Cancer Genetics in the Primary Care Setting

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Disclosure

- We have no conflicts of interest in relation to this program or presentation.

Objectives

1. Review genetic factors in cancer risk
2. Outline which patients to refer
3. Discuss the utility of genetic counseling
4. Acknowledge other ways that patients may encounter genetic concepts or obtain their genetic data

Who are Genetic Counselors

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Genetic Counselors

- Master's level training in medical genetics and psychosocial counseling.
- Meet with individuals or families before and after genetic testing.
- All specialized in **oncology**, prenatal, cardiology, pediatrics, neurology, ophthalmology, and psychiatry, among others.
- Non-clinical roles in research, education, industry, marketing, public health

Cancer Genetics

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Cell Cycle Regulation

- DNA repair genes
  - Fix errors made during DNA replication
  - Inactivation leads to cancer development
  - Ex: *MLH1, MSH2, MSH6, PMS2*
- Tumor suppressor genes
  - Negatively regulate the growth of cells
  - Inactivation leads to cancer development
  - Ex: *BRCA1/2*
- Oncogenes
  - Play roles in cell cycle regulation
  - Activation leads to cancer development
  - Ex: *RET*

labs.wsu.edu

Hereditary Cancer Assessment

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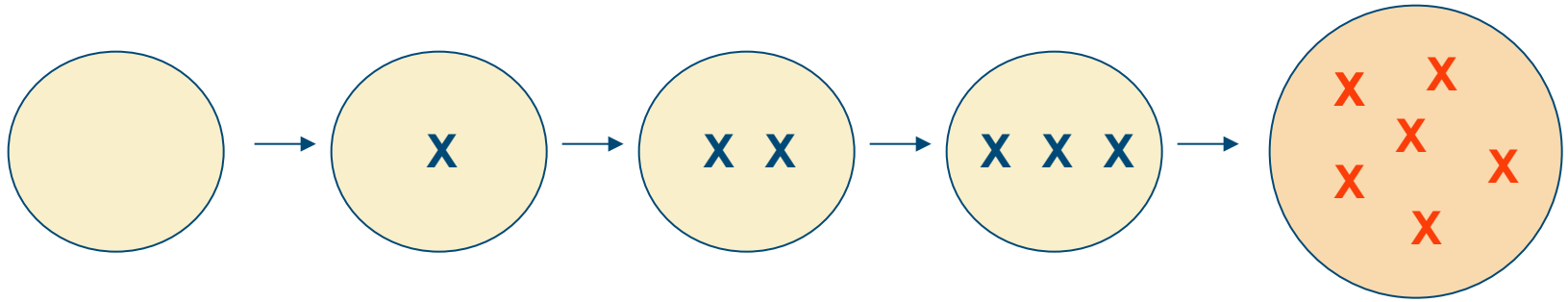
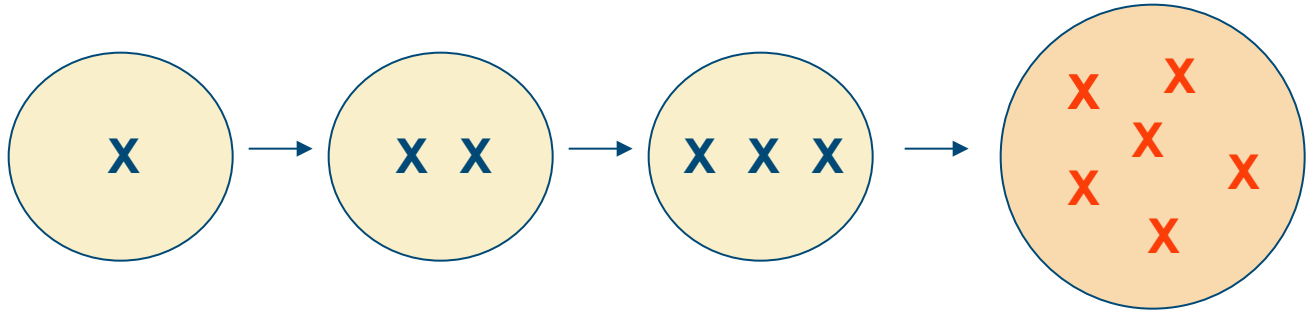
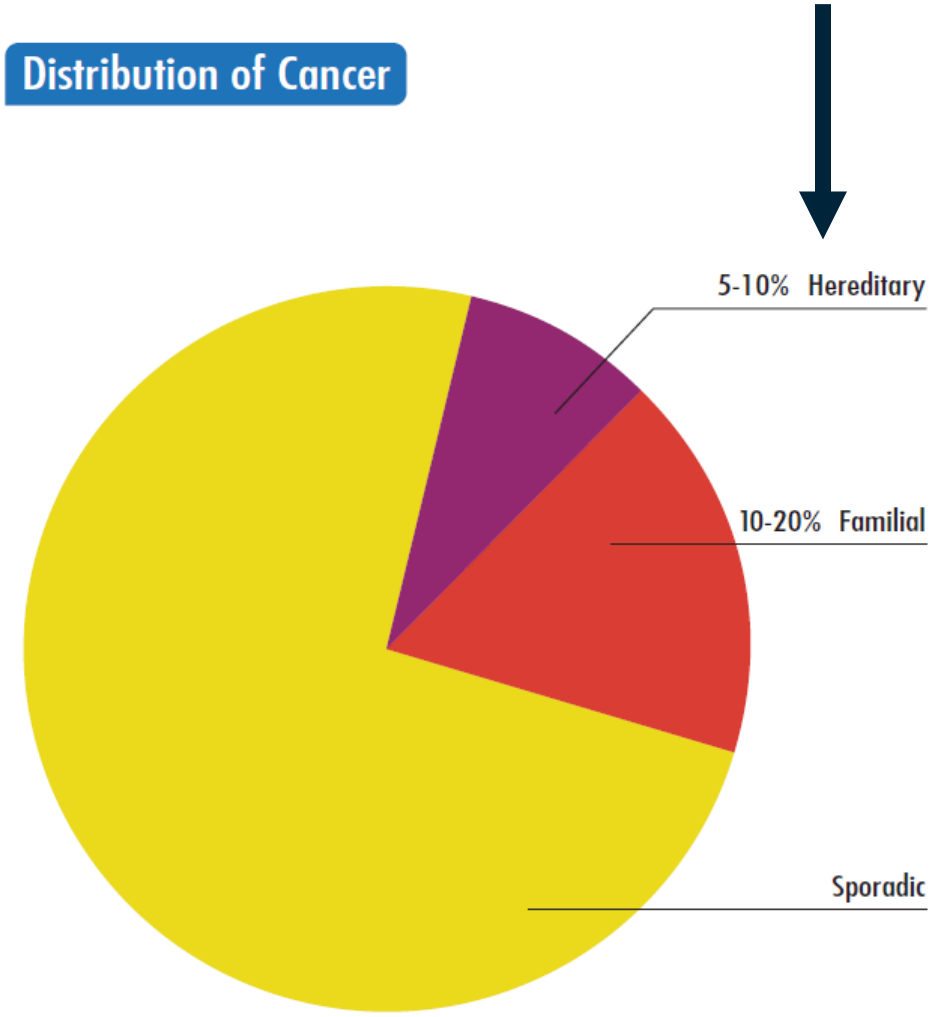
Sporadic Cancers



