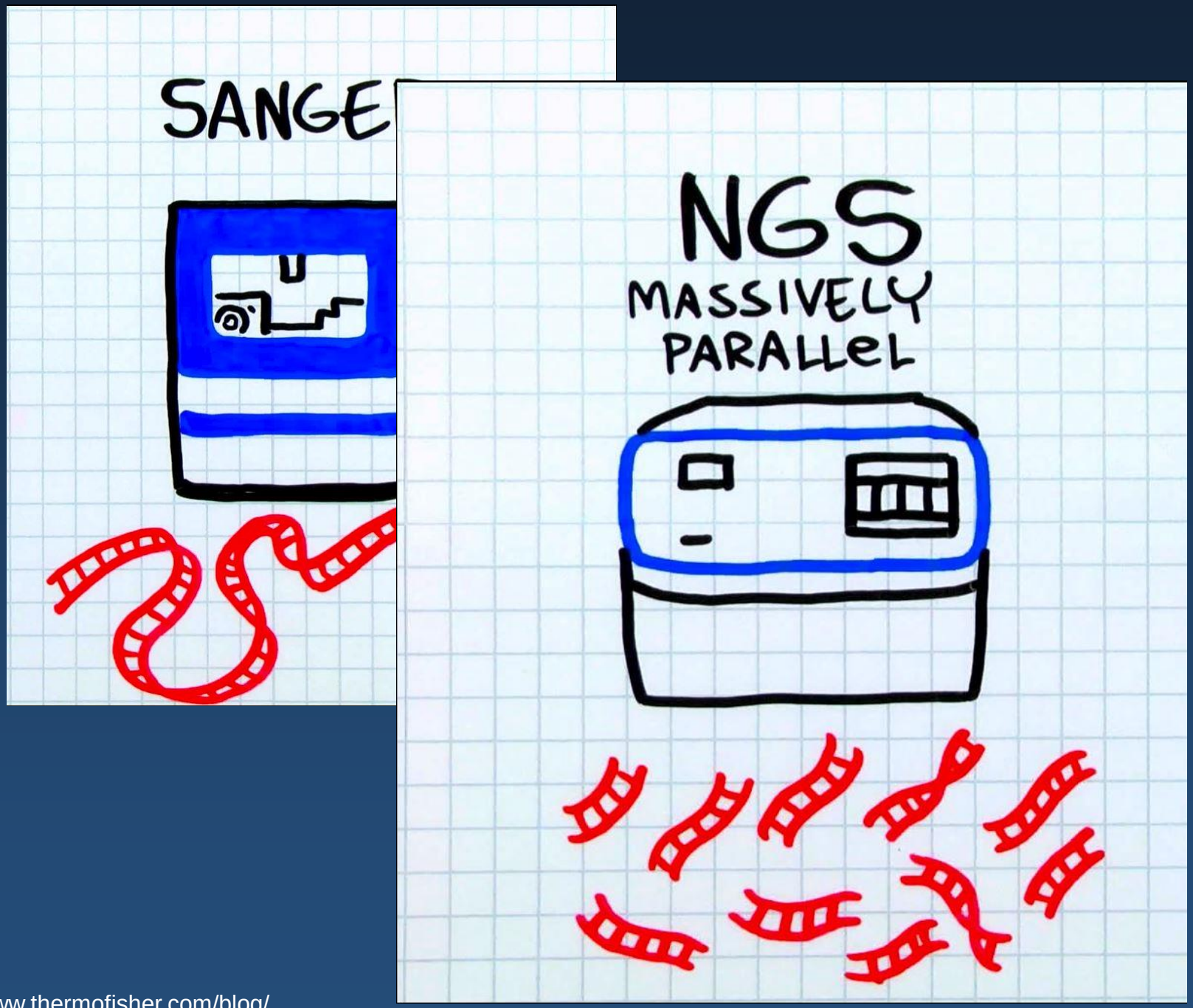
- Helps identify underlying cause of cancer
- Determines if there may be other cancer risks
  - MOST cancer syndromes associated with multiple cancer risks
  - Significantly changes screening recommendations
  - Focus on what can we do differently to help minimize those risks
- Helps to identify family members who are also at risk
- Implications for potential treatment options

Limitations to Genetic Testing……

Genetic Testing……
Then and Now

Evolution of Genetic Testing

- Prior to 2013
  - BRCA1/2 only done through Myriad
  - Other genes (Lynch, TP53, PTEN) only if indicated
- Starting in 2012-2013
  - Panel testing available through Next Generation Sequencing



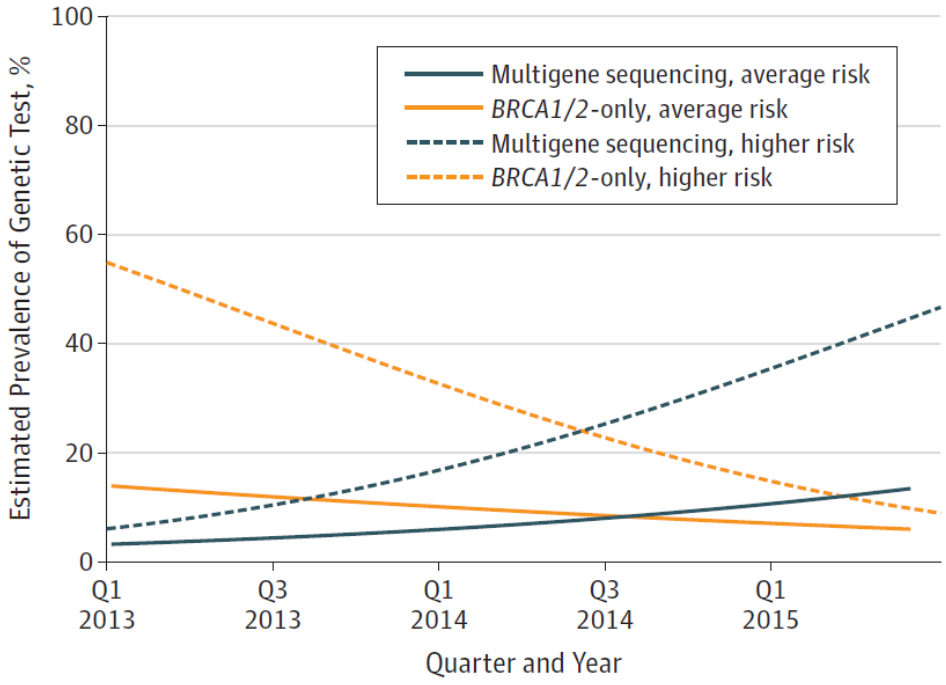
https://www.thermofisher.com/blog/

Current Testing Strategies

- Single gene testing
  - When family is suspicious of single syndrome or gene
    - BRCA1/2, TP53, Lynch syndrome
  - When gene mutation is known in family
- Multi-gene or panel testing
  - Testing for numerous genes at one time
  - Panels based on specific cancer
  - Broader panels that encompass genes linked to various types of cancers

