Genetic Risk Assessment for Cancer

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Banner MD Anderson Cancer Center

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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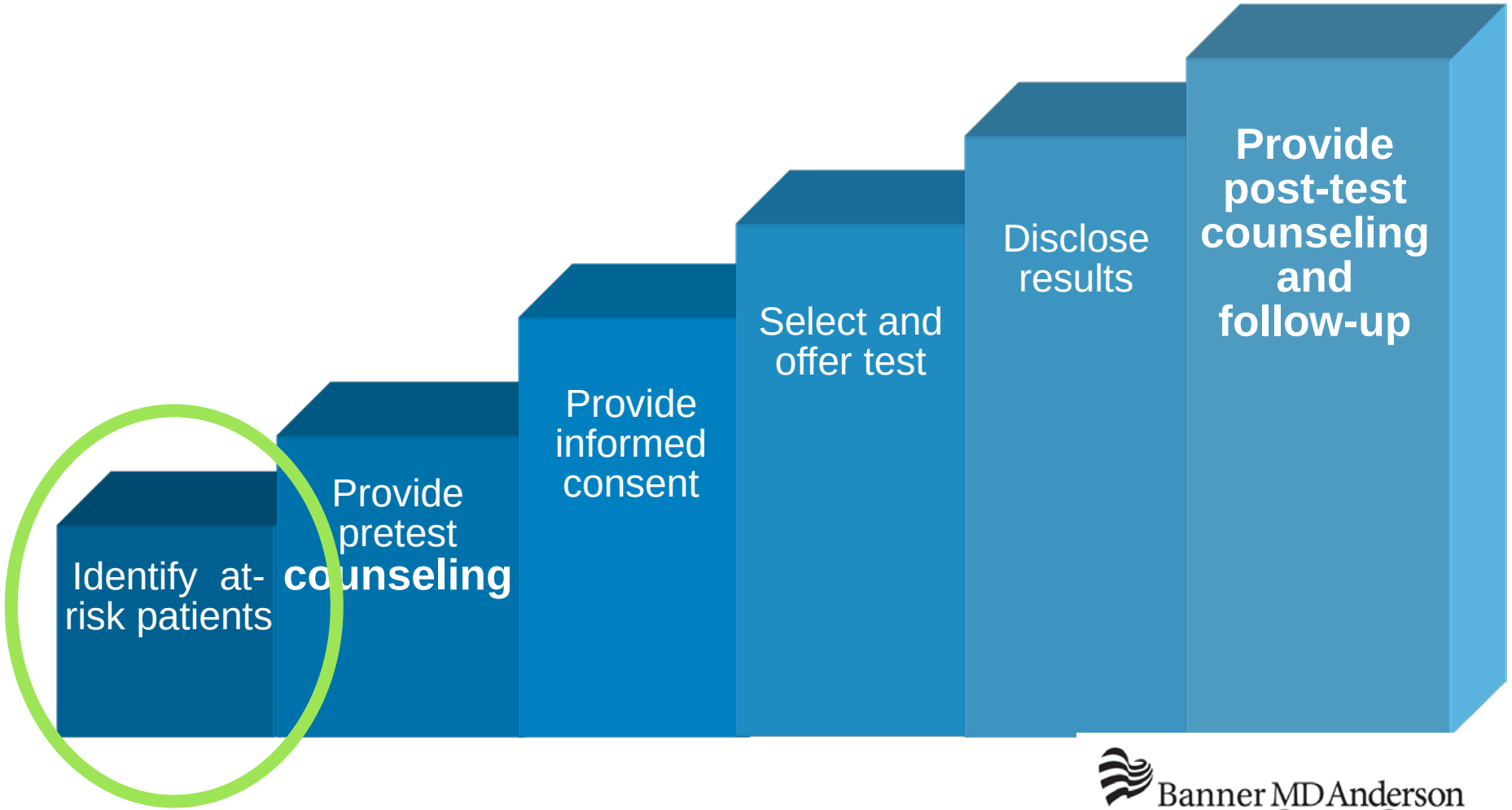
Genetic Predisposition Testing is a Multistep Process



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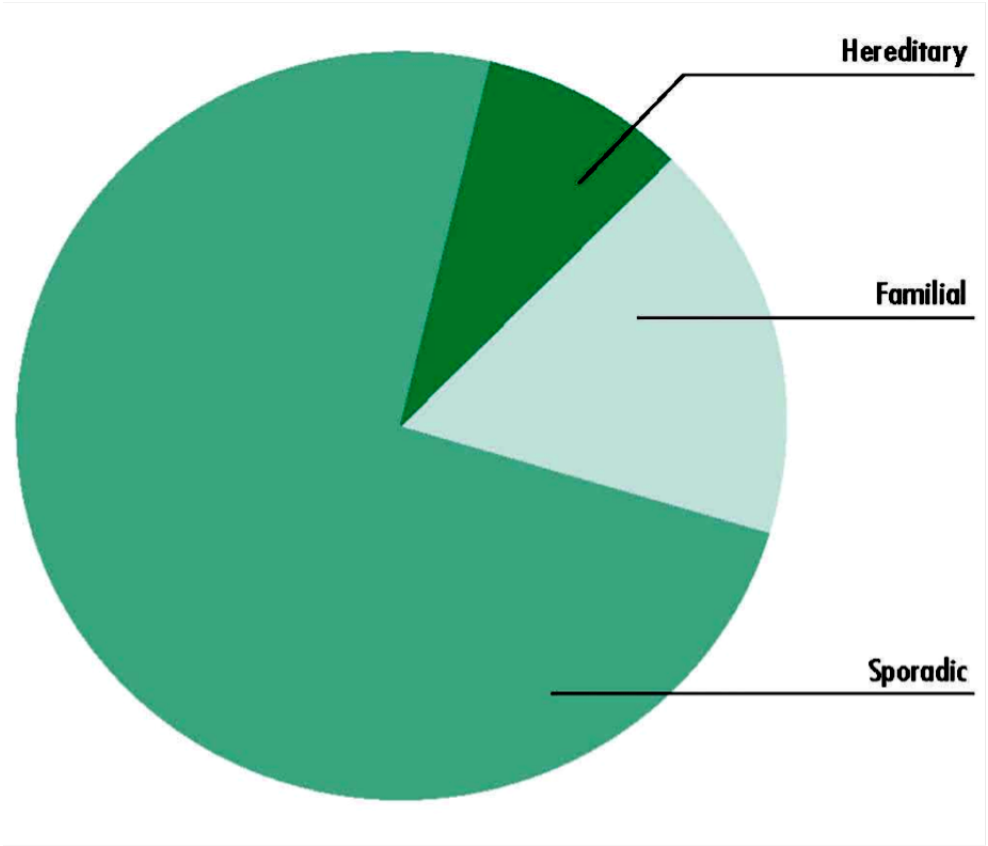
How Much Cancer is Hereditary?



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

- 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)
- Evidence of autosomal dominant transmission
  - Multiple affected generations
- Presence of congenital anomalies or syndrome-associated benign lesions