Hereditary Cancers



Distribution of Cancer



Hereditary

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

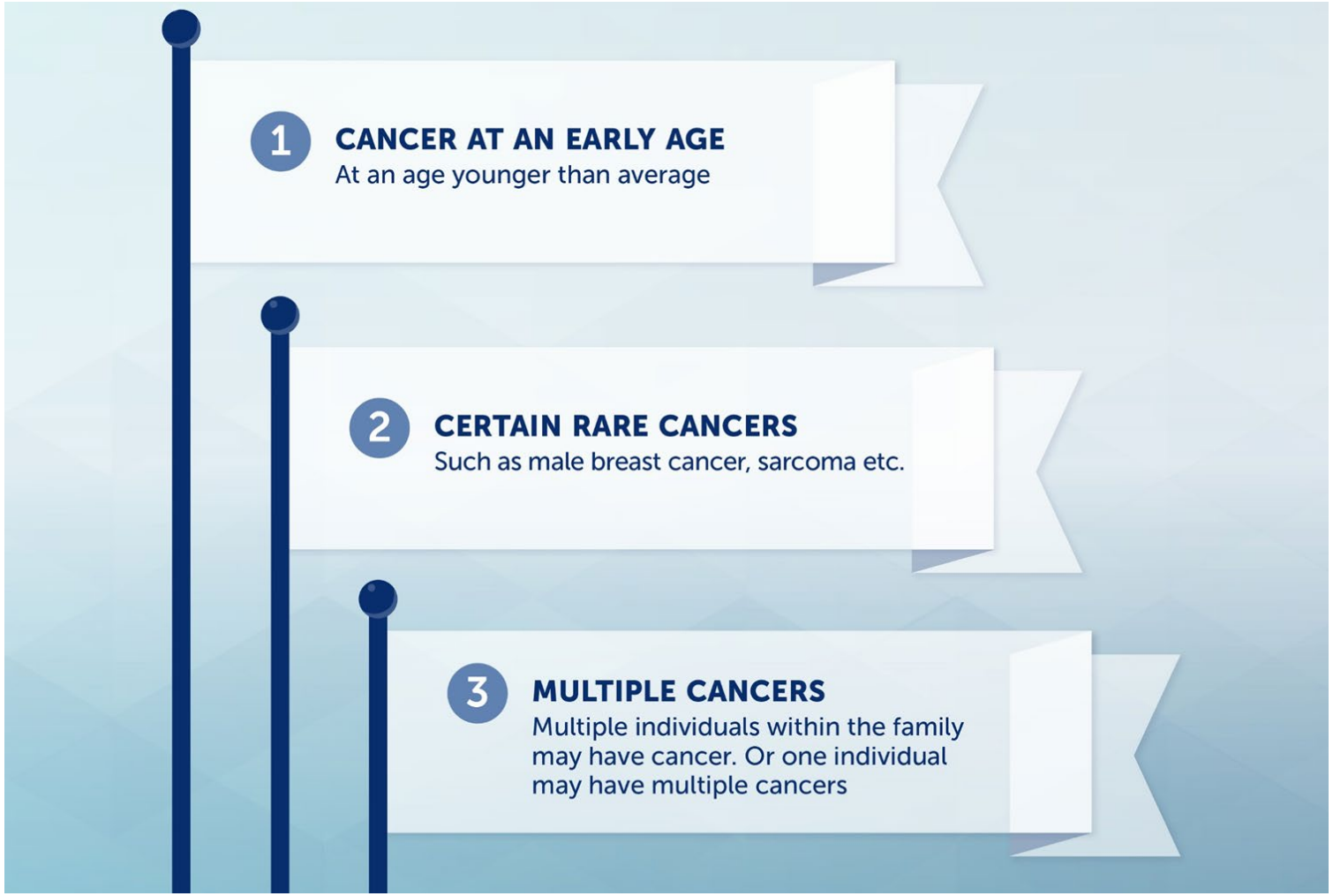
Familial

- 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

Hereditary Cancer Red Flags



Genetic Testing Criteria for Breast Cancer Genes

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Genes such as *BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11,* and *TP53.* See GENE-A)[a,f,g,h,i]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - Treatment indications
      - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k] (NCCN Guidelines for Breast Cancer)
      - To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER2-negative breast cancer[j]
    - Pathology/histology
      - Triple-negative breast cancer
      - Multiple primary breast cancers (synchronous or metachronous)[m]
      - Lobular breast cancer with personal or family history of diffuse gastric cancer (NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric)
    - Male breast cancer
    - Ancestry: Ashkenazi Jewish
  - Any age (continued):
    - Family history[n]
      - ≥1 close blood relative[o] with ANY:
        - breast cancer at age ≤50 y
        - male breast cancer
        - ovarian cancer
        - pancreatic cancer
        - prostate cancer with metastatic,[p] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer
- Family history criteria: unaffected; or affected but does not meet above criteria
  - Individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[q]
  - Individuals who have a probability >5% of a *BRCA1/2* P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).[r]

Genetic Testing Criteria for Colorectal Cancer Genes

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

NCCN Guidelines Index
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Discussion

CRITERIA FOR TESTING FOR LYNCH SYNDROME[m]

Testing is clinically indicated in the following scenarios:	
• Known LS PV in the family • Personal history of a LS-related cancer (CRC, EC, or other[e]) and any of the following: ▸ Diagnosed <50 y[n,o] ▸ A synchronous or metachronous LS-related cancer[e] regardless of age ▸ 1 first-degree or second-degree relative with an LS-related cancer[e] diagnosed <50 y ▸ ≥2 first-degree or second-degree relatives with an LS-related