Trends in Testing and Outcomes

Figure. Trends in Genetic Test Type



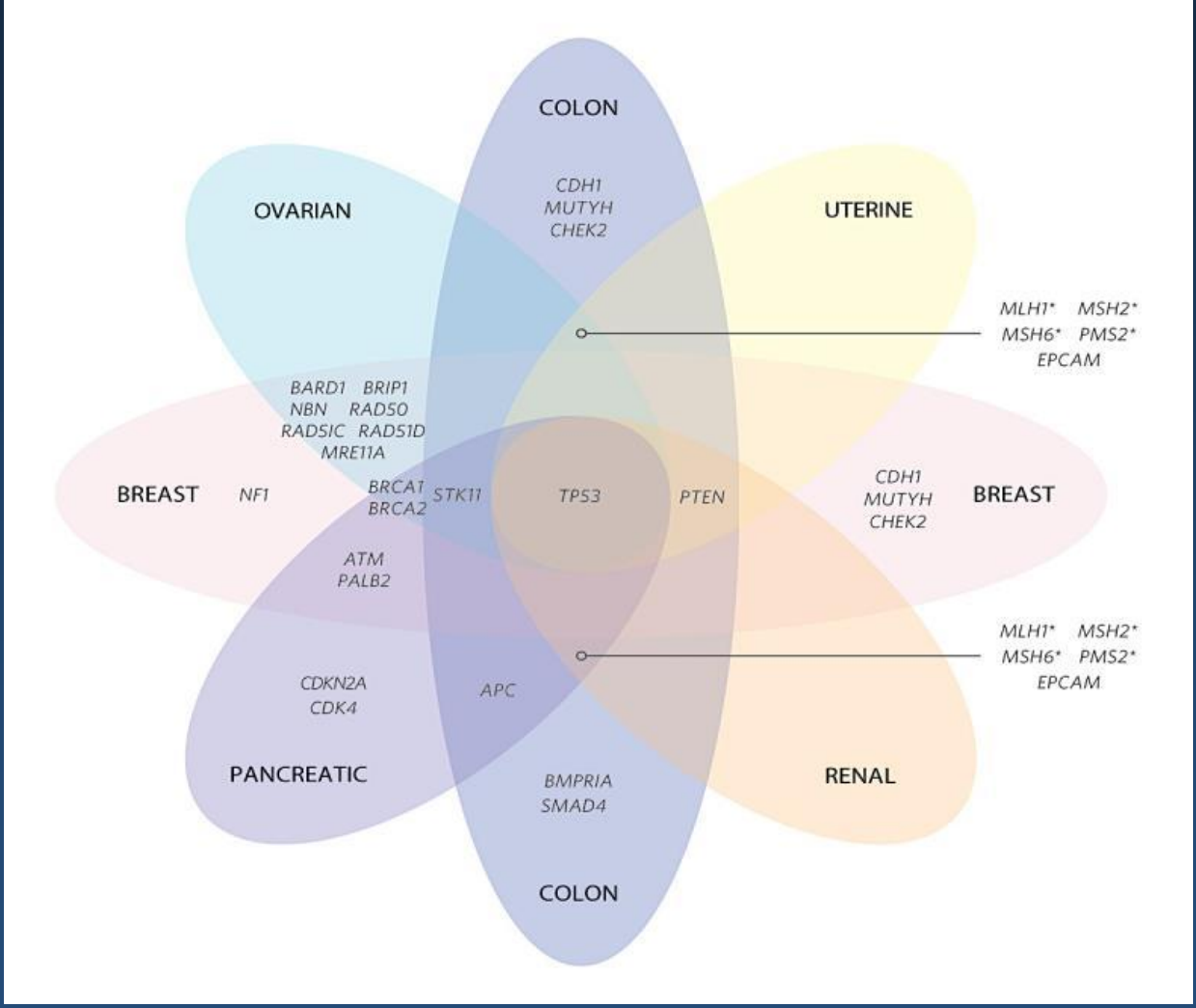
Panel testing increased detection rate from 7.8% to 12.5% in high-risk patients.

JAMA Oncol. Published online May 10, 2018. doi:10.1001/jamaoncol.2018.0644

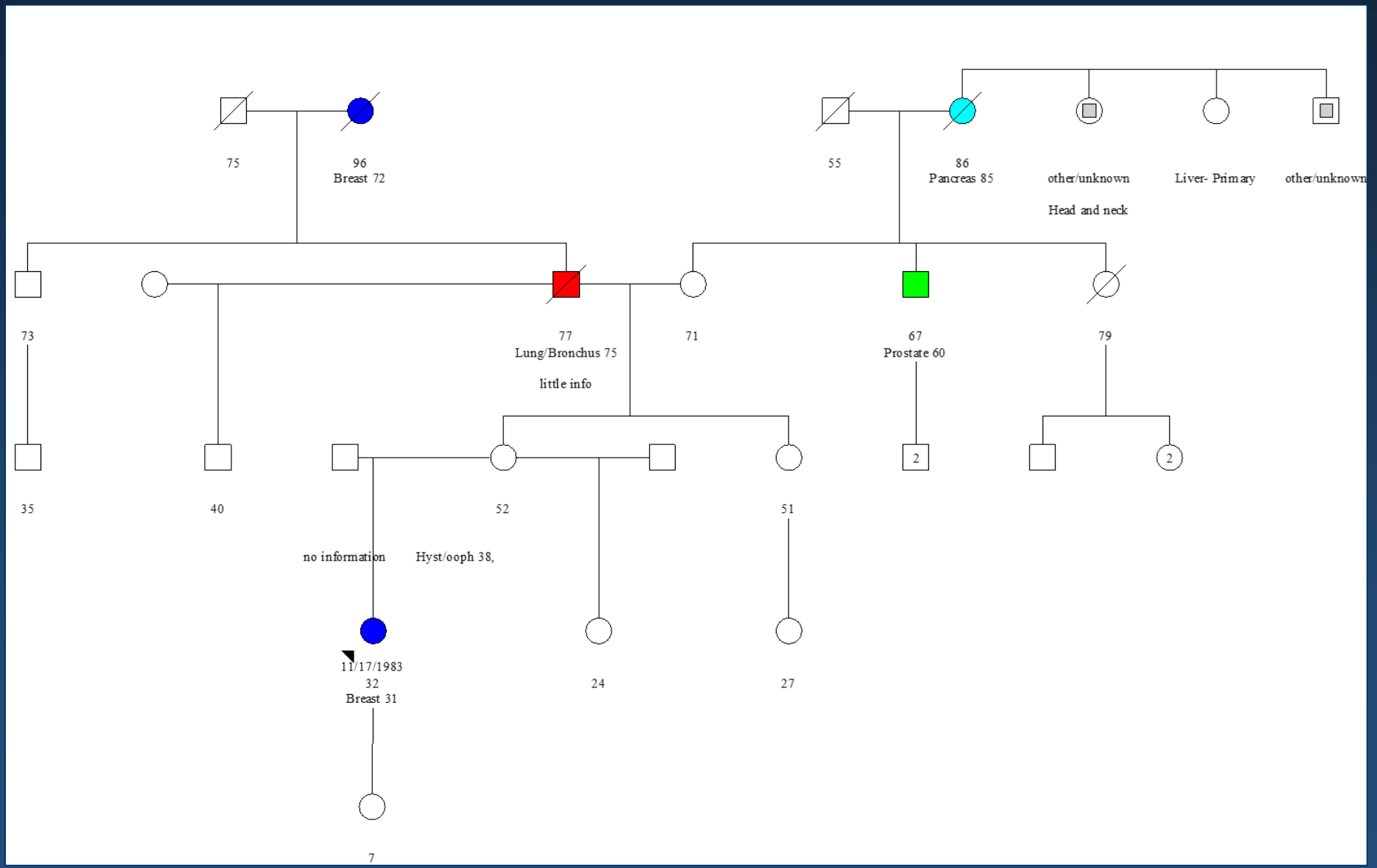
WHY are we changing the way we approach genetic testing?