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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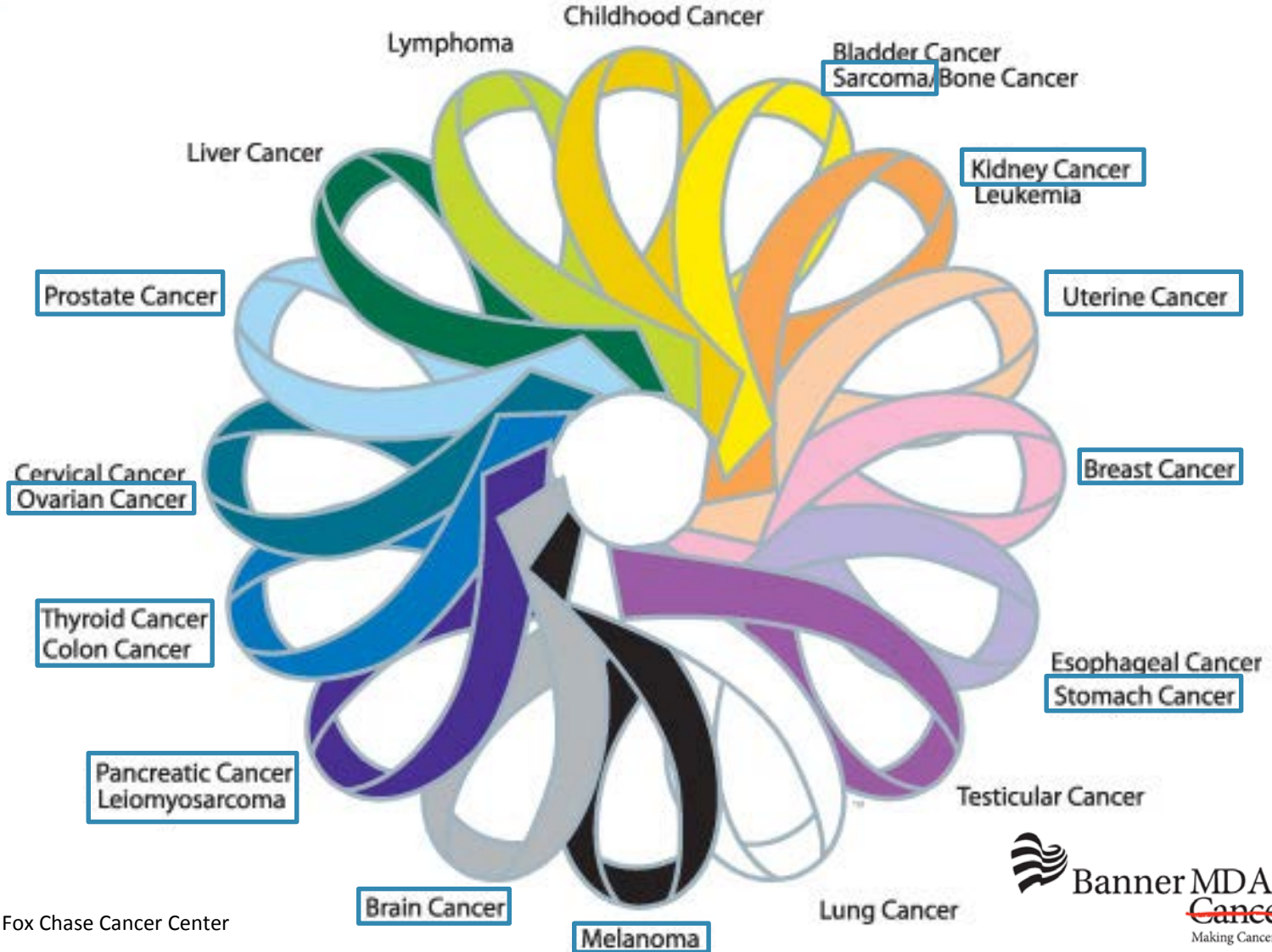
Suspicious Genetic Cancers



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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
  - Ashkenazi Jewish heritage

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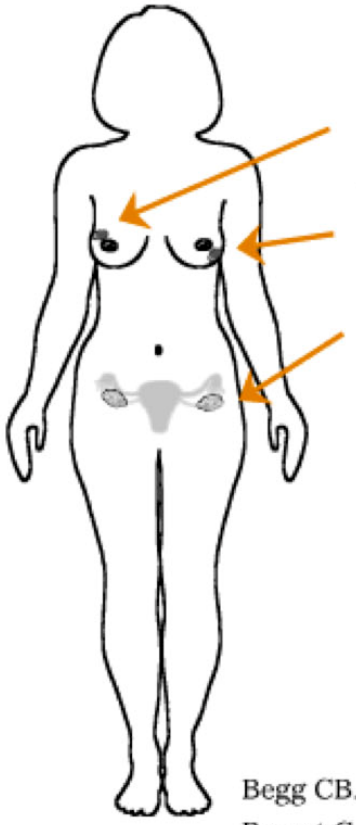
HBOC Lifetime Cancer Risks



Breast cancer: 50-85%
(often early age at onset)

Second primary breast cancer: 40-60%
(5%/yr vs. 1%/yr for sporadic BC)

Ovarian cancer: 15-45%

Absolute risk likely to be higher than 10%
- *Prostate cancer

Absolute risk 10% or lower
- *Male breast cancer
- *Fallopian tube cancer
- *Pancreatic cancer

Begg CB. *J Natl Cancer Inst.* 2002;94:1221-1226.

Breast Cancer Linkage Consortium. *J Natl Cancer Inst.* 1999;91:1310-1316.

Ford D et al. *Am J Hum Genet.* 1998;62:676-689.

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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

