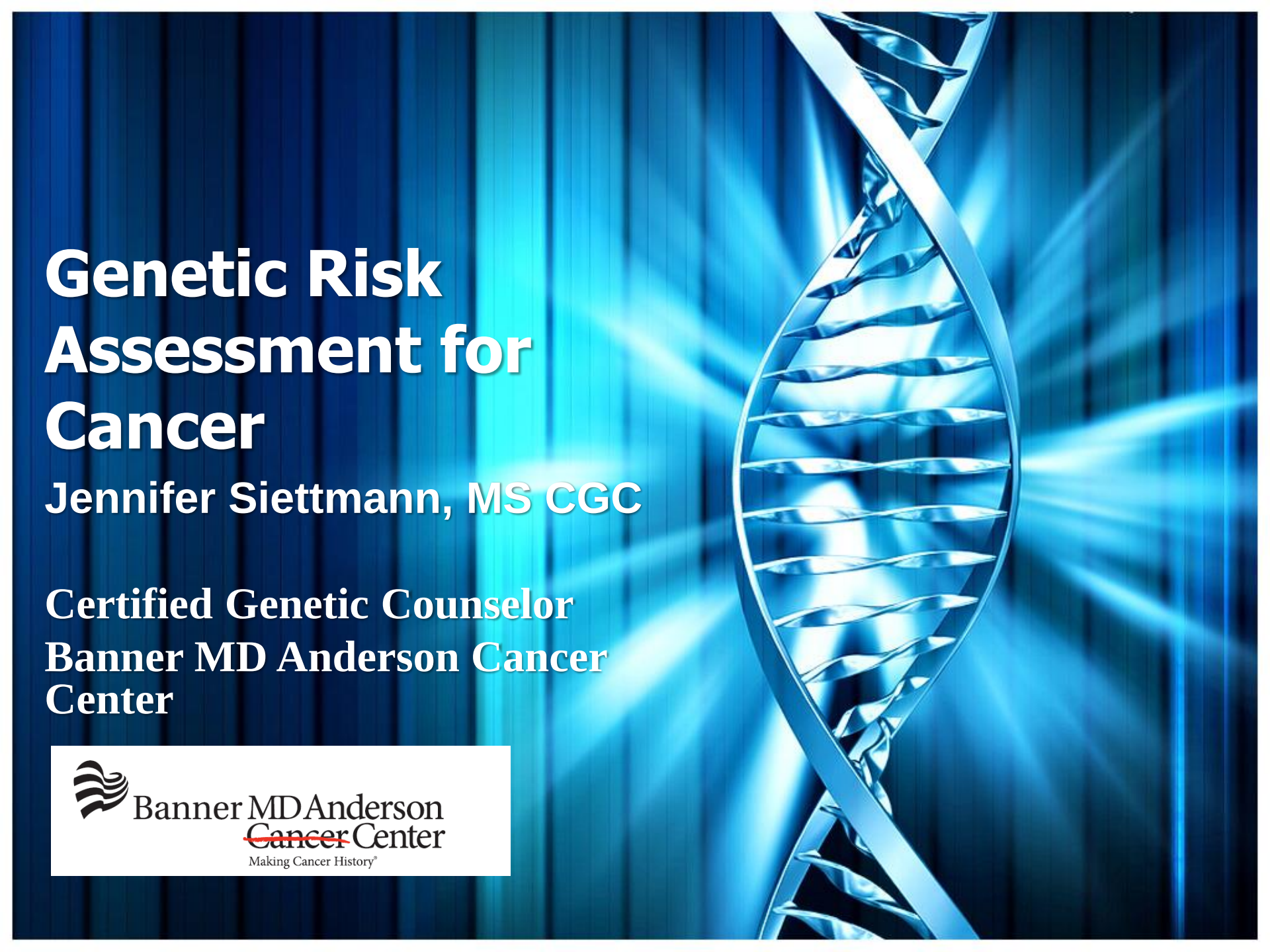

Genetic Risk Assessment for Cancer

Jennifer Siettmann, MS CGC

Certified Genetic Counselor
Banner MD Anderson Cancer Center

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Objectives

- Describe the role of genetic counseling and genetic testing in patient care
- List indications for referral for hereditary cancer genetic testing
- Describe features of common hereditary cancer syndromes
- Describe the genetic testing process and new testing advancements

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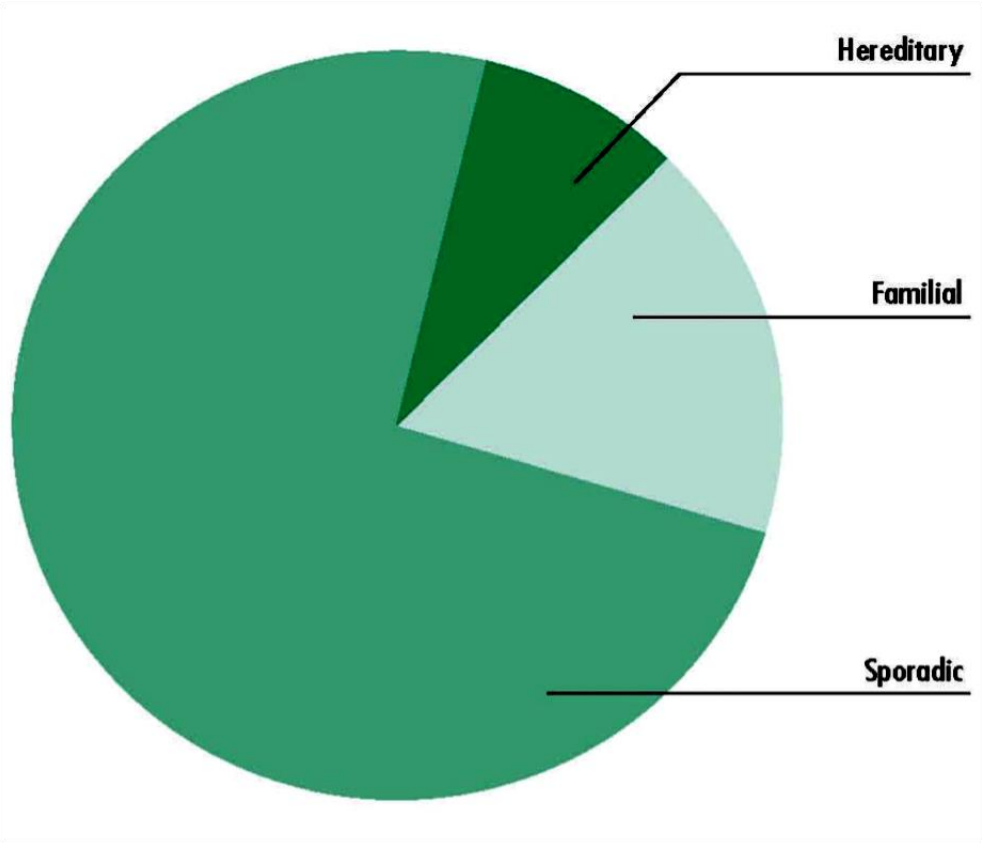
How Much Cancer is Hereditary?