cancer[e] regardless of age • Family history[p] of any of the following: ▸ ≥1 first-degree relative with a CRC or EC diagnosed <50 y ▸ ≥1 first-degree relative with a CRC or EC and a synchronous or metachronous LS-related cancer[e] regardless of age ▸ ≥2 first-degree or second-degree relatives with LS-related cancers[e] including ≥1 diagnosed <50 y ▸ ≥3 first-degree or second-degree relatives with LS-related cancers[e] regardless of age • Increased model-predicted risk for LS ▸ An individual with a ≥5% risk of having an MMR gene PV based on predictive models (ie, $PREMM_5$, MMRpro, MMRpredict) ◊ Individuals with a personal history of CRC and/or EC with a $PREMM_5$ score of ≥2.5% should be considered for MGPT. ◊ For individuals without a personal history of CRC and/or EC, some data have suggested using a $PREMM_5$ score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity.	Strategies for Testing for LS (LS-1)
• Personal history of CRC, EC, or of other tumor with MMR deficiency determined by polymerase chain reaction (PCR), next-generation sequencing (NGS), or IHC diagnosed at any age[q,r] • Personal history of a P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline[s,t]	Additional tumor-based testing (LS-A) OR Germline MGPT for LS and other hereditary cancer syndromes[y] Strategies for Testing for LS (LS-1)

Testing may be considered in the following scenarios:
• Personal history of CRC or EC at age ≥50 y and any of the following (category 2B):[u,v] ▸ untested for MMR deficiency status in tumor[w] ▸ absence of MMR deficiency in tumor[x] See Rationale, pros, and cons of multigene panel testing for Lynch syndrome and other cancer risk genes (HRS-A)

Genetic Counseling

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Appointment Structure

Initial Appointment

- Risk assessment of personal and family histories
- Education about basic genetics, inheritance, and hereditary cancer syndromes
- Explanation of testing process and insurance coverage
- Informed consent (if testing)
- Cancer risks and risk management recommendations if no test or if negative test

Results call

- Interpretation of results based on personal and family histories, stressing limitations of negative result
- Screening and risk management recommendations
- Psychosocial support
- Cascade testing for family members