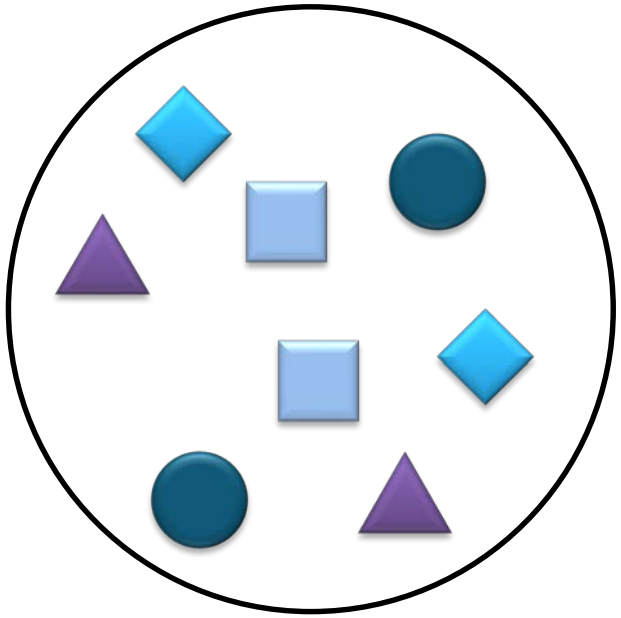
IHC Testing for Lynch Syndrome

MLHI

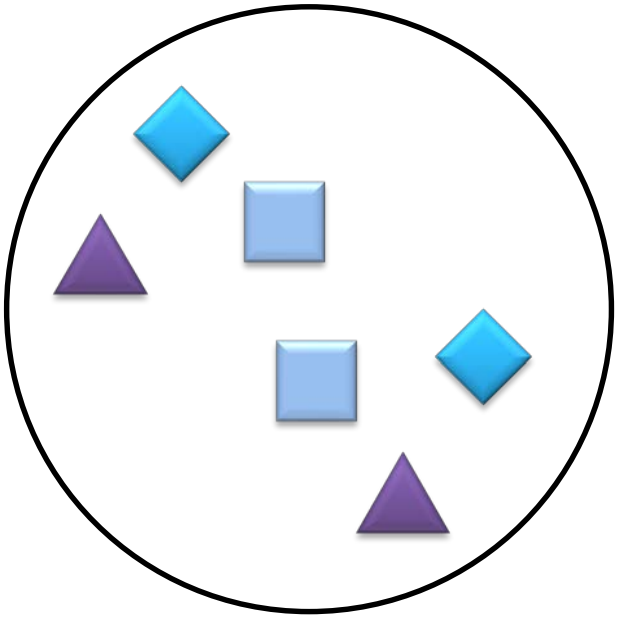
MSH2

MSH6

PMS2

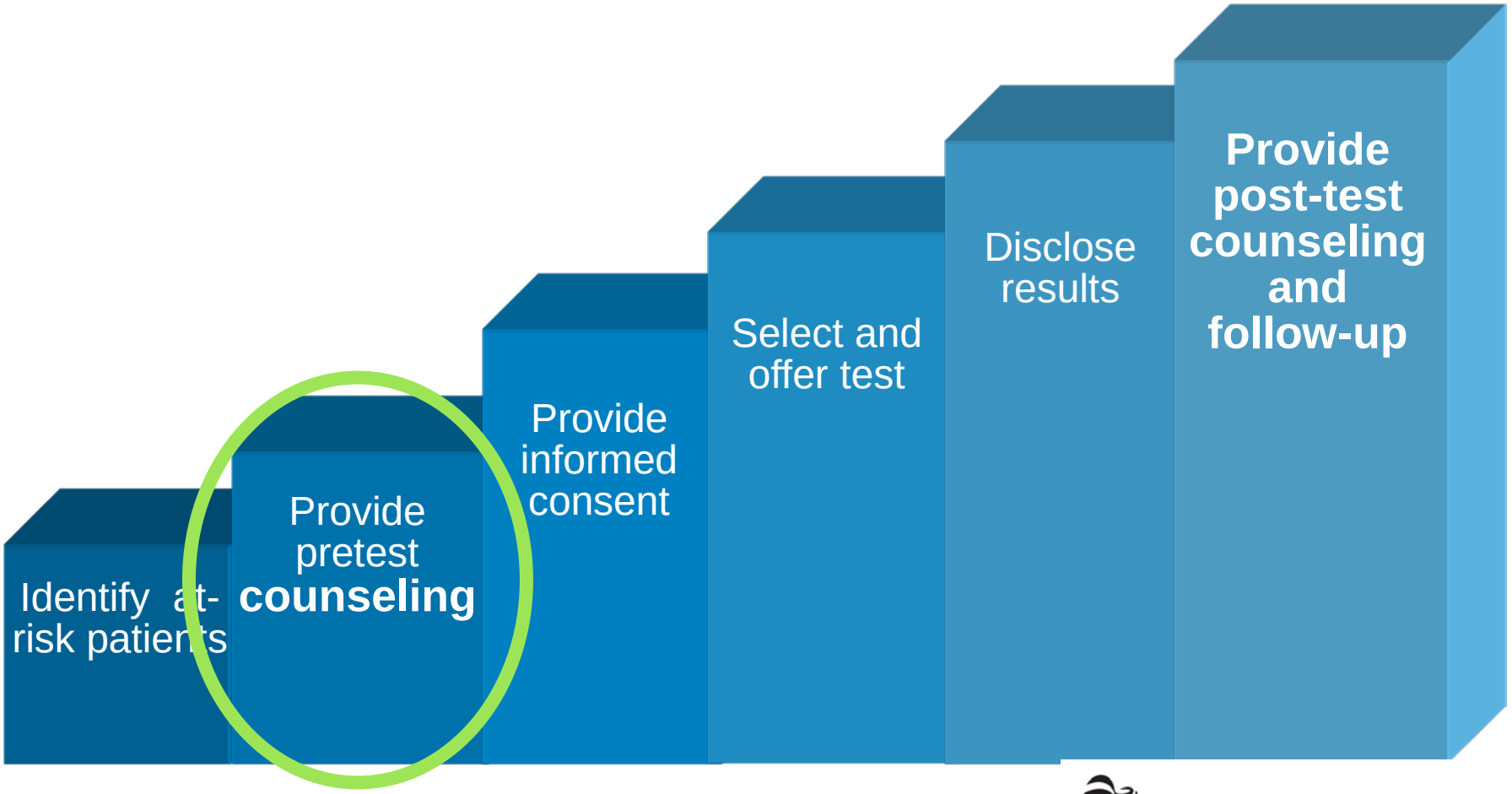


Normal



Suspicious of Lynch

Genetic Predisposition Testing is a Multistep Process



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Pretest 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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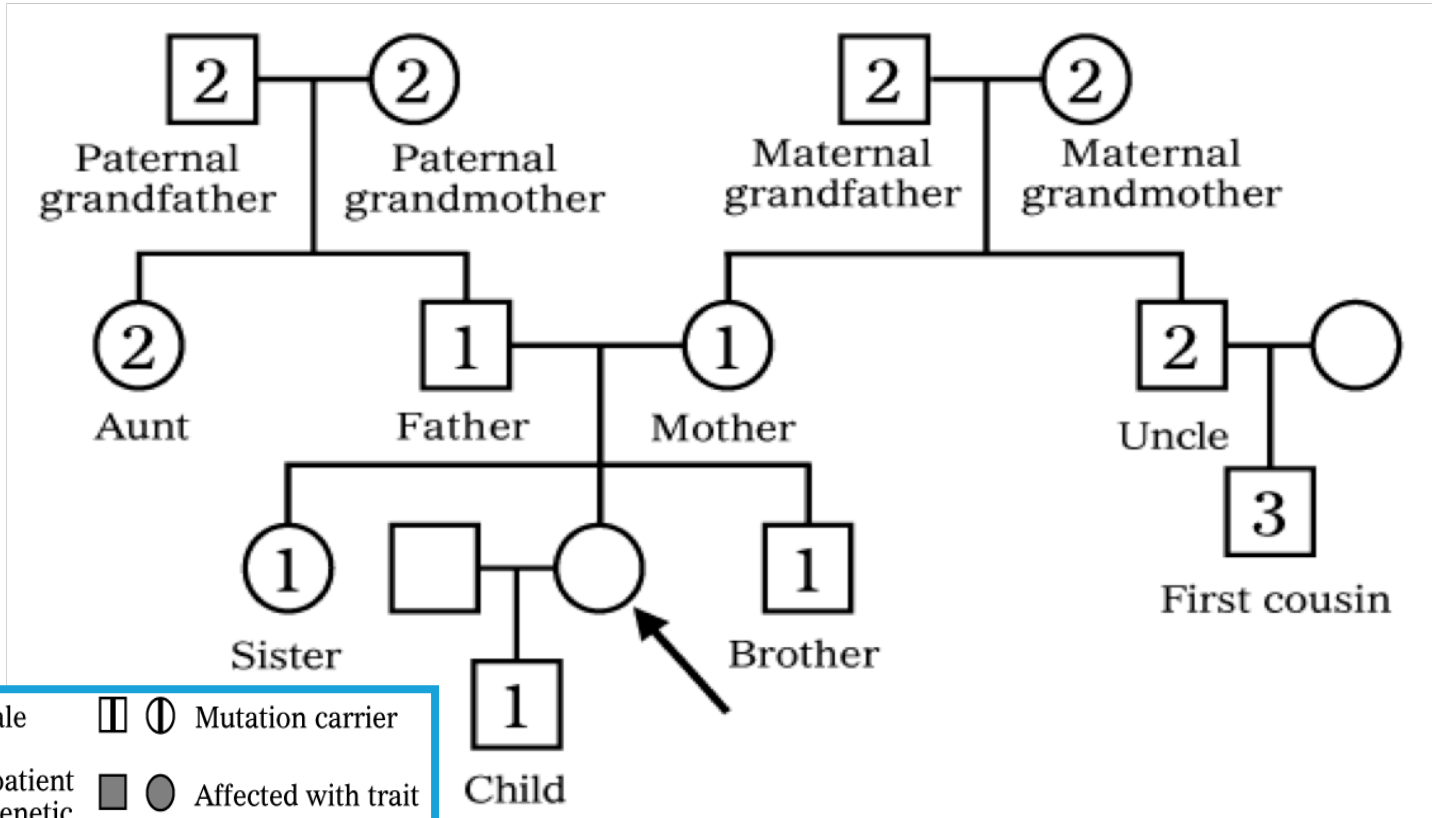
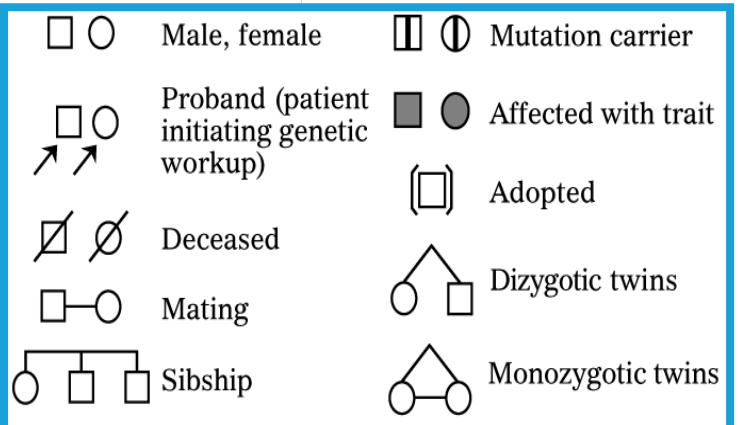
Creating a Family History or Pedigree