Hereditary

- Gene mutation is inherited in family
- Significantly increased cancer risk

Familial

- Multiple genes & environmental factors may be involved
- Some increase in cancer risk

Sporadic

- Cancer occurs by chance or related to environmental factors
- General population cancer risk

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When to Expect a Hereditary Cancer Syndrome

- Same cancer in two or more close relatives (on same side of family)
- Early age at diagnosis (<50)
- Multiple primary tumors in the same individual
- Bilaterality or multiple rare cancers
- Pattern of tumors consistent with specific cancer syndrome (e.g. breast *and* ovary or colon *and* uterine)
- Evidence of autosomal dominant transmission
  - Multiple affected generations

Lindor NM et al. *J Natl Cancer Inst*. 1998;90:1039-1071.
Schneider K. *Counseling About Cancer: Strategies for Genetic Counseling*. 2nd ed. New York: John Wiley & Sons; 2001.

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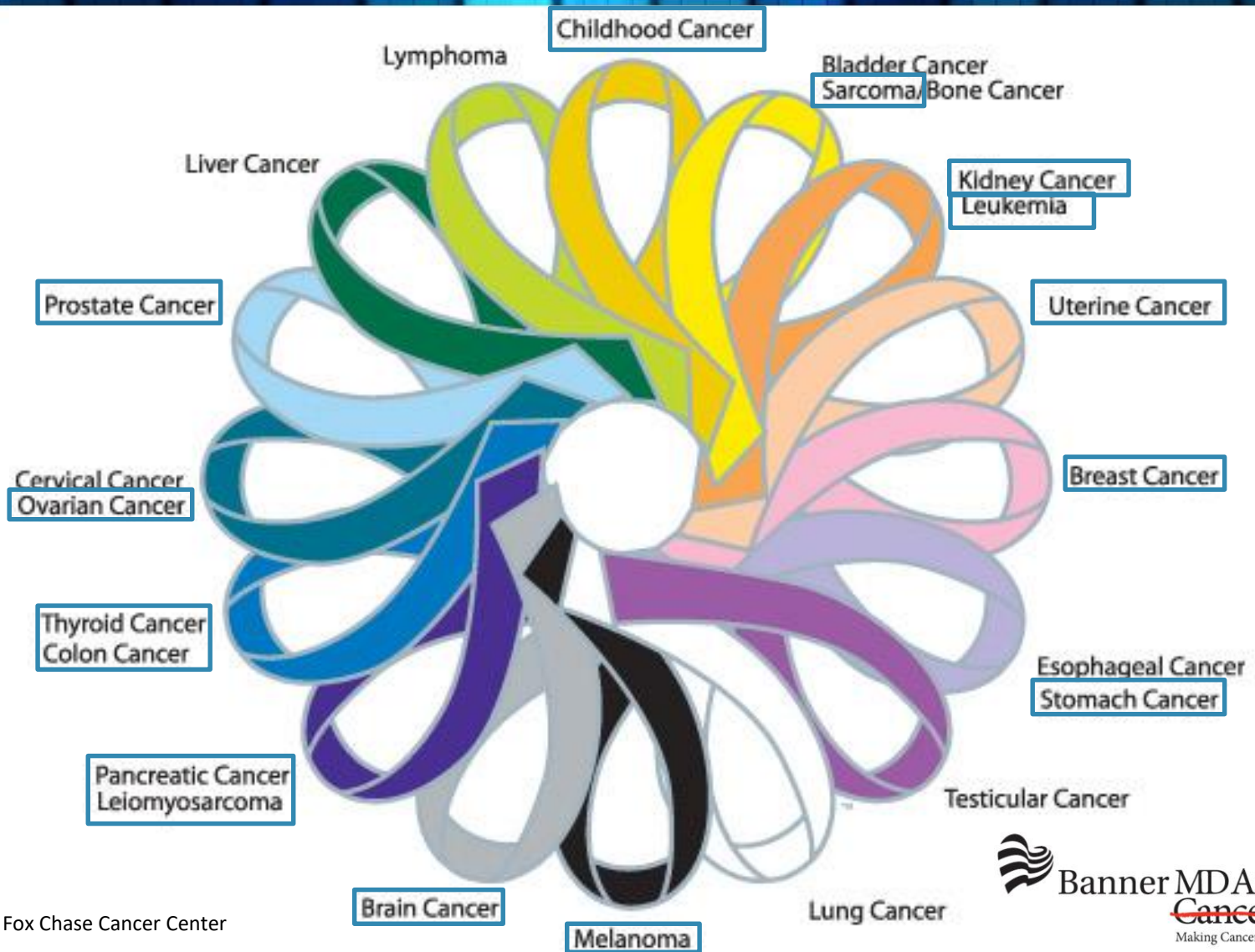
Question 1

- You see a patient who was diagnosed with breast cancer at age 55. She has a sister who had breast cancer at age 45 and a father with prostate cancer at age 70.
- Would you recommend genetic testing? Why or why not?