Syndromes are not matching the genes and vice versa

Overlap of Cancers, Genes and Risks



Case Example



Case Follow-up

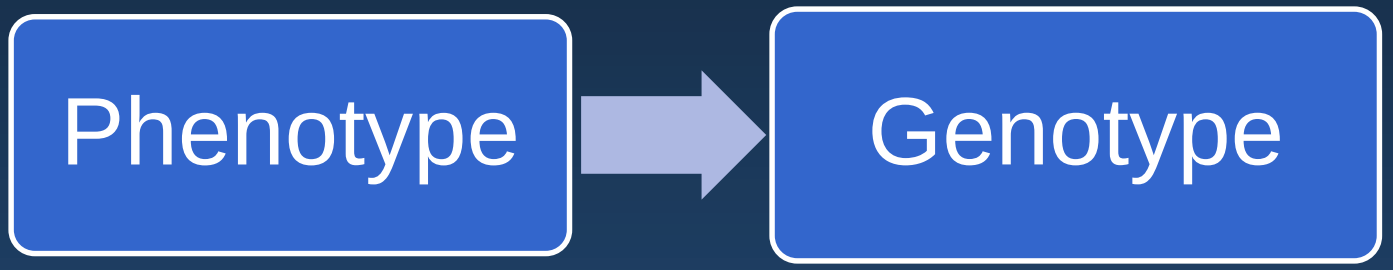
- Young age of onset warrants BRCA1/2, TP53
- Paternal family history unknown
- 32 Gene Multiple Cancer Panel ordered

MLH1 mutation = Lynch syndrome.

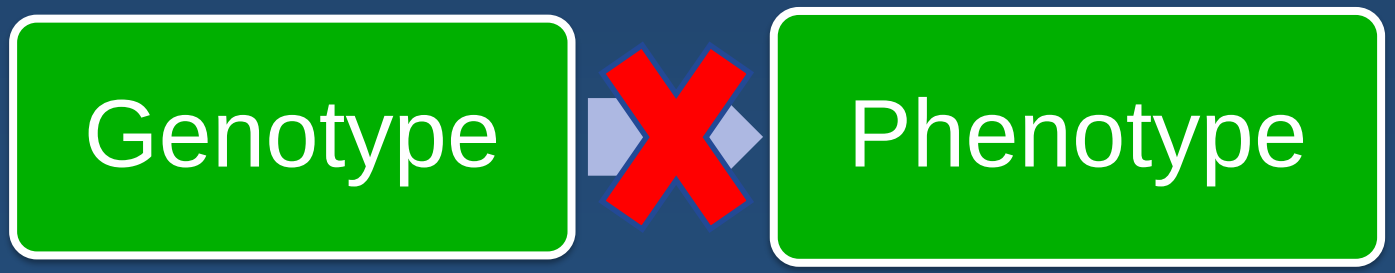
** Lifetime risks are up towards 85% to develop colon cancer and 60% for uterine cancer as well as other cancers.

Shift in Genetic Testing Paradigm

Old way:



NEW way:



Advantages to Panel Testing

- *Increased* detection rate of clinically significant mutation
- Detection of unexpected mutations
- Detection of more than one mutation
- Cost effective
- Saves time

*Dis*advantages to Panel Testing

- Detection of gene mutations with limited data
- Detection of gene mutations with no or unclear screening guidelines
- Variants of uncertain significance
- Insurance (although self-pay options reasonable)
- Unexpected gene mutations