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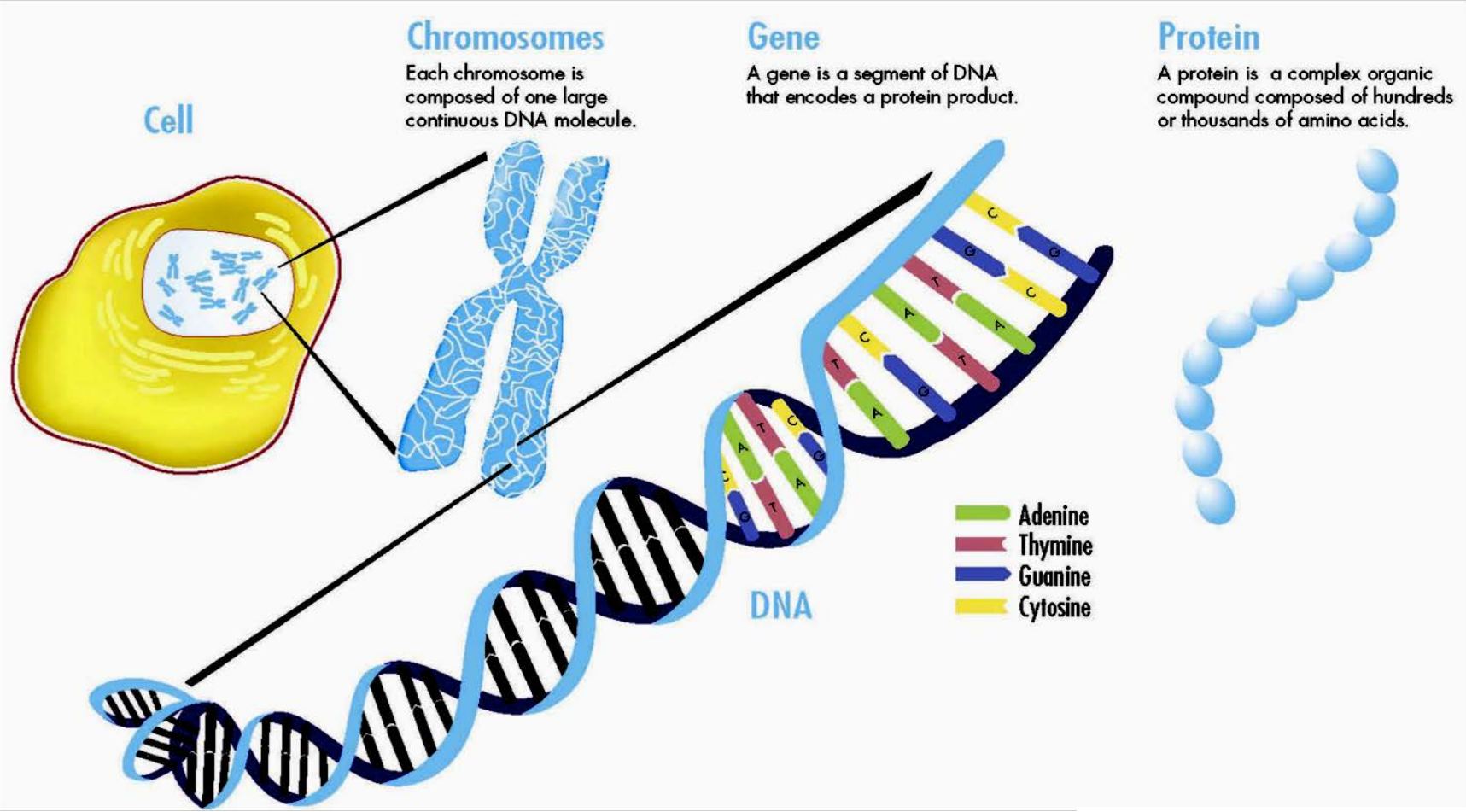
Basic Genetics



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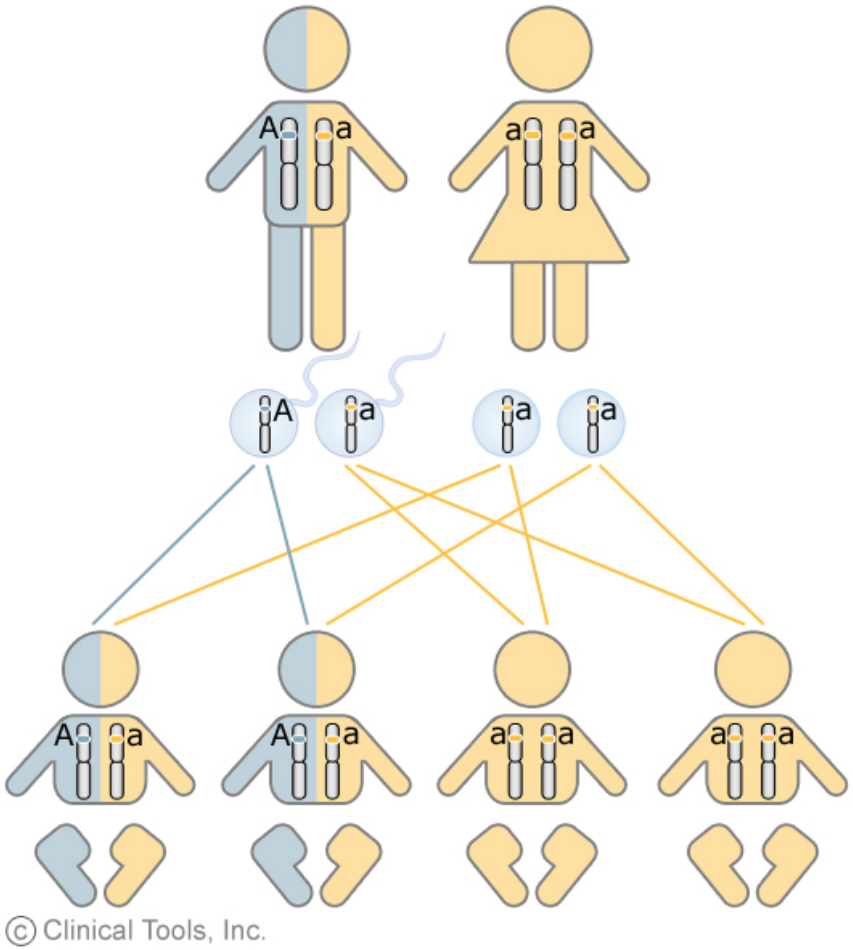
Inheritance: Typically Autosomal Dominant



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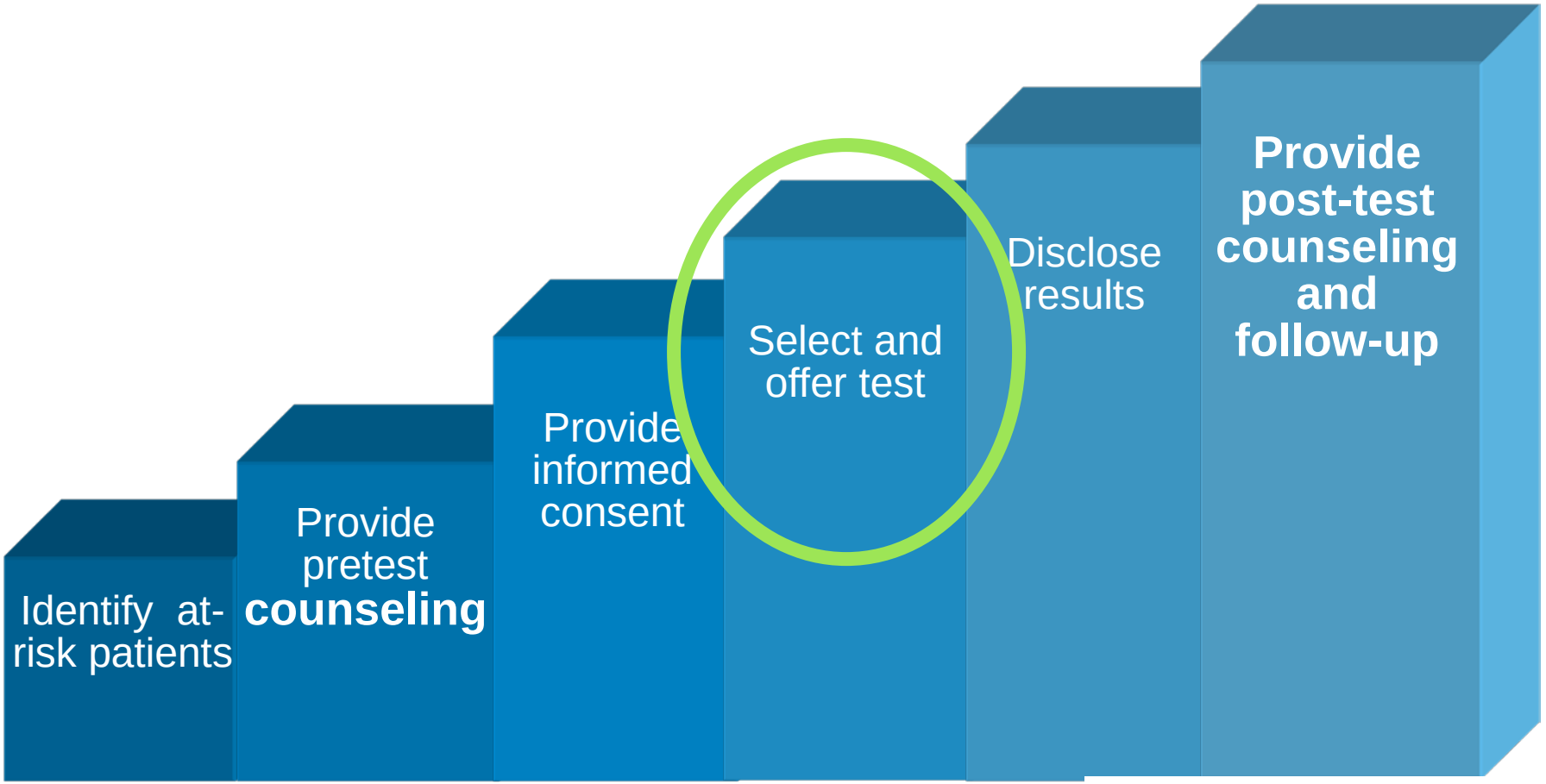
Genetic Predisposition Testing is a Multistep Process