Suspicious Genetic Cancers



Andrea Forman, Fox Chase Cancer Center

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Question 2

- You see a patient with colon cancer at age 75. His brother had esophageal cancer at age 60 and a father had bladder cancer at age 65. His paternal grandfather had lung cancer at age 70. Two paternal uncles had liver cancer in their 60s.
- Would you recommend genetic testing? Why or why not?

Hereditary Cancer Syndromes

- Breast
  - Hereditary Breast and Ovarian Cancer Syndrome (BRCA1, BRCA2)
  - Cowden (PTEN)
  - Hereditary Diffuse Gastric Cancer (CDH1)
  - Li Fraumeni Syndrome (TP53)
  - PALB2
  - Moderate Risk Syndromes (ATM, CHEK2, NBN, NF1)
- Ovarian
  - Moderate Risk Syndromes (RAD51C, RAD51D, BRIP1)
- Colon
  - Lynch Syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM)
  - Familial Adenomatous Polyposis (FAP)
  - MUTYH Associated Polyposis (MAP)
  - Peutz-Jeghers Syndrome (STK11)
  - Juvenile Polyposis Syndrome (SMAD4, BMPR1A)
  - Moderate Risk Syndromes (GREM1, POLD1, POLE)

Hereditary Cancer Syndromes

- Endocrine
  - Multiple Endocrine Neoplasia Type I (MEN1)
  - Multiple Endocrine Neoplasia Type II (RET)
  - Hereditary Paraganglioma and Pheochromocytoma (SDH1, SDHAF2, SDHC, SDHD, MAX, TMEM127)
- Melanoma
  - Hereditary Malignant Melanoma (CDK4, CDKN2A)
  - BAP1 Associated Hereditary Melanoma (BAP1)
- Renal
  - Von Hippel Lindau (VHL)
  - Hereditary Leiomyomatosis and Renal Cell Cancer (FH)
  - Birt-Hogg Dube Syndrome (FLCN)
  - Tuberous Sclerosis Compex (TSC1, TSC2)
  - Moderate Risk Syndromes (MET, MITF)

Rare Tumors That Warrant Genetic Evaluation

- Adrenocortical Carcinoma (*Tp53*)
- Carcinoid Tumors (specifically thymic gland) (*MEN1*)
- Diffuse Gastric Cancer (*CDH1*)
- Fallopian Tube/Primary Peritoneal Cancer (*BRCA1/BRCA2*)
- Leiomyosarcoma (*FH*)
- Medullary Thyroid Cancer (*RET*)
- Paraganglioma (*SDHA, SDHB, SDHC, SDHD, SDHAF2*)
- Pheochromocytoma (*SDHA, SDHB, SDHC, SDHD, SDHAF2, VHL, RET, NF1*)
- Chromophobe or Oncocytoic Renal Cell Cancer (*FLCN*)
- Sebaceous Neoplasms/Carcinomas (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
- Sex Cord Tumors with Annular Tubules (*STK11*)

*Banks, et al. *10 Rare Tumors that Warrant a Genetics Referral*. Fam Cancer. Epub 2012, Nov 28.

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Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

- Caused by mutations in the *BRCA1* and *BRCA2* tumor suppressor genes
- Incidence: 1 in 4,000
  - 1 in 40 in Ashkenazi Jewish families
- Features:
  - Early onset breast cancer (under age 50)
  - Ovarian cancer
  - Bilateral breast cancer
  - Male breast cancer
  - Metastatic prostate cancer

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HBOC Lifetime Cancer Risks

	General Population	*BRCA1* Mutation	*BRCA2* Mutation
Female Breast Cancer Risks	13%	50-85%	50-85%
2nd Primary Breast Cancer Risk	0.5% per year	40-60% (3-5% per year)	40-60% (3-5% per year)
Ovarian Cancer Risks	<2%	20-50%	10-20%
Male Breast Cancer Risks	<1%	Few reported cases	6%
Prostate Cancer	17%	20%	20%
Other Cancers		~6% for melanoma and pancreatic cancer	

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Lynch Syndrome

- Caused by mutations in mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*
- Features:
  - Early age of colon cancer diagnosis (~45 years)
  - Right-sided cancers
  - Cancers outside the colon:
    - Uterine/Endometrial
    - Ovarian
    - Stomach, small bowel, urinary tract, bile ducts, brain, pancreas

Lynch Syndrome Lifetime Cancer Risks

	General Population	MLH1 and MSH2 Mutation	MSH6 Mutation	PMS2 Mutation
Colon	5.5%	40-80%	10-22%	15-20%
Endometrial	2.7%	25-60%	16-26%	15%
Stomach	<1%	1-13%	≤3%	Combined Risk of 6%
Ovarian	1.6%	4-24%	1-11%	
Bile Duct	<1%	1.4-4%	Not reported	
Urinary Tract	<1%	1-4%	<1%	
Small Bowel	<1%	3-6%	Not reported	
Brain/CNS	<1%	1-3%	Not reported	
Sebaceous neoplasms	<1%	1-9%	Not reported	Not reported
Pancreas	<1%	1-6%	Not reported	Not reported