Genetic Information Nondiscrimination Act of 2008 (GINA)

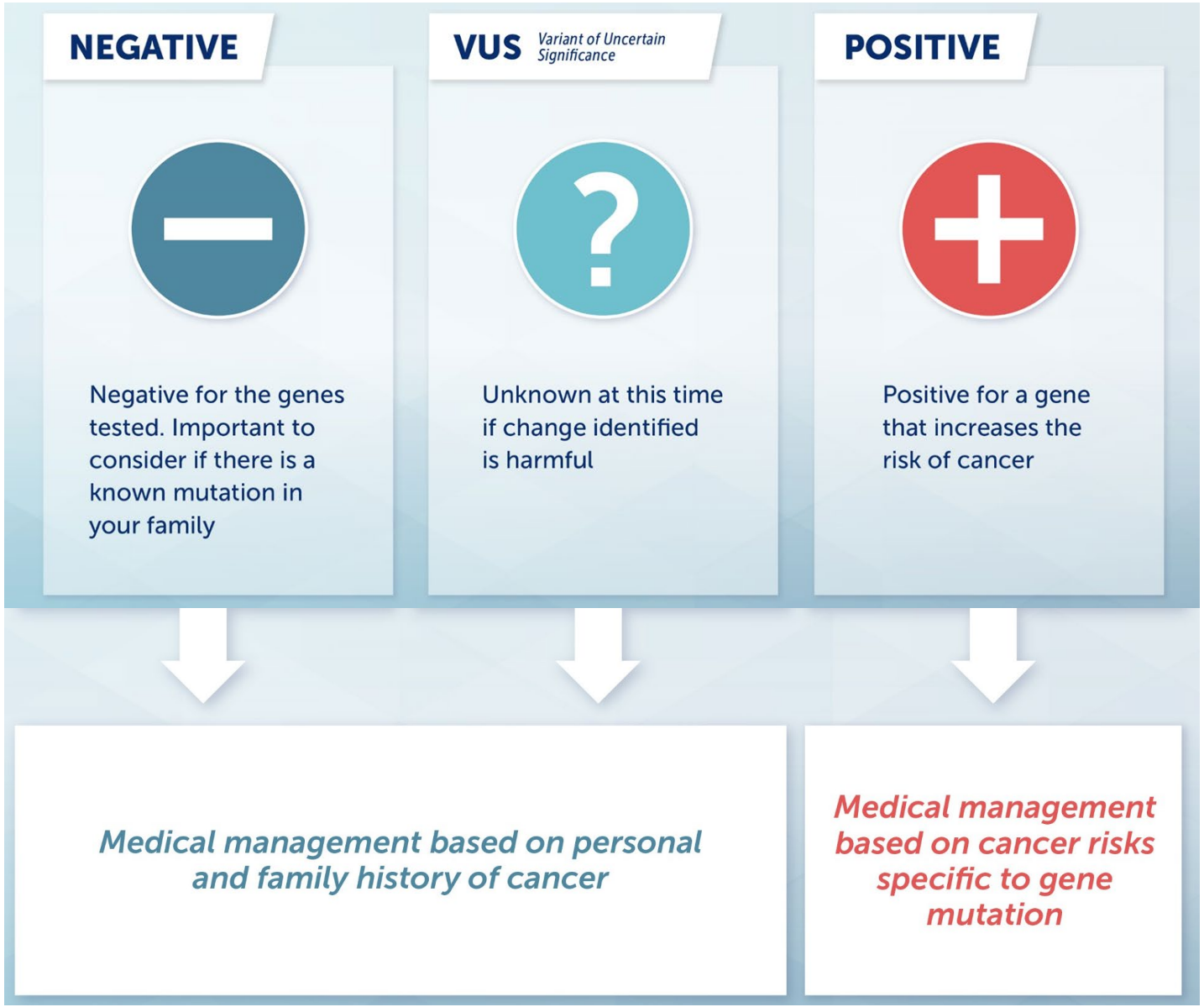
Genetic Testing

- DNA sequencing and deletion/duplication analysis of genes related to inherited cancer syndromes
- Multi-gene panels are commonly used to test for multiple genes at once

		GENES	BREAST & GYN	ENDOCRINE	GASTROINTESTINAL	GENITOURINARY	HEMATOLOGIC	NERVOUS SYSTEM/BRAIN	PROSTATE	SARCOMA	SKIN
INVITAE BREAST CANCER GUIDELINES-BASED PANEL	INVITAE BREAST CANCER STAT PANEL	ATM	■		■		■		■		
		BRCA1	■		■	■			■		
		BRCA2	■		■	■			■		■
		CDH1	■		■						
		CHEK2	■	■	■	■			■		
		PALB2	■		■				■		
		PTEN	■	■	■	■		■			■
		STK11	■		■						
		TP53	■	■	■	■	■	■	■	■	■
		NBN	■			■	■		■	■	
		NF1	■	■	■		■	■		■	