Classification of Test Results

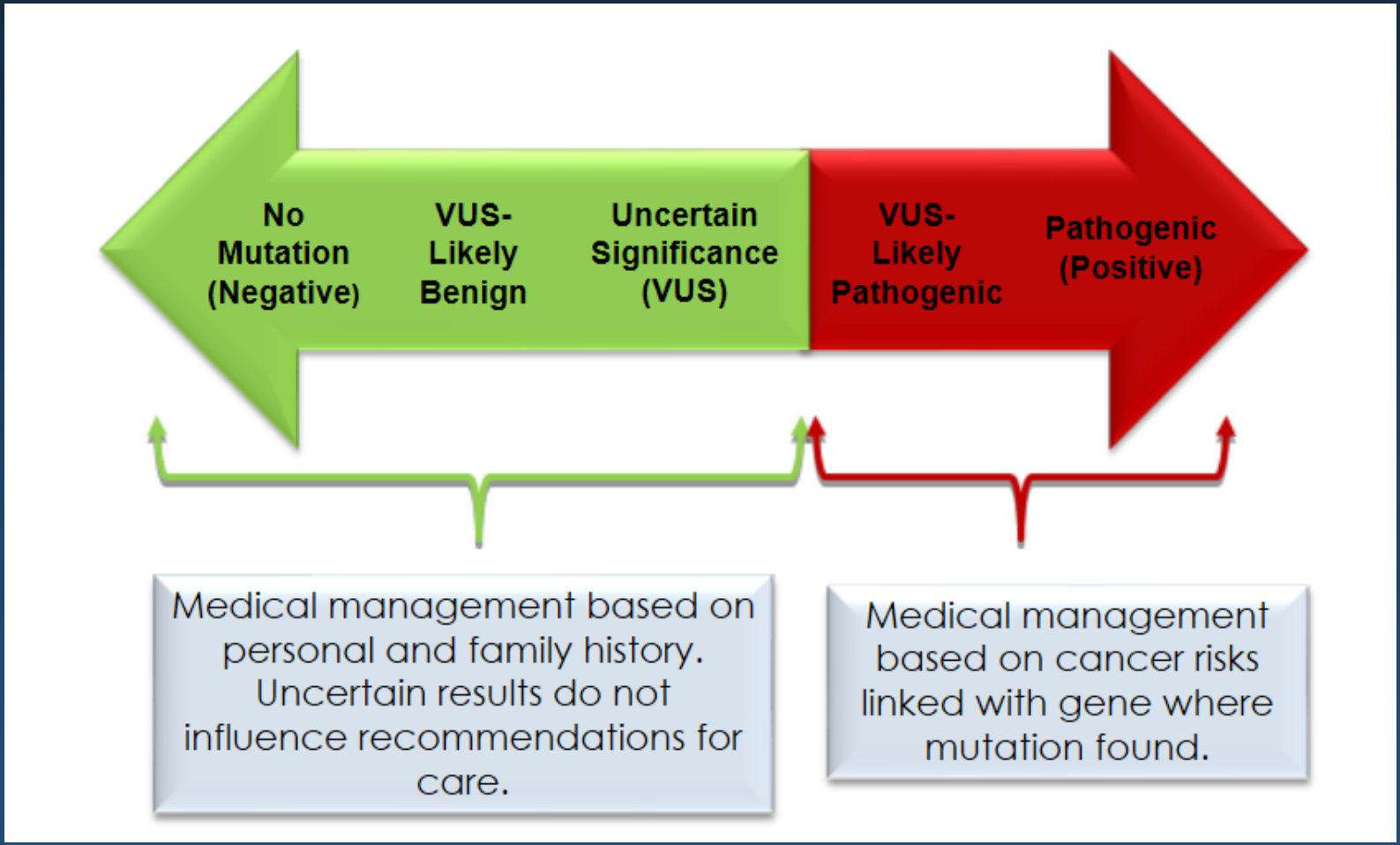


Figure from University of Pennsylvania COGENT study
http://rt5.cceb.med.upenn.edu/public/cogent/APPENDIX_F_Modified_VAP_for_all_scenarios_20141210.pdf

What Have We Learned About Hereditary Breast Cancer?

What percentage of hereditary *breast* cancers are due to mutations in the BRCA genes?