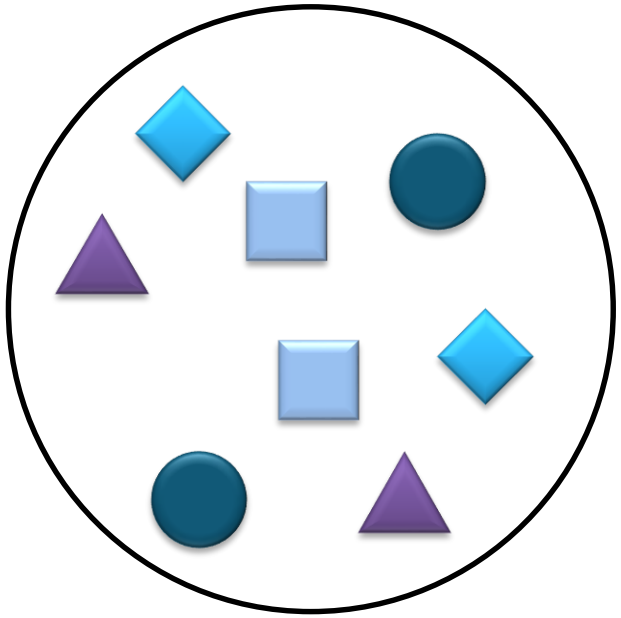
IHC Testing for Lynch Syndrome

MLHI

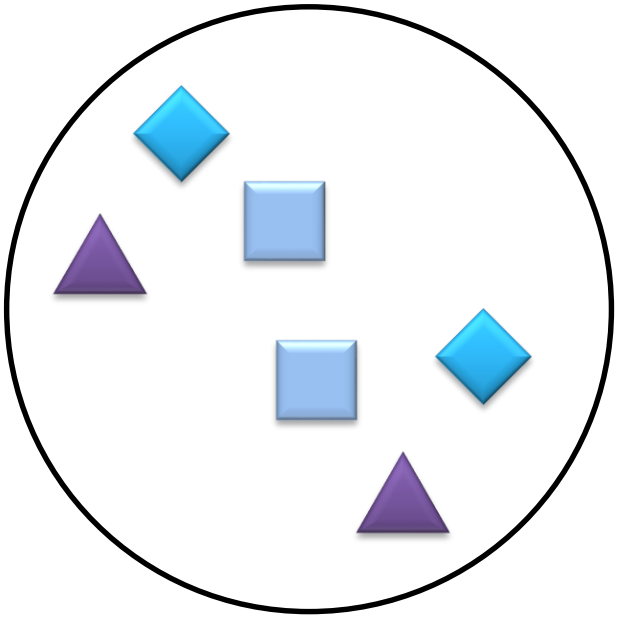
MSH2

MSH6

PMS2



Normal



Suspicious of Lynch

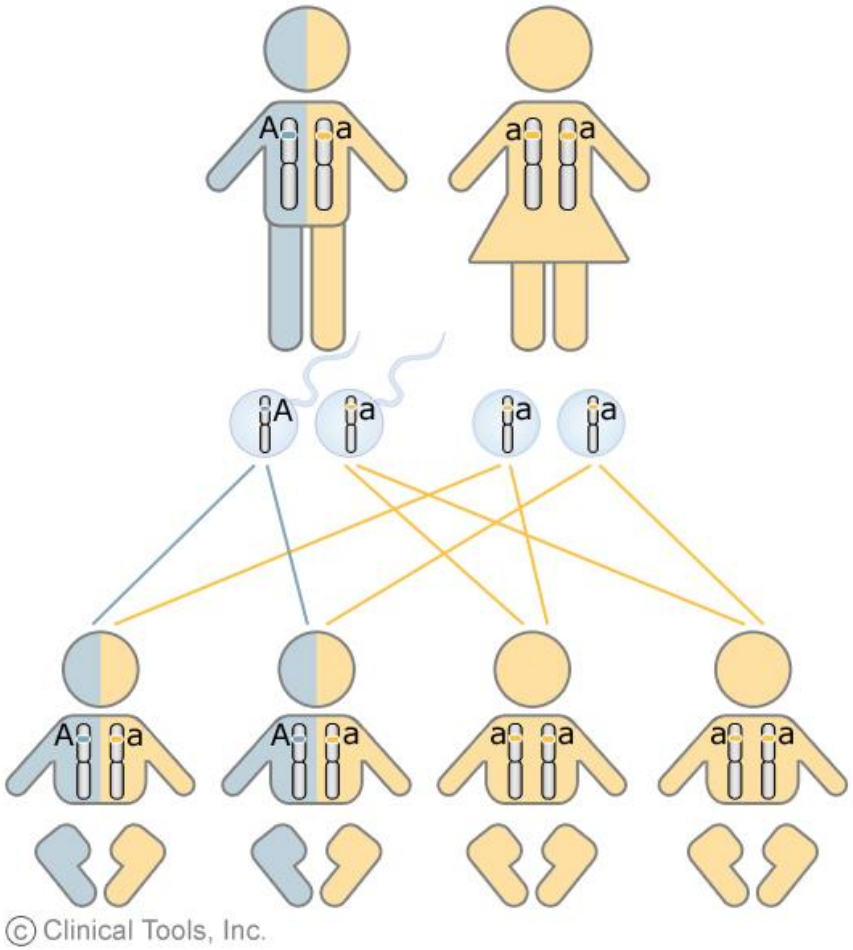
Question 3

- You see a patient with colon cancer at age 45. Family history of colon and uterine cancer at young ages. He had loss of MSH2 and MSH6 on his IHC testing performed on his colon tumor.
- Does he have Lynch syndrome?

Question 4

- You see a male patient whose mother has tested positive for an ATM mutation, which you remember increases the risk for breast, pancreatic, and prostate cancer.
- Do you need to test your patient for this mutation? Why or why not?

Inheritance: Typically Autosomal Dominant



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Genetic Testing Options

- Single-Site Testing
  - known BRCA mutation in family
- Single Gene Testing
  - (TP53)
- Single Syndrome Testing
  - (BRCA1, BRCA2)
- High Risk Breast Panel
  - (BRCA1, BRCA2, CDH1, PALB2, PTEN, TP53)
- Guidelines-Based Breast Panel
  - (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, TP53)
- Expanded Breast Panel
  - (17+ genes)
- Pan-Cancer Panel
  - ex. CancerNext (32+ genes)
- Pan-Cancer Expanded Panels
  - (40+ genes)

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Genetic Testing Labs

progenity®

Quest Diagnostics™

ARUP® LABORATORIES

LabCorp

Ambry Genetics®

Counsyl

GeneDx DNA DIAGNOSTIC EXPERTS

INVITAE

BAYLOR GENETICS

myriad® WHEN DECISIONS MATTER

color

PREVENTION GENETICS

DISEASE PREVENTION THROUGH GENETIC TESTING

Important Considerations

- Insurance Coverage/Price
  - Insurances requiring to meet with 'genetic expert'
  - Cost ranges from ~$250-$4,000 OOP
  - Insurance has a "one time only" policy on testing
- Turnaround Time
  - 1 – 3 weeks
- Correct Test for Indication
  - Pan Cancer Panels vs. Single Cancer Panel
- Possible Results
  - Positive vs. Negative vs. Variants
- High vs. Low Risk Genes
  - Future management?