Invitae

Potential Results of Genetic Testing



Case Examples

2 case examples within one family

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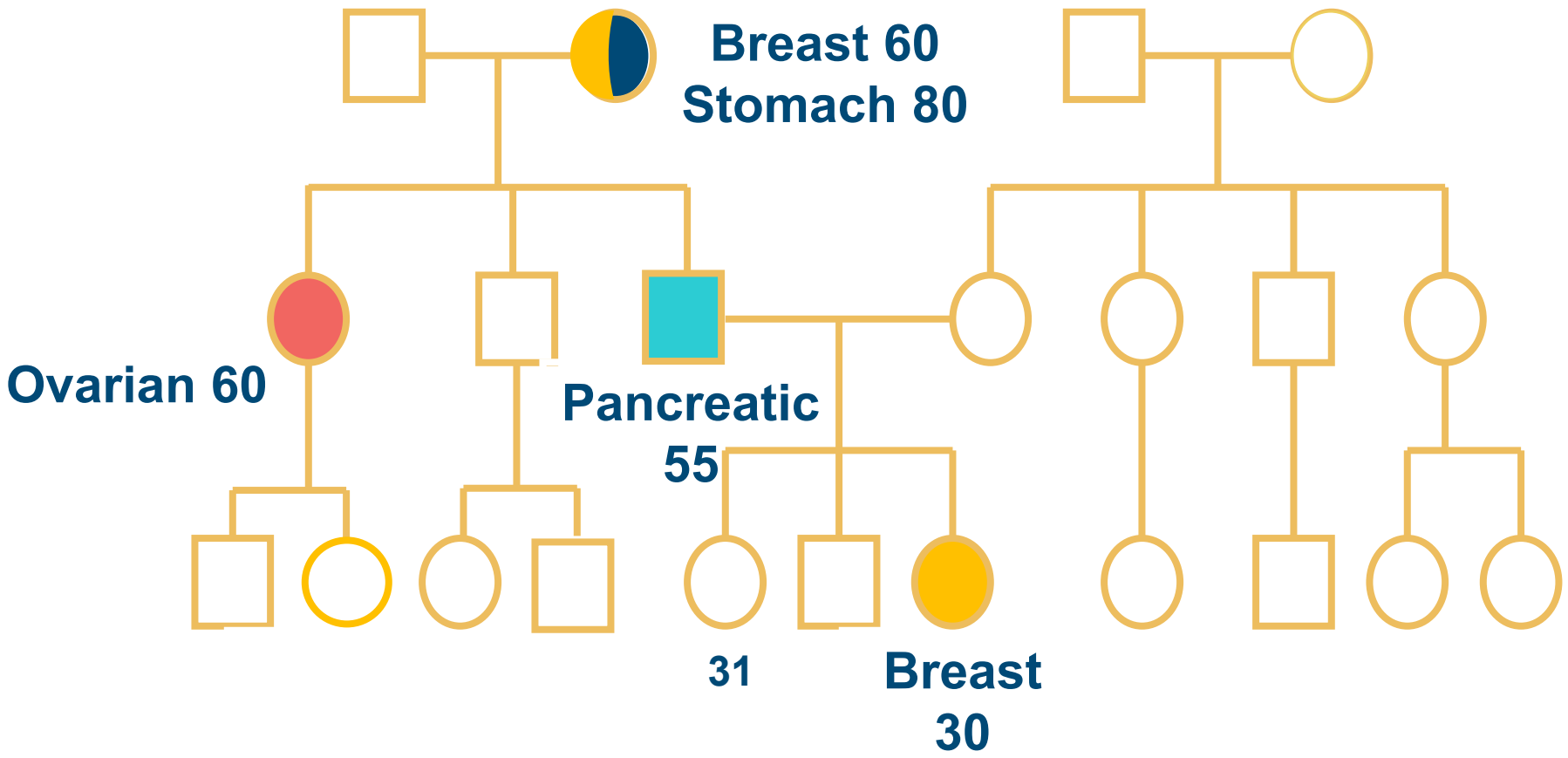
Family History Evaluation



Case 1: Affected with Pancreatic

- 55 yo male
- Presented to the ER with unintentional weight loss and abdominal pain
- Diagnosed with metastatic adenocarcinoma of the pancreas
- Port placed and is about to begin chemotherapy