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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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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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Genetic Testing Labs

Quest Diagnostics™

ARUP LABORATORIES

LabCorp

Ambry Genetics®

INVITAE

GeneDx DNA DIAGNOSTIC EXPERTS

Counsyl

color

PREVENTION GENETICS

DISEASE PREVENTION THROUGH GENETIC TESTING

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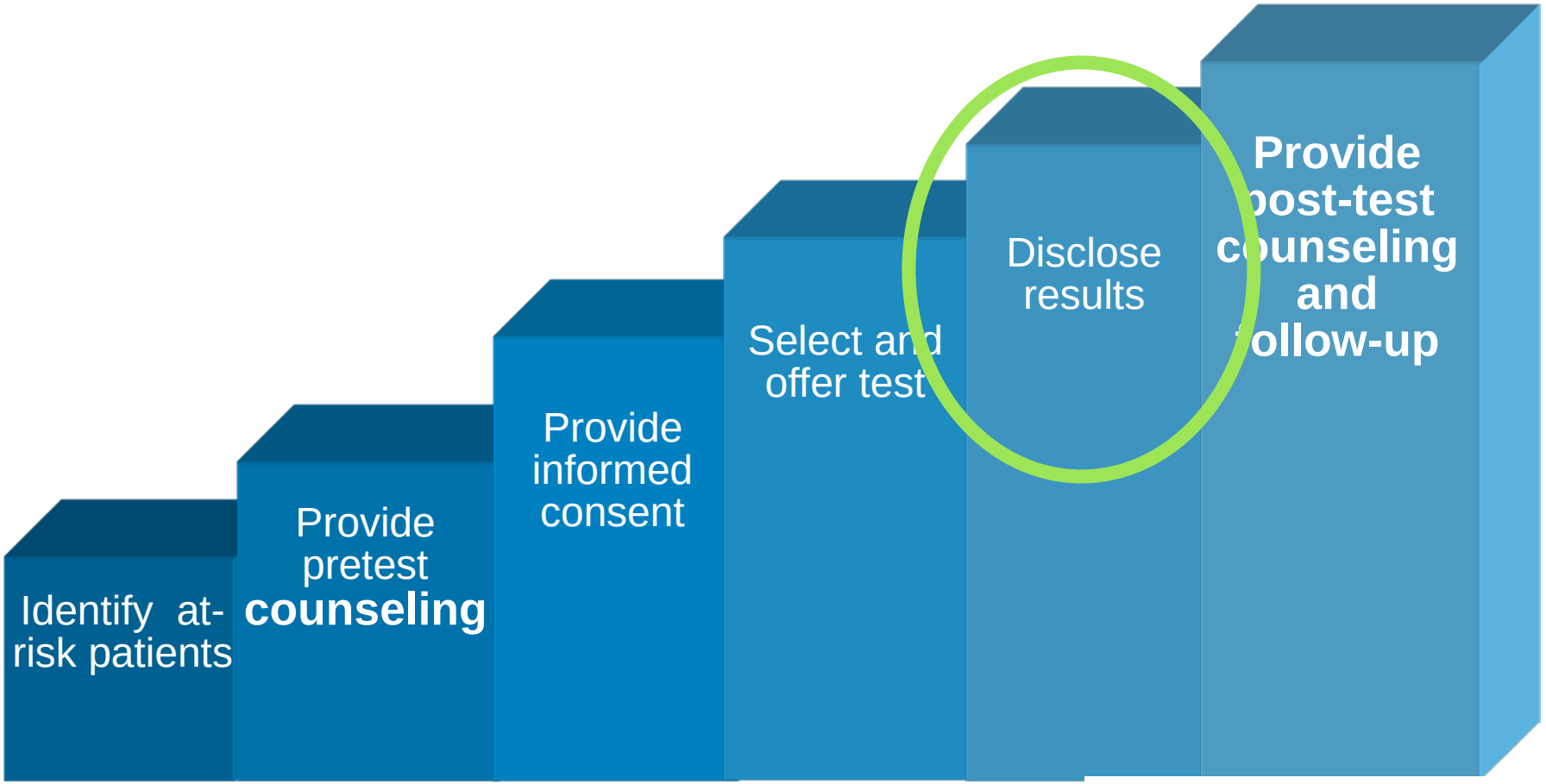

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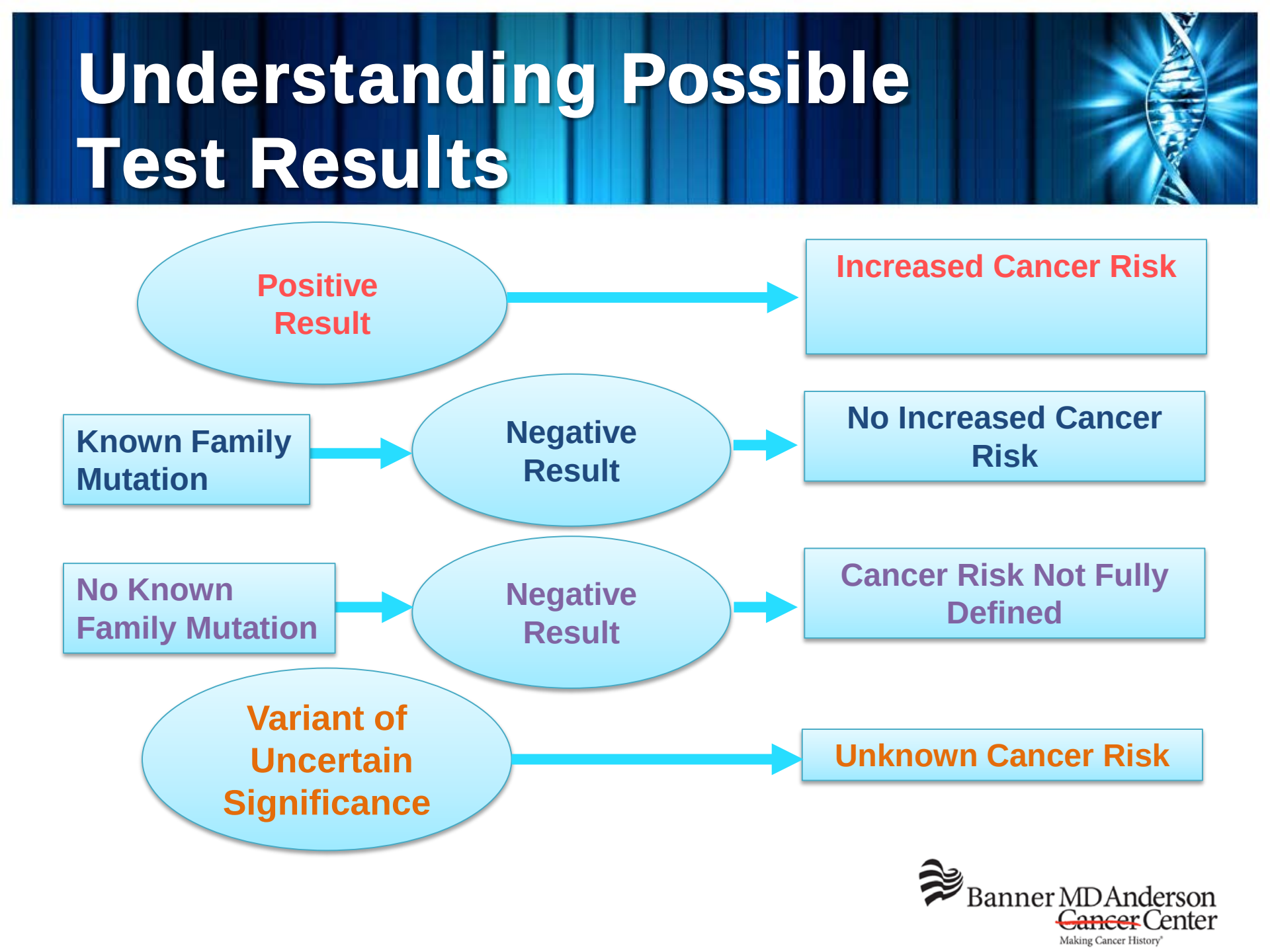
Understanding Possible Test Results