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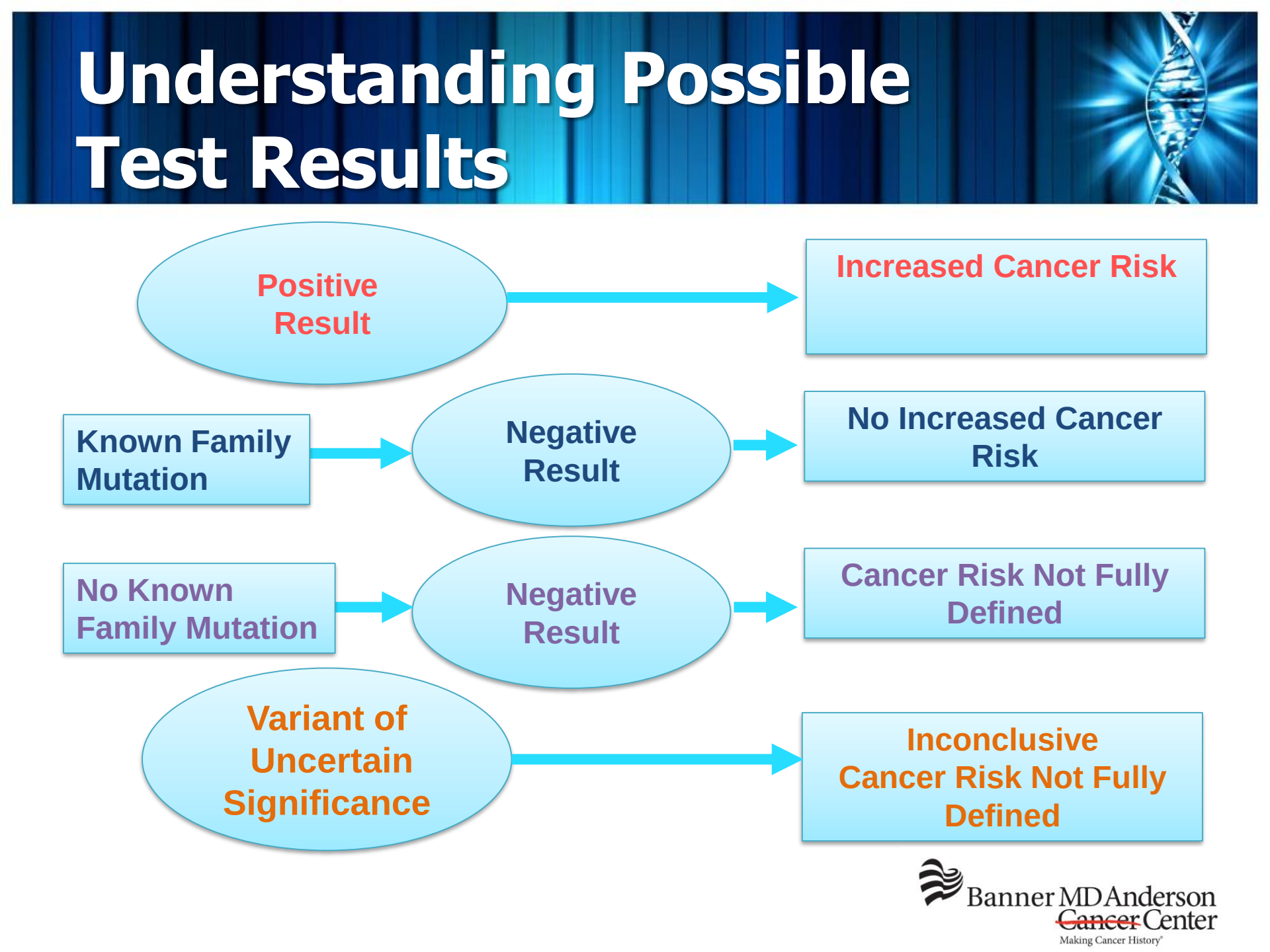
Question 5

- You see a patient who has a strong family history of breast cancer. She tells you she already had negative genetic testing for the BRCA1 and BRCA2 genes.
- Do you recommend additional genetic testing? Why or why not?
- If yes, what test would you order?