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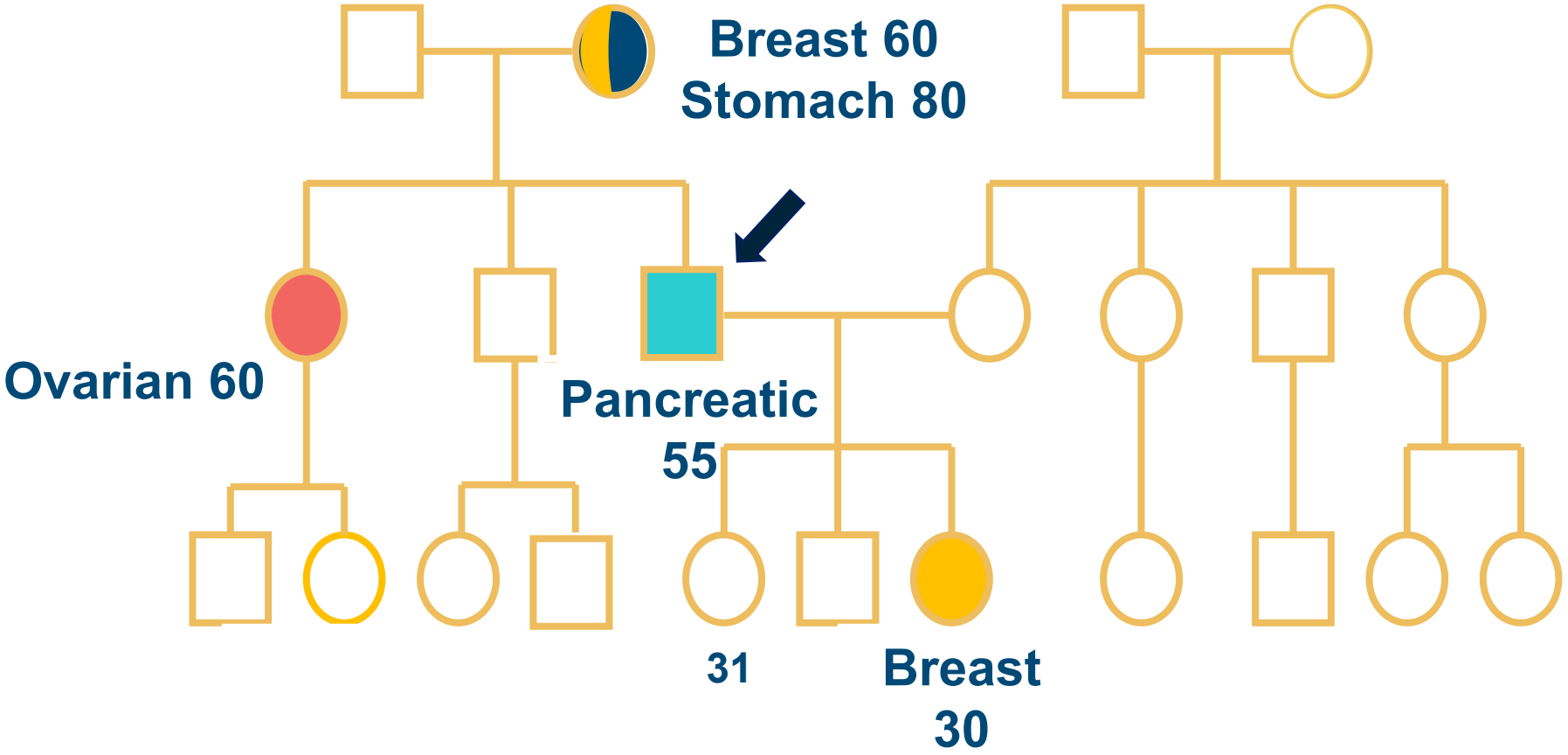
Family History Evaluation



Genetic Testing Result: BRCA2 mutation

RESULT: POSITIVE

One Pathogenic variant identified in BRCA2. BRCA2 is associated with autosomal dominant hereditary breast and ovarian cancer syndrome and autosomal recessive Fanconi anemia.