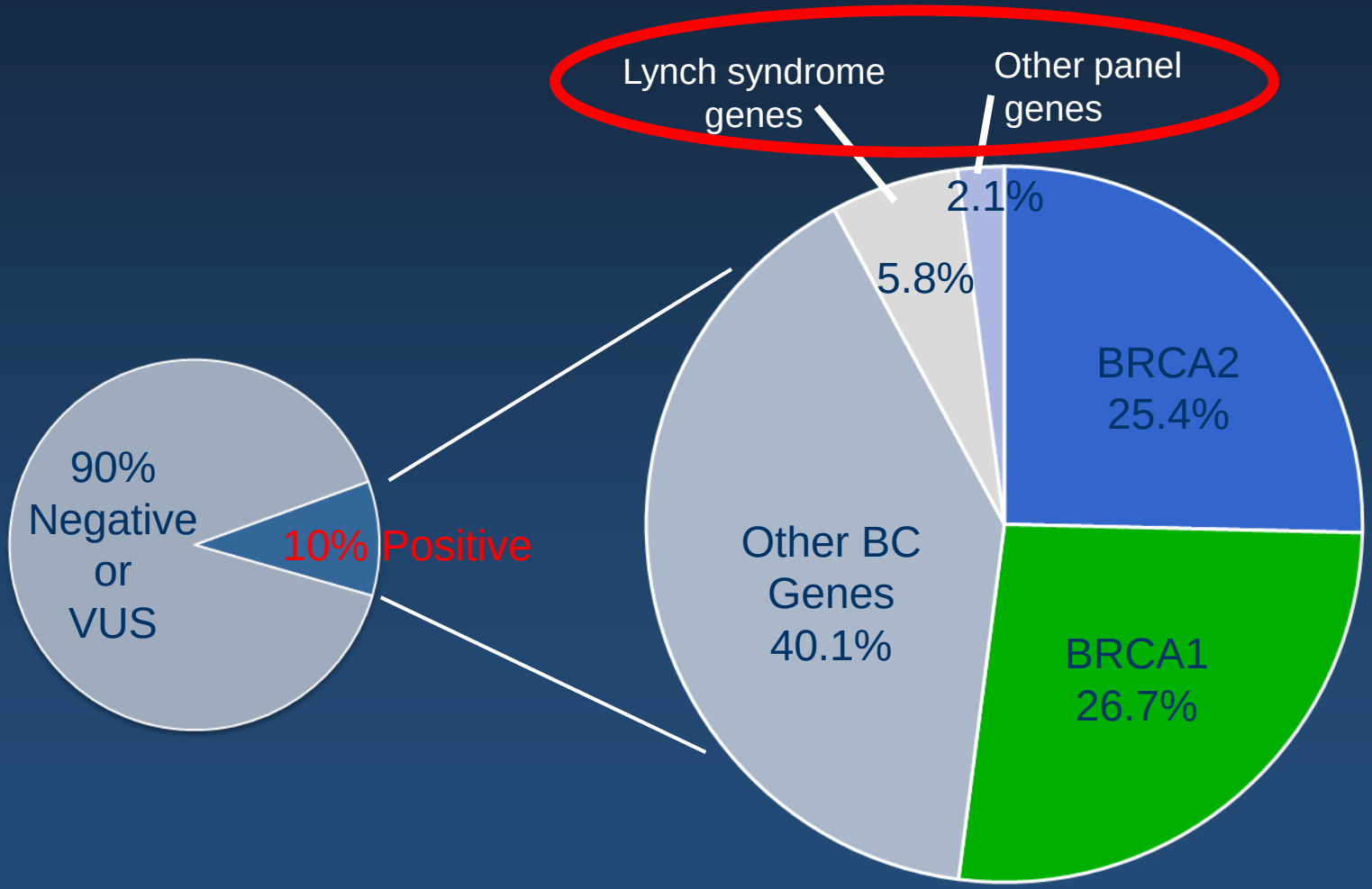
1.90%

2.75%

3.50%

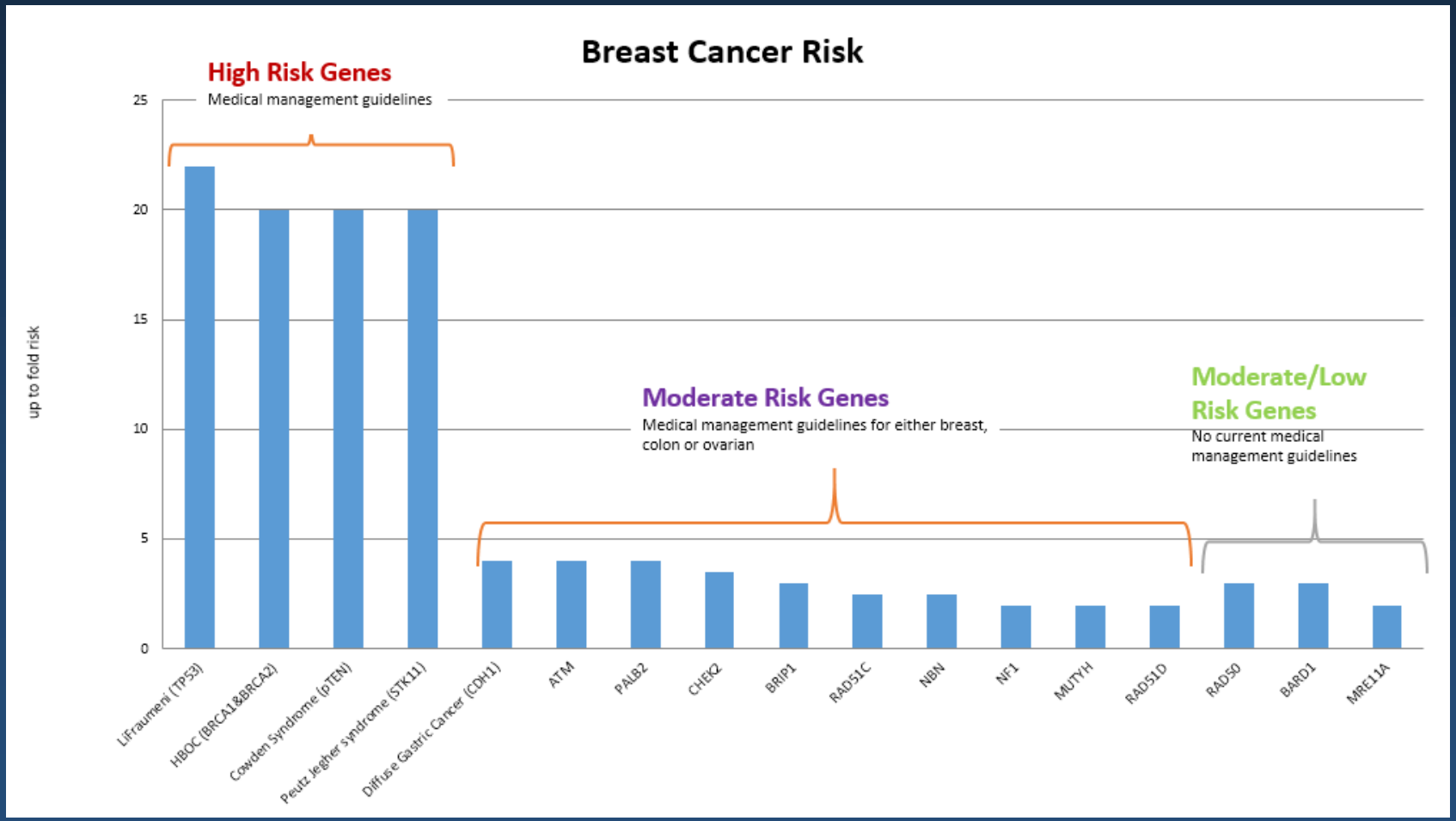
4.What?!?!?! You mean there are genes other than BRCA1 and BRCA2???