Understanding Possible Test Results



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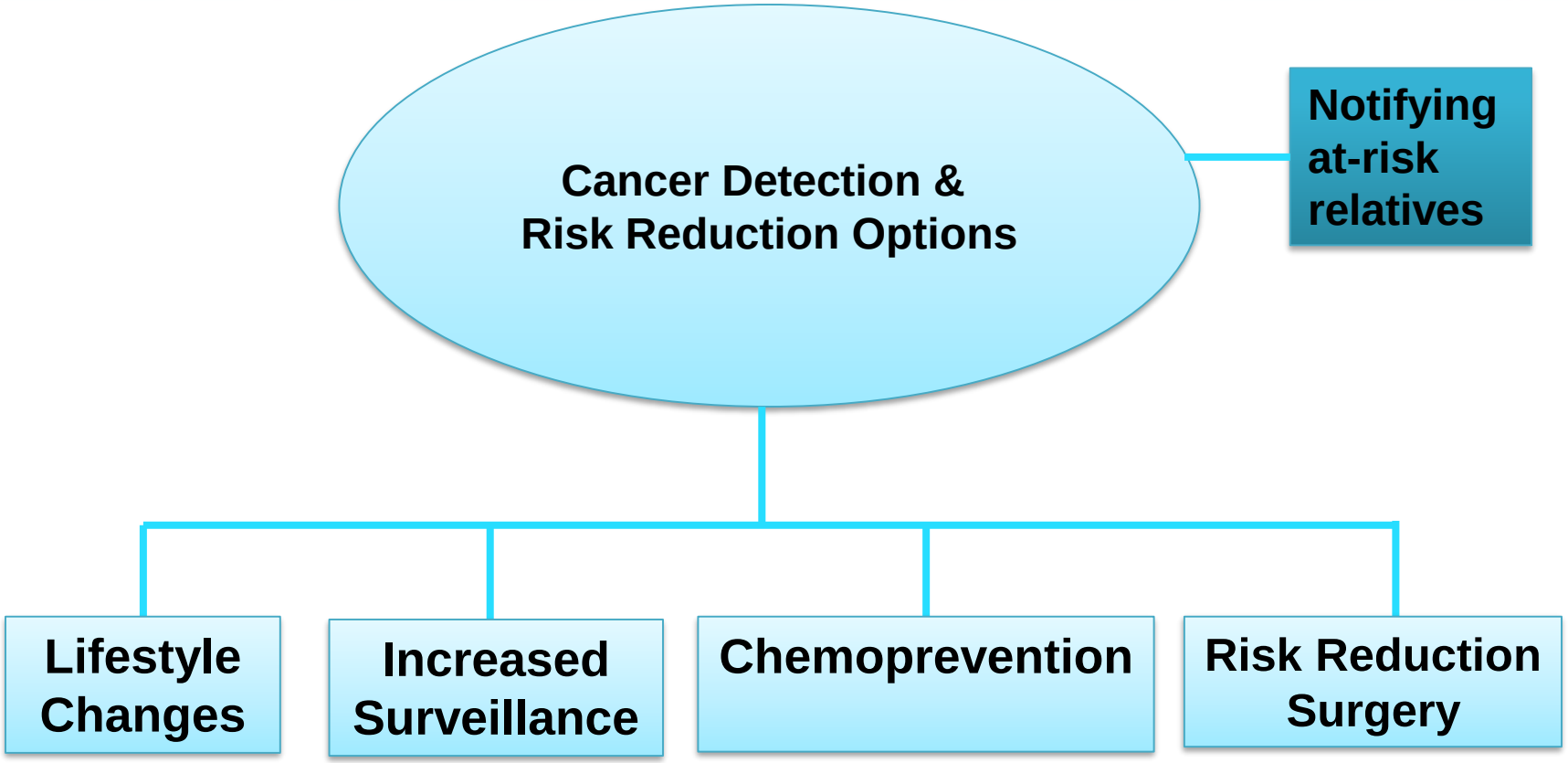
High-Risk Clinical Management



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Question 6

- You see a patient with breast cancer at age 35. You order genetic testing and she has a variant of uncertain significance (VUS) in the BRCA1 gene.
- What recommendations do you make for her based on this result?

Question 7

- You see a 45 y.o. patient who is unaffected. Her sister had breast cancer at age 36. Her mother had breast cancer at age 49. You order genetic testing for your patient and she comes back negative for a panel of 47 genes.
- Does she have any remaining risk for breast cancer?
- What would be your next step to manage the family?

Benefits of Genetic Counseling

- Assess
  - Personal and family medical history
  - Risk perception and motivation for testing
- Educate
  - Basic genetics and inheritance
  - Cancer genetics and risk
- Discuss
  - Risks, benefits, and limitations of testing
  - Test procedure
  - Alternatives to testing
  - Management options
- Counsel
  - Provide anticipatory guidance
  - Walk them through “what if” scenarios
  - Support them

Lerman C et al. *J Natl Cancer Inst*. 1997;89:148-175.

Masood E. *Nature*. 1996;379:389-392.

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Referral to a Genetic Counselor

- Before Testing
  - Patient meeting these criteria:
    - Breast cancer <50
    - Any triple negative breast cancer
    - 2+ breast cancer in the family
    - Ovarian cancer in patient or family
    - Breast and pancreatic cancer
    - Uterine or colon cancer under age 50
    - Patients with multiple types of cancer
    - Patients with significant family history of cancer not fitting typical pattern
  - Questions about which panel to order
  - Patients with insurances requesting genetic counseling
  - Patients with large out-of-pocket cost for testing

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Referral to a Genetic Counselor

- After Testing
  - Any patient with:
    - Positive test result
    - Variant of uncertain significance
    - Negative test report but significant family history
    - Additional questions

You are always welcome to contact any of us with any questions or concerns!

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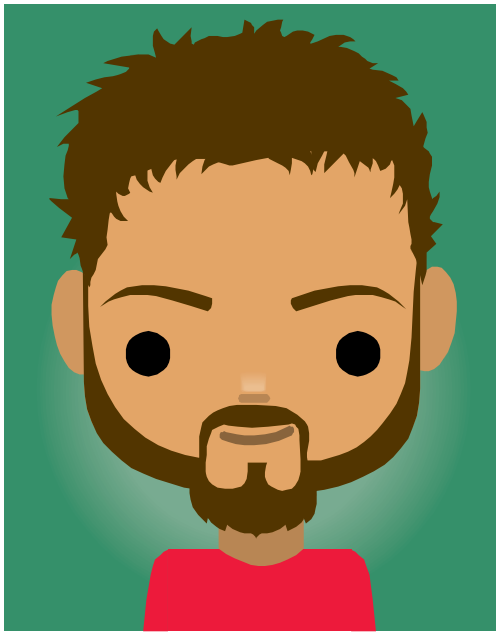
Case Example 1: TF

- TF is a 58 y.o. man diagnosed with colon caner @56. His colon cancer had loss of MSH6 on IHC
  - Maternal cousin breast cancer @25
  - Paternal cousin breast cancer @34

- European descent on both sides



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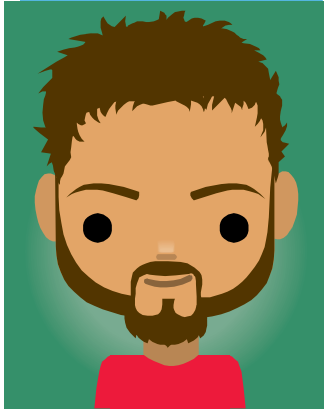