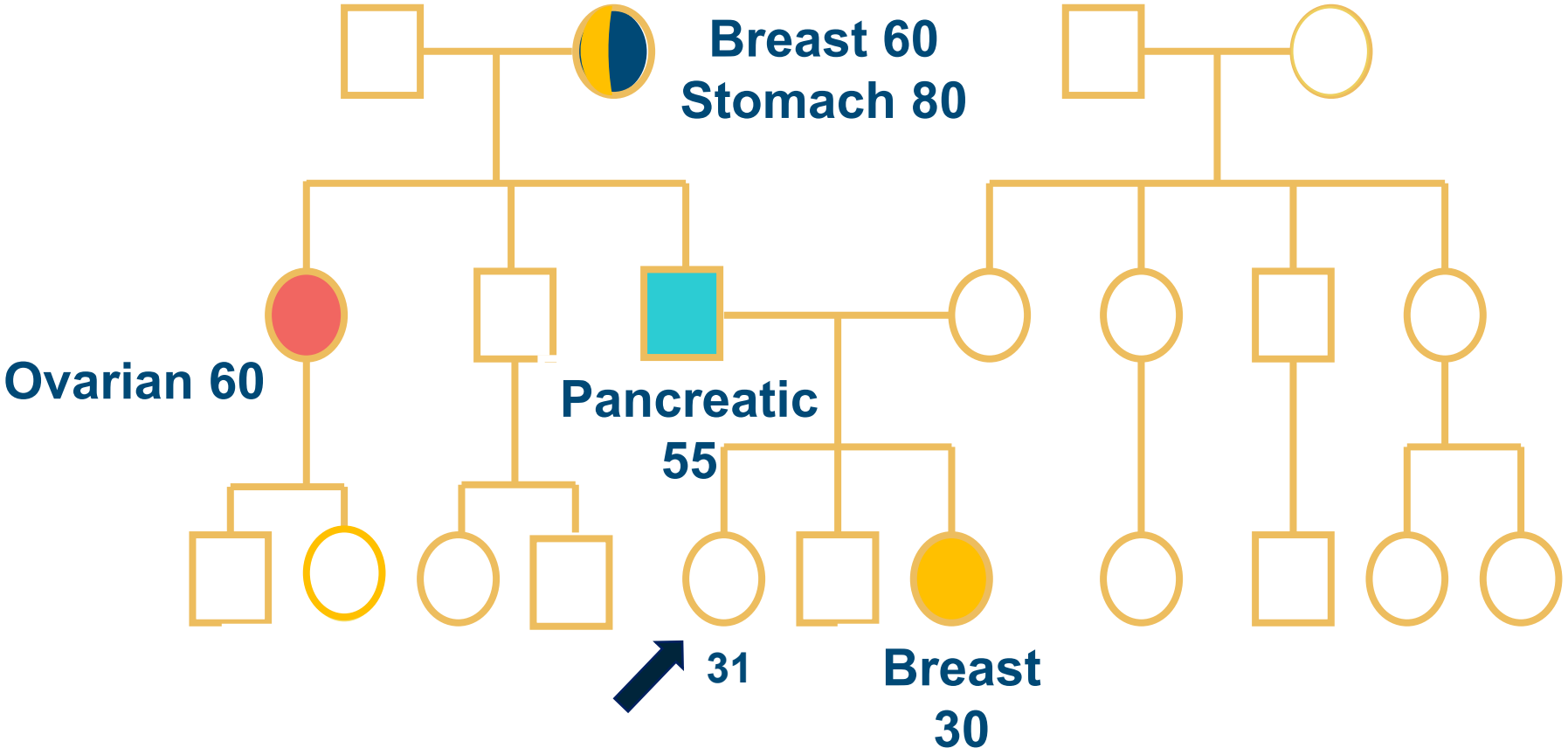
GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BRCA2	c.3744_3747del (p.Ser1248Argfs*10)	heterozygous	PATHOGENIC

BRCA2 considerations for treatment

- Consider PARP inhibitors
  - PARP inhibitors are a type of targeted cancer drug
  - PARP (poly-ADP-ribose polymerase) is an enzyme that helps damaged cells repair themselves.
  - PARP inhibitors stop the PARP from doing its repair work in cancer cells and the cell dies.
  - Cancer cells with BRCA mutations already have a poor repair system.
  - So blocking PARP can take advantage of this fact by further inhibiting cell repair in these mutation cells.

Case 2: Family History of Breast

Family History Evaluation



Family history of breast cancer

- Referral often placed by PCP or OBGYN (GCs can self-refer)
- Scheduled in a “routine” or “ASAP”
- Genetic testing discussion, best to test affected, can test unaffected, but limitations
- Risk modeling
- Counsel regarding screening implications, future risk reduction, and familial risk

Risk modeling

- IBIS risk model
  - Personal history (menarche, menopause, breast density, HRT, age at first child, etc)
  - Family history
  - Genetic test results if done
- Qualify for high-risk screening if risk greater than 20%. High-Risk screening includes MRI/mammogram yearly alternating every 6 months, can be done at High-Risk Program

Risk Model #1

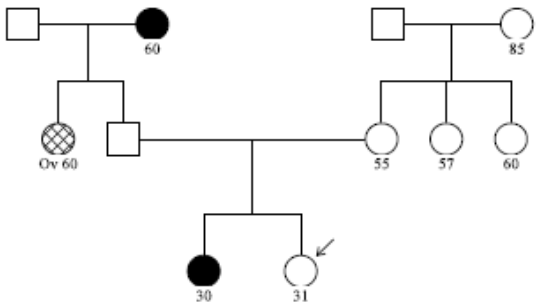
- No genetic testing
- Risk 29%
- Qualifies for high-risk screening

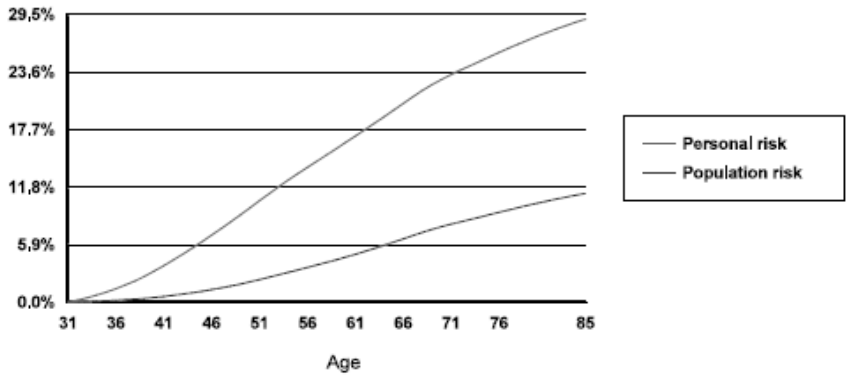
IBIS Risk Evaluation, v8

April 02, 2025

ID:
Age is 31-yrs.
Age at menarche 13-yrs.
Age at first birth 26-yrs.
Premenopausal.
Height is 1.6 m.
Weight unknown.
Never used HRT.