Pathogenic Mutations Detected in ~2700 Women with Breast Cancer

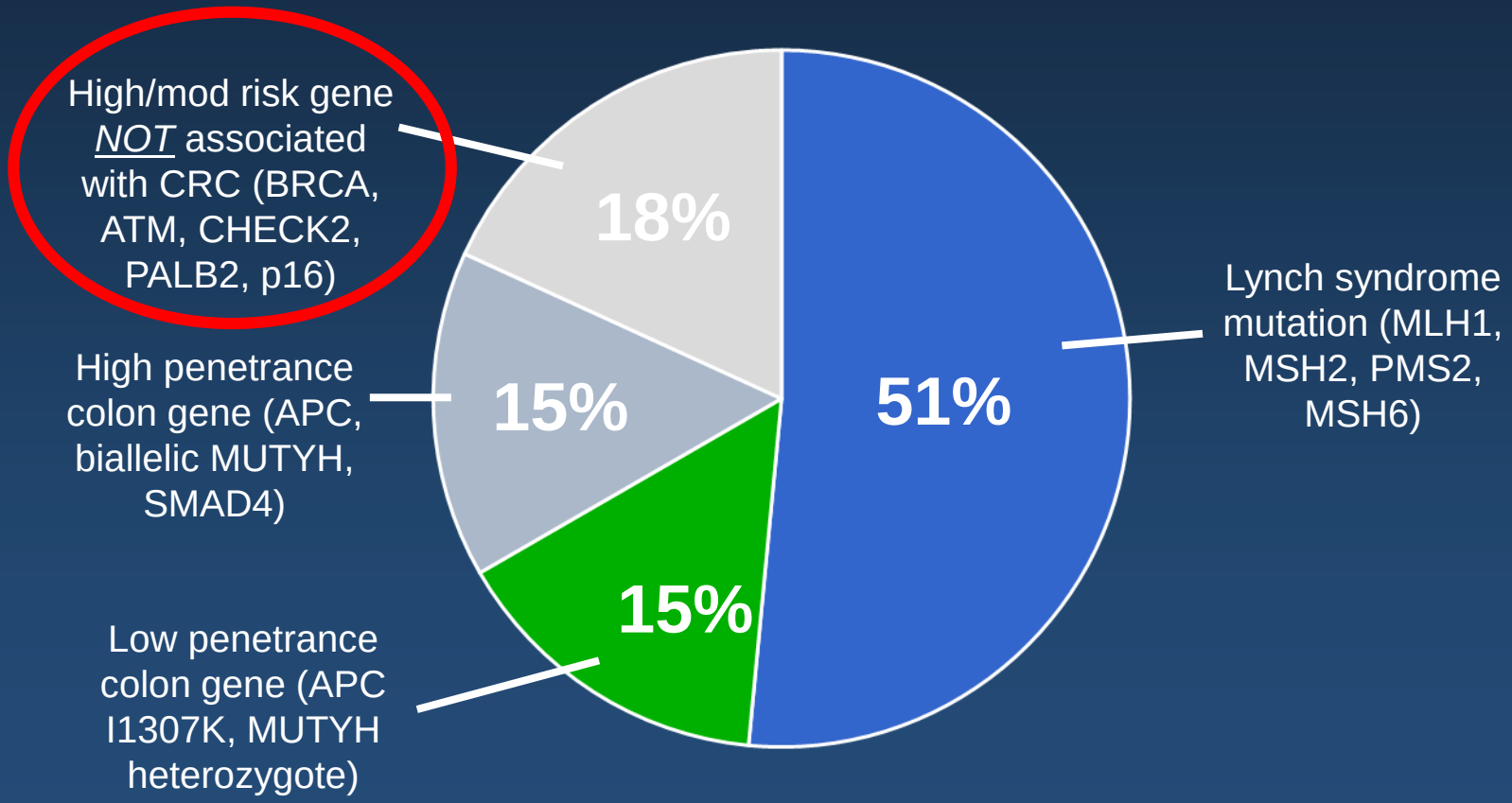


Myriad Data, ASCO 2016

Some Considerations……Not All Genes Have Equal Risks



Spectrum of Mutations in Colon Cancer <50; 16% Positive



JAMA Oncol, 2016

So, What Should Patients Expect…….
And What are the Red Flags for Referrals??

Genetic Counseling is
SOOOOO much more
than just testing!

Which Patients Do We See?

- Individuals *with cancer*
  - Making surgical and/or treatment decisions
  - Concerns for additional cancers
- Individuals *with previous diagnosis of cancer*
- Individuals *with no cancer, but + family hx*
  - Assessing risk for cancer(s)
  - Making screening/surgical decisions
  - Making lifestyle decisions

What do We Discuss with High-Risk Patients?

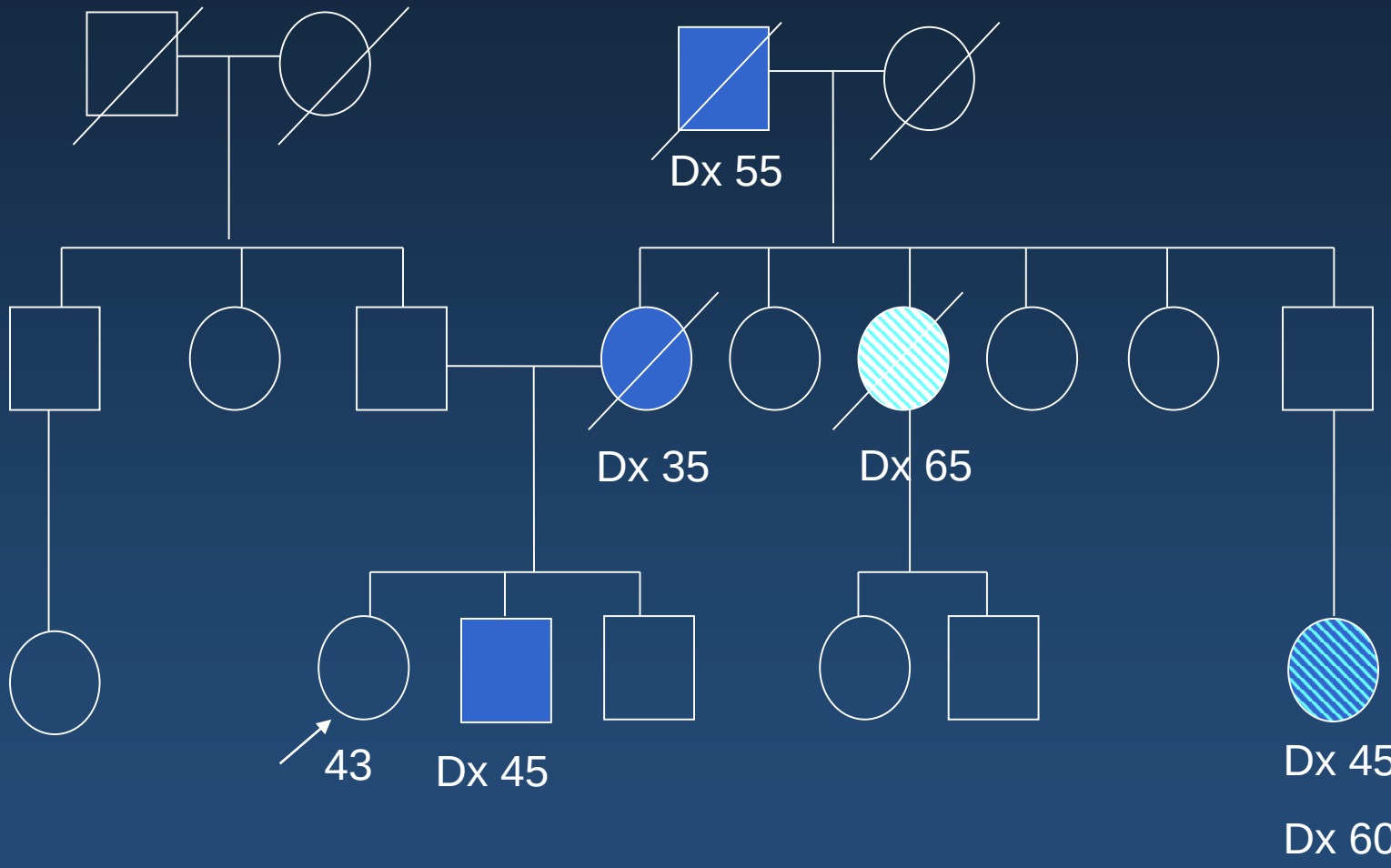
- Likelihood:
  - developing cancer based on family history
  - inherited cancer syndrome
- Medical management recommendations
- Recommendations for at risk family members
- Discussion of genetic testing, options, benefits AND limitations
- Insurance and self-pay options
- GINA