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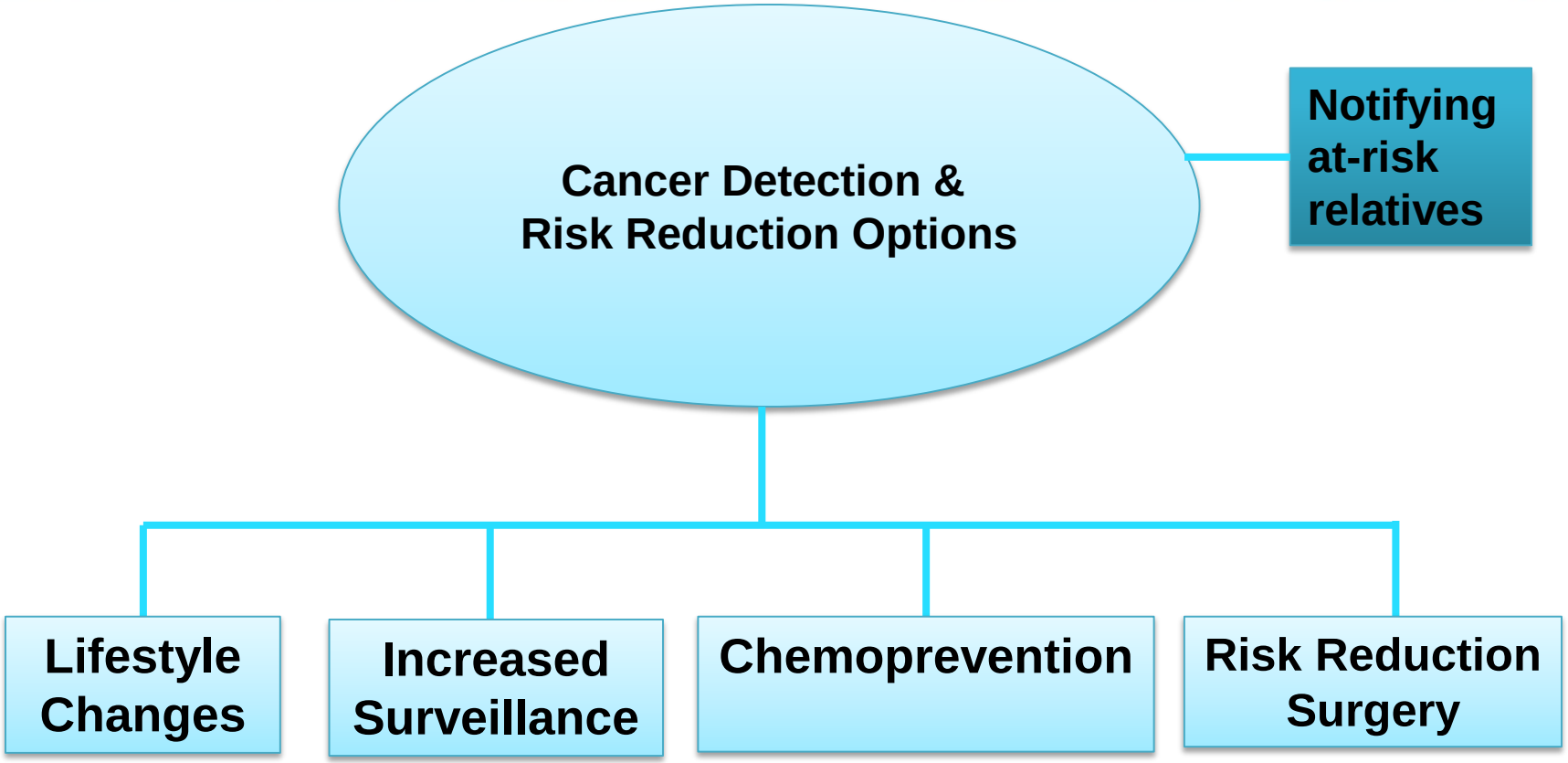
High-Risk Clinical Management



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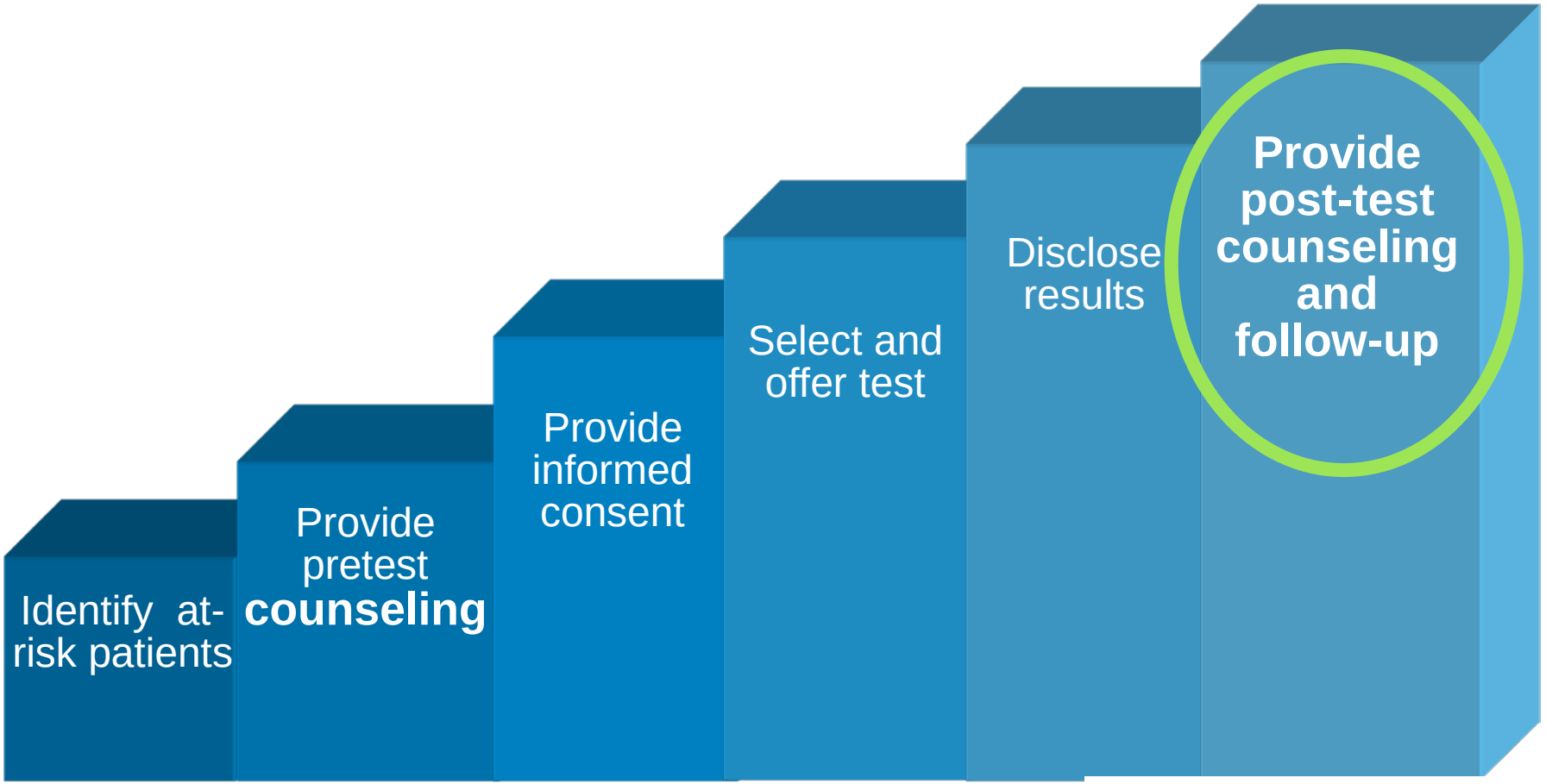
Genetic Predisposition Testing is a Multistep Process



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Genetic Discrimination

- In 2008, a federal law called the Genetic Information Nondiscrimination Act (GINA) was passed
  - Prevents health insurance and employers from discriminating based on genetic test results
  - Doesn't apply to life insurance or long-term disability
  - Doesn't apply to the military

Quick Guide to GINA

What GINA does

Prohibits group and individual health insurers from using a person's genetic information in determining eligibility or premiums

Prohibits an insurer from requesting or requiring that a person undergo a genetic test

Prohibits employers from using a person's genetic information in making employment decisions such as hiring, firing, job assignments, or any other terms of employment

Prohibits employers from requesting, requiring, or purchasing genetic information about persons or their family members

Will be enforced by the Department of Health and Human Services, the Department of Labor, and the Department of Treasury, along with the Equal Opportunity Employment Commission; remedies for violations include corrective action and monetary penalties

What GINA does not do

Does not prevent health care providers from recommending genetic tests to their patients

Does not mandate coverage for any particular test or treatment

Does not prohibit medical underwriting based on current health status

Does not cover life, disability, or long-term-care insurance

Does not apply to members of the military

Key terms

"Genetic information" includes information about:

- A person's genetic tests
- Genetic tests of a person's family members (up to and including fourth-degree relatives)
- Any manifestation of a disease or disorder in a family member
- Participation of a person or family member in research that includes genetic testing, counseling, or education

"Genetic tests" refers to tests that assess genotypes, mutations, or chromosomal changes

Examples of protected tests are:

- Tests for *BRCA1*/*BRCA2* (breast cancer) or *HNPCC* (colon cancer) mutations
- Classifications of genetic properties of an existing tumor to help determine therapy
- Tests for Huntington's disease mutations
- Carrier screening for disorders such as cystic fibrosis, sickle cell anemia, spinal muscular atrophy, and the fragile X syndrome

Routine tests such as complete blood counts, cholesterol tests, and liver-function tests are not protected under GINA

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: KM

- KM breast cancer @ 47
  - Mother: Br.Ca @ 28

    Died of Ov. Ca. @ 37
  - Maternal Aunt: Br. Ca @ 50
  - Maternal Aunt: Br. Ca. @ 58
  - Maternal Grandma: Br. Ca died in 50s
  - Father: Lung Ca @ 73

- European descent both sides

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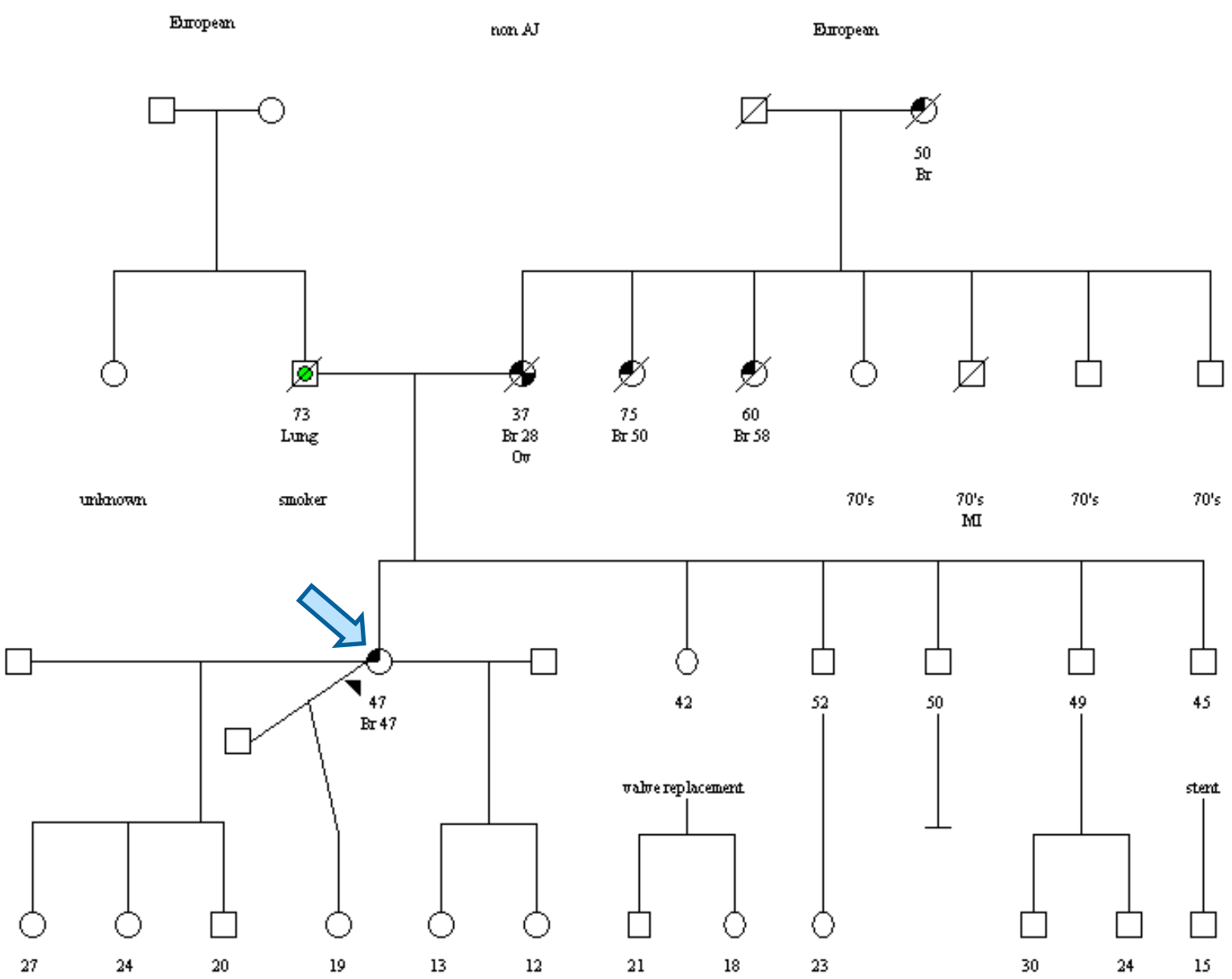

Diagnosis = Br Diagnosis = Lung Diagnosis 2 = Ov

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Case 1: KM Test Results and Plan

- Ordered a panel of 17 breast cancer genes
- Test Result:
  - Positive for a *BRCA2* mutation
    - Up to 85% risk for breast cancer
      - 60% Risk for second primary
    - Up to 40% risk for ovarian/fallopian tube cancer
    - 6% risk for Male breast cancer

- Prevention Method
  - Bilateral salpingo-oophortectomy
  - Bilateral mastectomy

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

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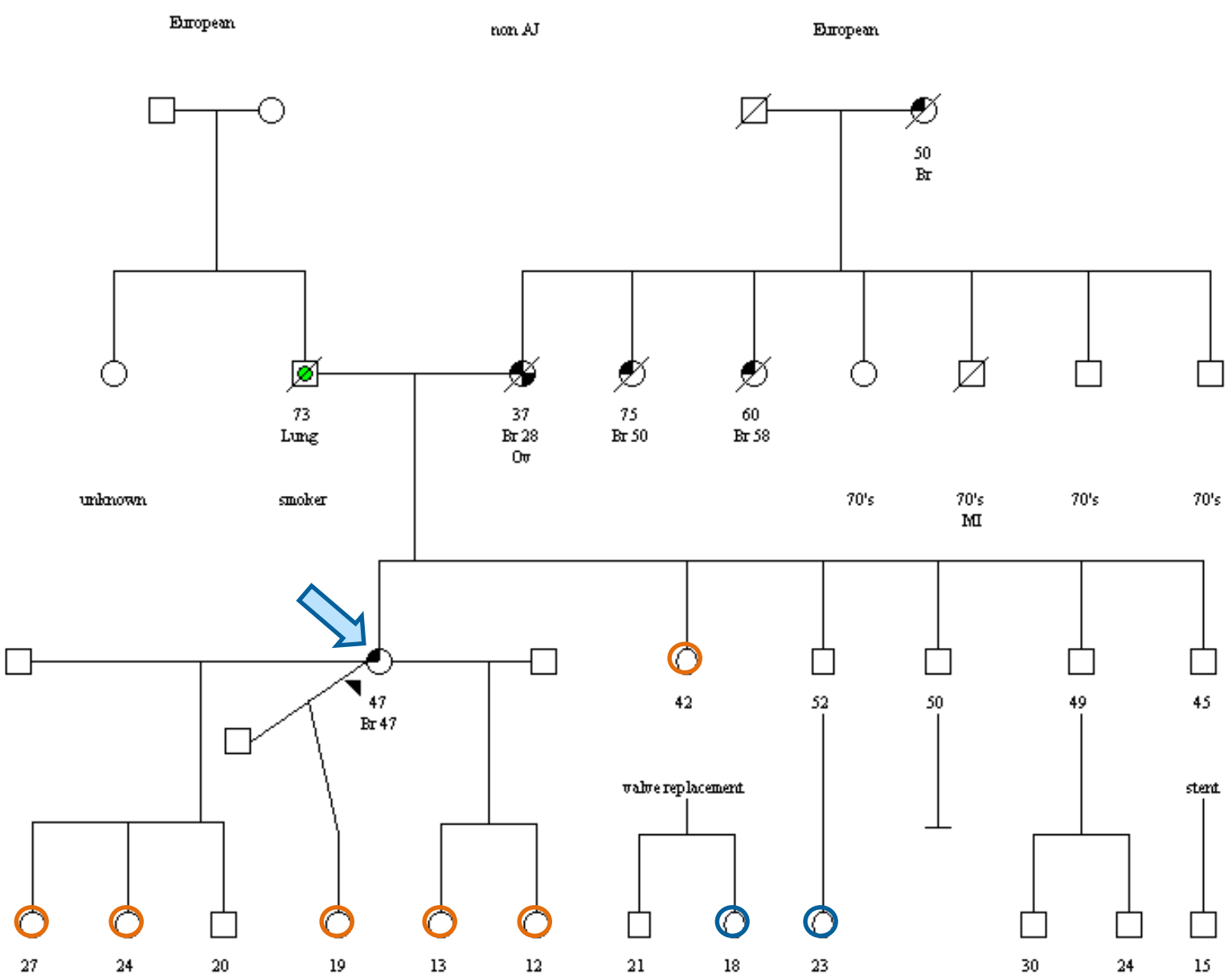