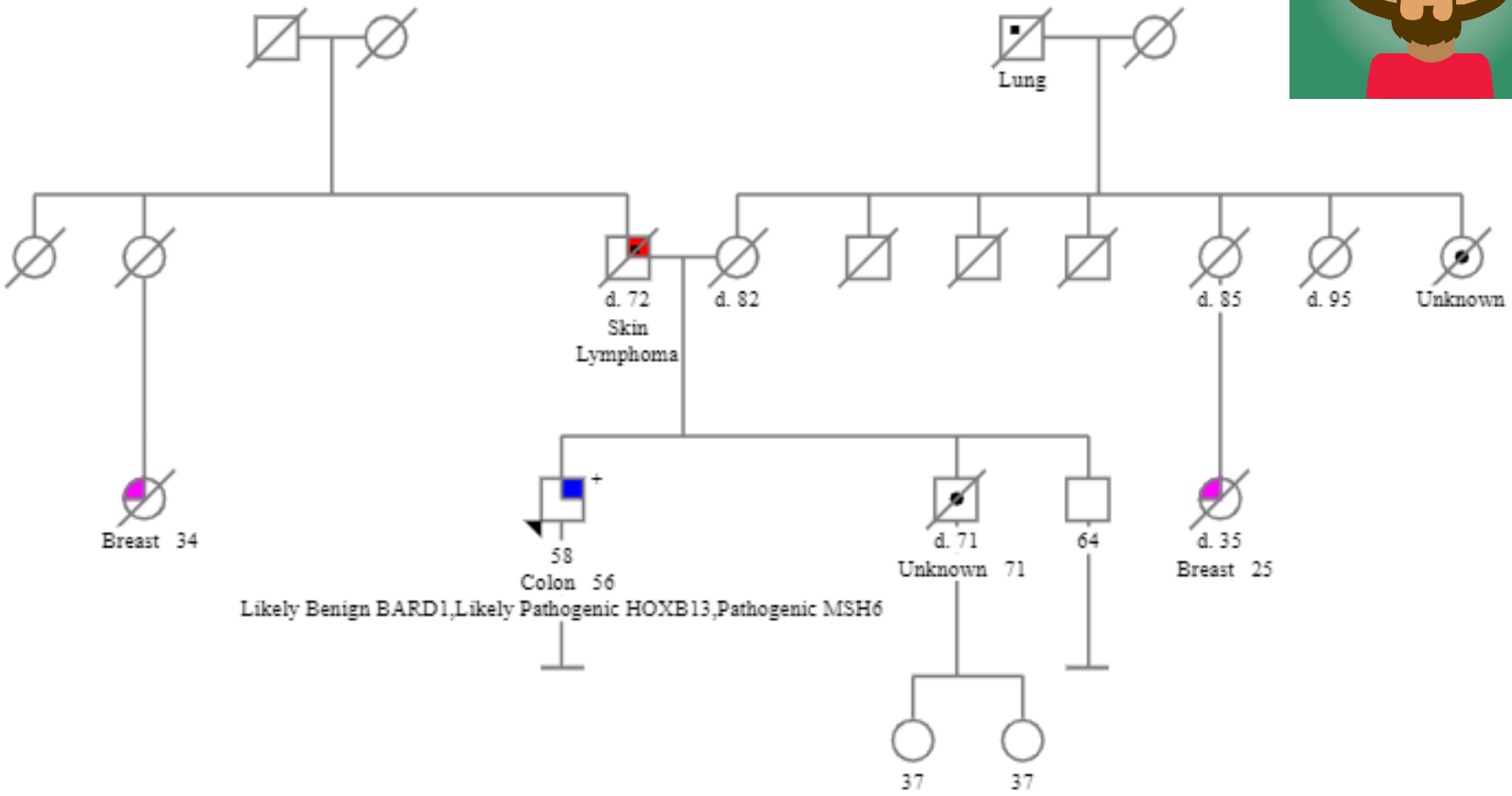
Lung
d. 72
Skin
Lymphoma
d. 82
d. 85
d. 95
Unknown
Breast 34
58
Colon 56
Likely Benign BARD1,Likely Pathogenic HOXB13,Pathogenic MSH6
d. 71
Unknown 71
64
d. 35
Breast 25
37
37

Case 2: TF Test Results and Plan

- Ordered a panel for 35 cancer genes
- Test Result:
  - Positive for a *MSH6* mutation
    - Up to 22% risk for colon cancer
    - Up to 26% risk for uterine cancer
    - Up to 11% risk for ovarian cancer
    - Increased risk for stomach, urinary tract, and possibly breast cancers
  - Positive for a *HOXB13* mutation
    - Up to 60% risk for prostate cancer
  - Variant of uncertain significance (VUS) in *BARD1*
    - True mutations associated with moderately increased risk for ovarian cancer

- Prevention Method:
  - Colonoscopy every 1-2 years beginning age 25-30
  - Upper endoscopy every 3-5 years beginning age 30-35
  - For women, consideration of hysterectomy with bilateral salpingo-oophorectomy
  - Annual PSA and digital rectal exams
  - No screening is recommended for the *NBN* VUS as it is an inconclusive result and we cannot make recommendations for an inconclusive result

- Family Prevention:
  - Offer testing and high risk prevention options to all close family members

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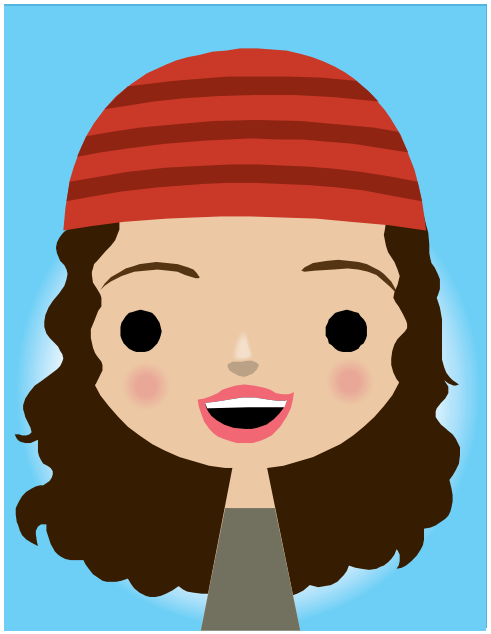
Case Example 2: JB