First Step…….Family History

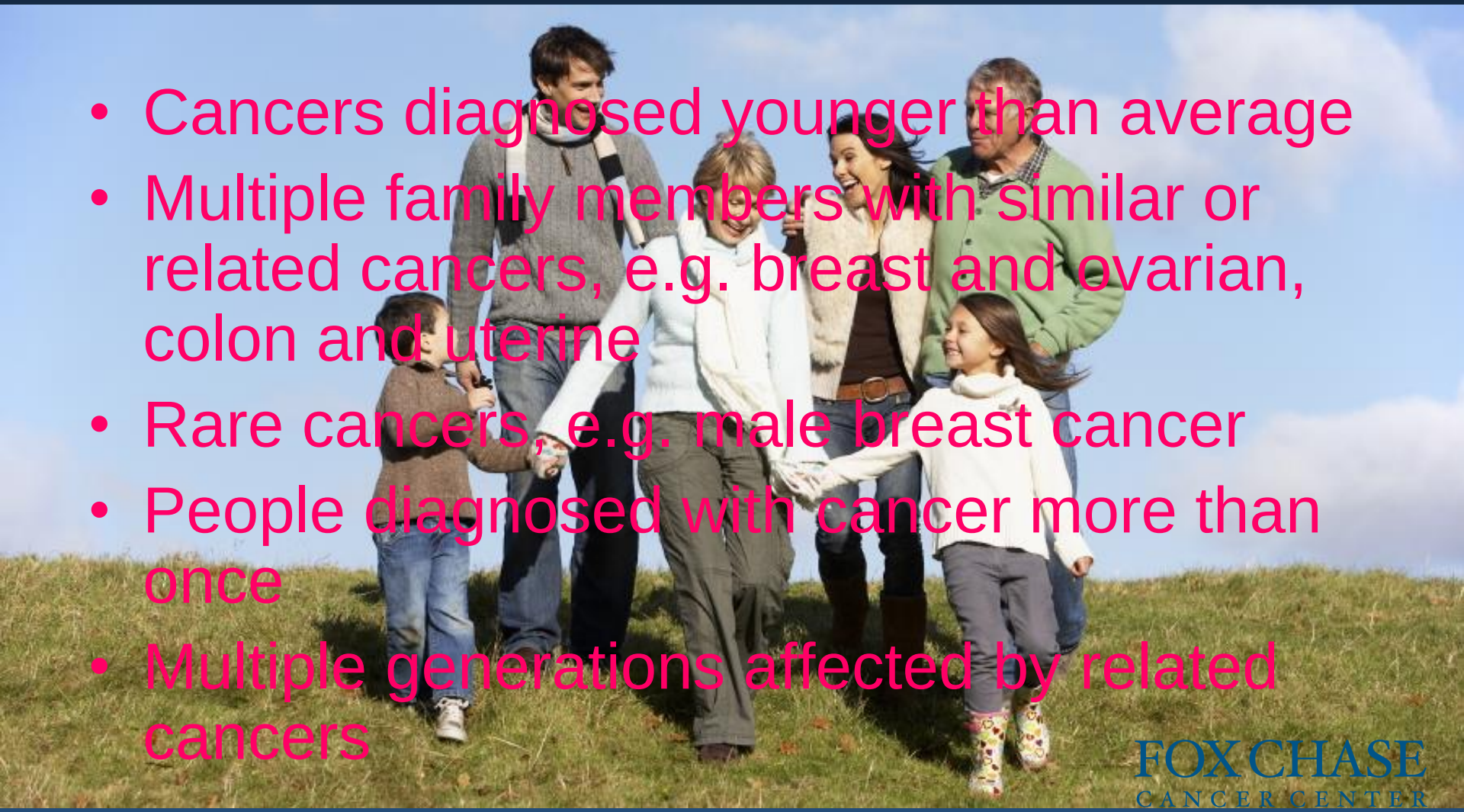
- A thorough family history can be the **key** to diagnosing a hereditary cancer syndrome
- A specific pattern of cancers in a family may indicate there is an inherited syndrome
  - And it may not be what we originally suspect!

****Family history also helps guide screening recommendations when testing is uninformative*

Inherited Cancer



Is the Cancer in My Family Hereditary?



- Cancers diagnosed younger than average
- Multiple family members with similar or related cancers, e.g. breast and ovarian, colon and uterine
- Rare cancers, e.g. male breast cancer
- People diagnosed with cancer more than once
- Multiple generations affected by related cancers

FOX CHASE CANCER CENTER

BRCA1/2 Testing/Referral Guide (simplified)

- Breast Cancer ≤45
- Breast Cancer ≤50 + BrCa or OvCa in relative
- Triple negative breast cancer ≤60
- ALL Ovarian Cancer (except for germ cell and borderline tumors)
- ALL Male Breast Cancer
- ALL Metastatic Prostate Cancer
- ALL Pancreatic Cancer

Modified from NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian v.2.2019

Testing/Referral Guide (con't)

- Breast cancer at any age + Ashkenazi Jewish ancestry
- Two or three Strikes- any breast, ovary, prostate, pancreatic at any age
- ALL colon cancer ≤50
- ALL uterine cancer ≤50
- ≤10 adenomatous colon polyps
- Unaffected, but close family history meeting any of the above

Modified from NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian v.2.2019
and NCCN Genetic/Familial High-Risk Assessment: Colorectal v.1.2018

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
BRCA-Related Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
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Discussion

BRCA1/2 TESTING CRITERIA[a,b]

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known *BRCA1/2* pathogenic/likely pathogenic variant, including such variants found on research testing[b]
- Personal history of breast cancer[c] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed 46-50 y with:
    - An additional breast cancer primary at any age[d]
    - ≥1 close blood relative[e] with breast cancer at any age
    - ≥1 close blood relative[e] with high-grade (Gleason score ≥7) prostate cancer
    - An unknown or limited family history[a]
  - Diagnosed ≤60 y with:
    - Triple-negative breast cancer
  - Diagnosed at any age with:
    - ≥1 close blood relative[e] with:
      - breast cancer diagnosed ≤50 y; or
      - ovarian carcinoma;[f] or
      - male breast cancer; or
      - metastatic prostate cancer;[g] or
      - pancreatic cancer
    - ≥2 additional diagnoses[d] of breast cancer at any age in patient and/or in close blood relatives
  - Ashkenazi Jewish ancestry[h]
- Personal history of ovarian carcinoma[f]
- Personal history of male breast cancer
- Personal history of pancreatic cancer[i]
- Personal history of metastatic prostate cancer[g]
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with
  - ≥1 close blood relatives[e] with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer[g] at any age or breast cancer <50 y; or
  - ≥2 close blood relatives[e] with breast, or prostate cancer (any grade) at any age; or
  - Ashkenazi Jewish ancestry[h]
- *BRCA1/2* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis
- Regardless of family history, some individuals with an *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted treatment[j]
- An individual who does not meet the other criteria but with ≥1 first- or second-degree blood[e] relative[k] meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.

BRCA testing criteria met → See Follow-up (BRCA-2)

If *BRCA* testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

[a] For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

[b] Irrespective of degree of relatedness.

[c] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

[d] Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously.

[e] Close blood relatives include first-, second-, and third-degree relatives on same side of family. (See BR/OV-B)

[f] Includes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

[g] Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence.