Diagnosis = Br Diagnosis = Lung Diagnosis 2 = Ov

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Case Example 2: PA

- PA is a 65 y.o. woman diagnosed with uterine cancer @ 61 and bladder cancer @ 65
  - Sister: pancreatic @ 64
  - Mom: colon @ 56
  - Maternal aunt: colon @ 89
  - Maternal aunt: ovarian
  - Maternal cousin: colon in 40s
- European descent on both sides

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Sicilian
92
old age
MI
90
85
96
89
90
73
Stomach
89
Ca-Nos
old age
old age
Alzheimer's
MI
old age
Ca-Nos
Br 40
d. war
ca in eye
MI, gout
65
Ut 61
Bladder 64
65
Pan 64
55
45
Ca-Nos
CVA 54
thy iss.
ca throughout
lung, pe[illegible], bone
42
41
45
50
48
20
31
18
15
21
p
2
Russian
TB
old age
65
CRC 56
Lung 64
MI
76
Brain 76
war veteran
d. during surgery
TB
Lung
70
CRC
dx 40s
89
CRC 89
CRC
69
Ov
Lung
CP
No AJ
No consanguinity
Diagnosis = Brain
Diagnosis = Ut
Diagnosis = Pan
Diagnosis = Ov
Diagnosis = CRC
Diagnosis = Pan
Diagnosis = Brain
Diagnosis = Stomach
Diagnosis 2 = Bladder
Diagnosis = Ca-Nos
Diagnosis = Lung
Diagnosis 2 = Lung
Diagnosis = Br

Case 2: PA Test Results and Plan

- Ordered a panel for 32 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
  - Variant of uncertain significance (VUS) in *NBN*
    - True mutations associated with moderately increased risk for breast and ovarian cancer

- Prevention Method:
  - Colonoscopy every 1-2 years beginning age 25-30
  - Patient already had hysterectomy and bilateral salpingo-oophorectomy
  - 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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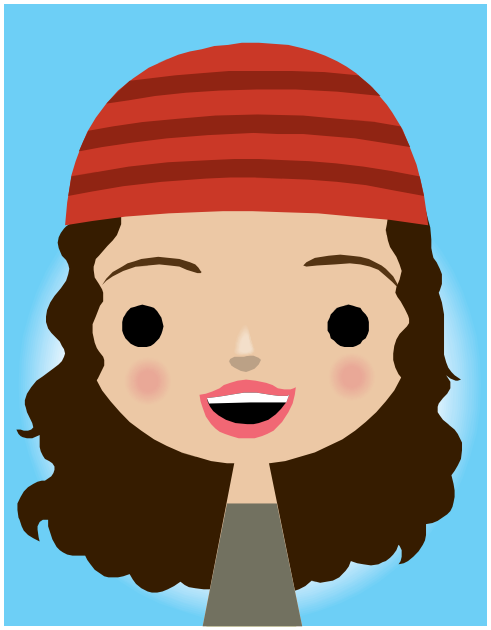
Case Example 3: BB

- BB diagnosed with breast cancer @ 49
  - Mother: breast @ 76
  - Maternal aunt: breast @ 44
  - 2 maternal uncles: brain @ 56 and 64
  - Paternal aunt: breast
  - Paternal cousin: breast @ 44
  - Paternal grandma: breast @ 31



- European descent on both sides

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Hungarian/German

German

64

32
Br 31

58

68

Br

CVA

dx 30s

72
Br

88

79
Pr 74
Skin-NOS

79
Br 76

70

84
Br 44

83

65
Brain 64

58
Brain 56

4

unk

d. Korean war

heart iss.

mult. skin

Alzheimer's

MI

unk

d. young accident

46
Br 44

49
DCIS 49

50

47

47

n

2

2

n

2

+/+

SA

>8

4

4

5

8

11

7

neutropenia

neutropenia

Diagnosis = Brain

Diagnosis = DCIS

Diagnosis = Pr

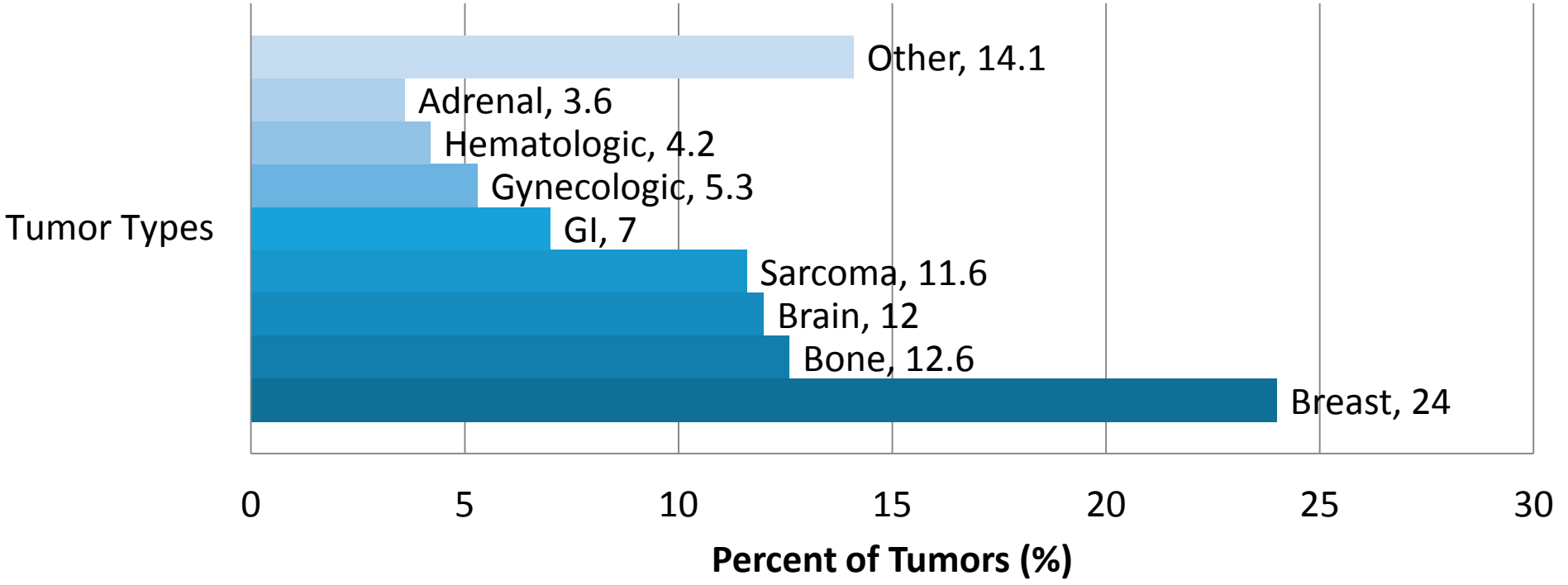
Diagnosis 2 = Skin-NOS

Diagnosis = Brain

Diagnosis = Br

Case 3: CD Test Results and Plan

- Ordered a panel for 17 breast cancer genes
- Test Result:
  - Positive for a *Tp53* mutation, responsible for Li Fraumeni Syndrome
    - 50% risk for any type of cancer by age 40
    - 90% risk for any type of cancer by age 60



Case 3: CD Test Results and Plan

- Prevention Method

Cancer	0-1 Years
General	Biannual physical exam (neurological, thyroid) Avoid radiation treatment when possible
Adrenocortical and Sarcoma	Annual Testosterone levels
	Annual WB-MRI*
Brain	Annual brain MRI*
Leukemia	Annual CBC, Erythrocyte labs
Melanoma	Annual dermatologic exam
Breast (begin at 25)	Biannual clinical breast exam
	Annual MRI and mammogram
	Consider prophylactic mastectomy
Colon (begin at 25)	Colonoscopy and upper endoscopy every 2-5 years
Ovarian (begin at 35)	Biannual CA-125 and transvaginal U/S
	Consider removing ovaries and uterus


Questions?
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