- JB diagnosed with breast cancer @ 31
  - Paternal aunt colon @52
  - Paternal grandmother breast @68
  - Paternal great aunt breast @60 and 62, colon @59
- European descent on both sides



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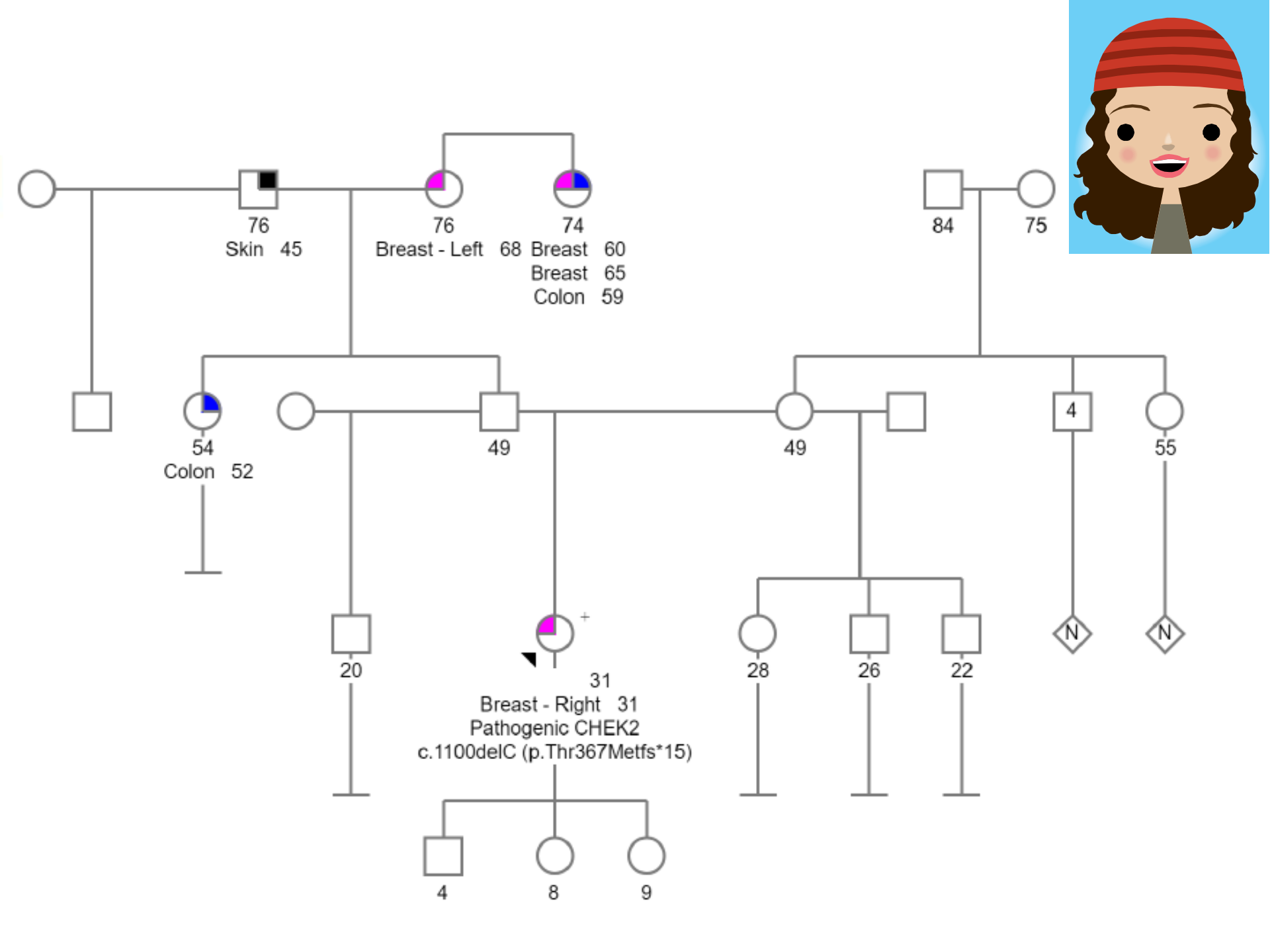
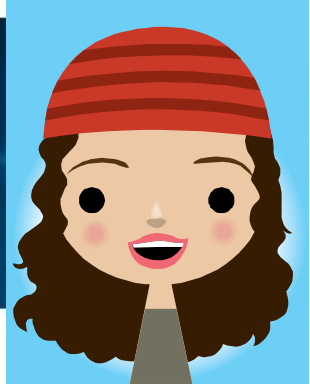

76
Skin 45
76
Breast - Left 68
74
Breast 60
Breast 65
Colon 59
84
75
54
Colon 52
49
49
4
55
20
31
Breast - Right 31
Pathogenic CHEK2
c.1100delC (p.Thr367Metfs*15)
28
26
22
N
N
4
8
9

Case 2: JB Test Results and Plan



- Ordered a panel for 47 cancer genes
- Test Result:
  - Positive for a *CHEK2* mutation
    - 20-44% risk for breast cancer
    - Up to 11% risk for colon cancer
    - Increased risk for prostate cancer
    - Possibly increased risk for renal, thyroid, melanoma, ovarian, and leukemia
- Prevention Method:
  - Continue with increased screening for breast cancer, including alternating MRIs and mammograms
  - Colonoscopy every 5 years beginning age 40
  - No official screening recommendations for other cancers
- Family Prevention:
  - Offer testing and high risk prevention options to all close family members


Questions?
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