[h] Testing for Ashkenazi Jewish founder-specific pathogenic/likely pathogenic variant(s), should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other *BRCA*-related criteria are met. Founder pathogenic/likely pathogenic variants exist in other populations.

[i] Approximately 2%–5% of unselected cases of pancreatic adenocarcinoma will have a *BRCA1/2* pathogenic/likely pathogenic variant. However, the disease is highly lethal and the option to test the affected relative may not be available in the future. Thus, there may be significant benefit to family members in testing these patients near the time of diagnosis. In addition, increasing evidence suggests that identification of a *BRCA1/2* pathogenic/likely pathogenic variant may direct use of targeted therapies for patients with pancreatic cancer (See NCCN Guidelines for Pancreatic Adenocarcinoma). (Holter S, Borgida A, Dodd A, et al. J Clin Oncol 2015;33:3124-3129. Shindo K, Yu J, Suenaga M, et al. J Clin Oncol 2017;35:3382-3390.)

[j] Eg, PARP inhibitors for ovarian cancer and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer. See the relevant NCCN treatment guidelines (eg, NCCN Guidelines for Breast Cancer; NCCN Guidelines for Prostate Cancer) for further details.

[k] This may be extended to an affected third-degree relative if related through two male relatives (eg, paternal grandfather's mother or sister).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

What About Testing Children and Hereditary Cancers in the Pediatric Setting?

- For most ***adult*** hereditary cancer conditions (HBOC, Lynch), testing is generally not recommended until adulthood
  - Considered when patient's screening would change ***if*** they tested positive
  - Exceptions: if early-onset cancer (<25) in family OR if syndrome has implications during childhood (Li-Fraumeni, FAP, etc.)

Pediatric Hereditary Cancer Syndromes

Test automatically if:

- Adrenocortical carcinoma
- Optic pathway tumor
- Retinoblastoma
- Pheochromocytoma
- Paraganglioma
- Carcinoid tumors
- Medullary thyroid carcinoma
- Diffuse gastric cancer
- Retinal or cerebellar hemangioblastoma
- Endolymphatic sac tumors
- Atypical teratoid and malignant rhabdoid tumors (ATRT)
- Acoustic or vestibular schwannomas

Pediatric Hereditary Cancer Syndromes

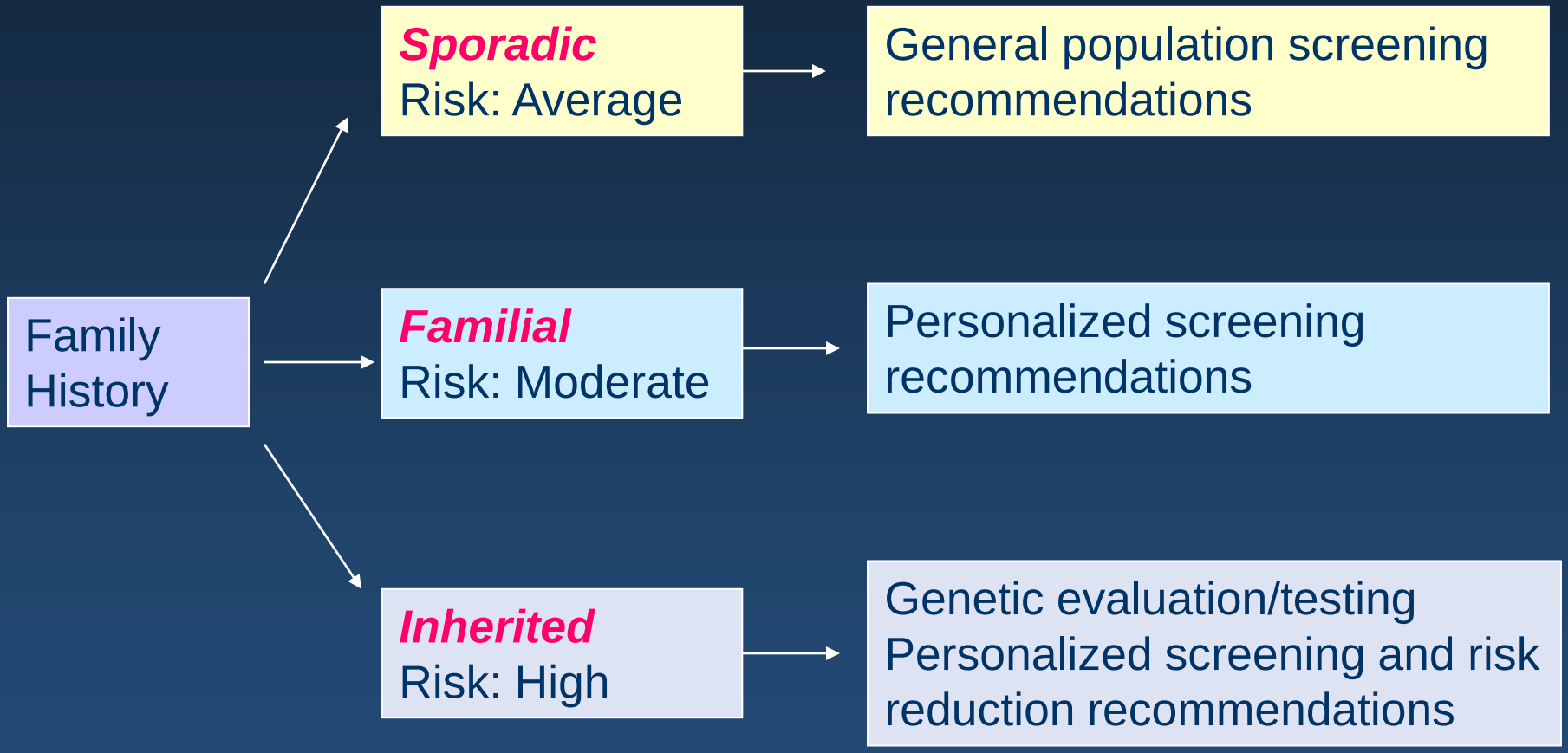
Referral for further evaluation if:

- Wilm's tumor
- Sarcoma
- Family history of certain hereditary cancer syndromes
  - FAP, Li-Fraumeni, MEN, NF, VHL, Cowden syndrome (PTEN)
- Blood diseases associated with specific syndromes
  - e.g. bone marrow failure syndromes
- Rare tumors
  - e.g. infantile myofibroma

The Ultimate Question……

If I Have a Family History of Cancer, What Are My Future Risks?

Classification: Who Needs What?




#breastcancerawareness
Knowledge
is power.

We can't change our genes….

But ..... we can potentially change the outcome!!!

Questions?

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