Competing mortality projection
Risk after 10 years is 3.7%.
10 year population risk is 0.6%.
Lifetime risk is 29%.
Lifetime population risk is 11.2%.
Probability of a BRCA1 gene is 9.88%.
Probability of a BRCA2 gene is 7.71%.





Risk Model #2

- Additional information
- Negative genetic test for patient
- Risk 20.8%
- Qualifies for high-risk screening

RESULT: NEGATIVE

About this test

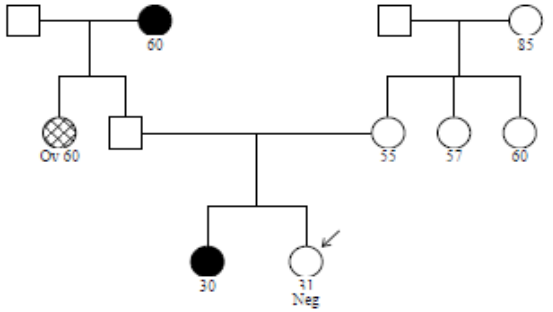
This diagnostic test evaluates 70 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

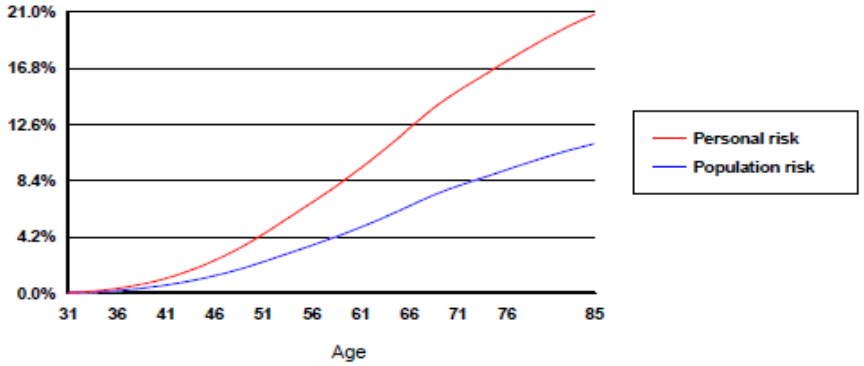
IBIS Risk Evaluation, v8

April 02, 2025

ID:
Age is 31-yrs.
Age at menarche 13-yrs.
Age at first birth 26-yrs.
Premenopausal.
Height is 1.6 m.
Weight unknown.
Never used HRT.

Competing mortality projection
Risk after 10 years is 1.1%.
10 year population risk is 0.6%.
Lifetime risk is 20.8%.
Lifetime population risk is 11.2%.
Probability of a BRCA1 gene is 0%.
Probability of a BRCA2 gene is 0%.





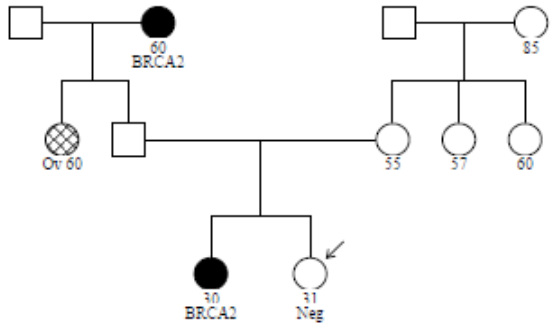
Risk Model #3

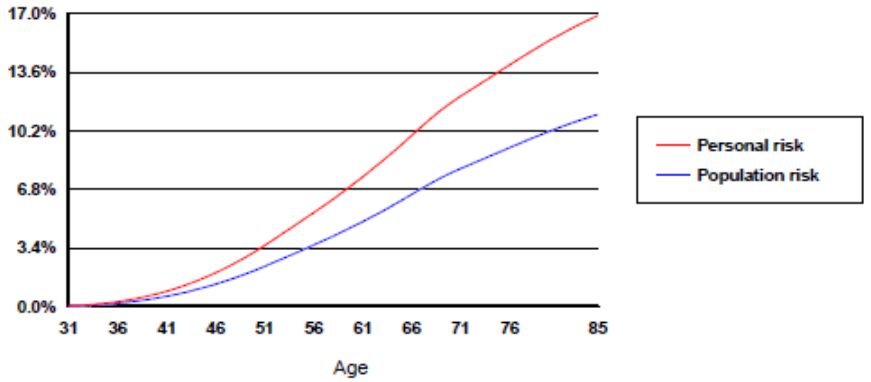
- Even more information
- Positive test results for affected relatives
- Negative result for patient
- Risk 16.9%
- Does NOT qualify for high-risk screening

IBIS Risk Evaluation, v8 — April 02, 2025

ID:
Age is 31-yrs.
Age at menarche 13-yrs.
Age at first birth 26-yrs.
Premenopausal.
Height is 1.6 m.
Weight unknown.
Never used HRT.

Competing mortality projection
Risk after 10 years is 0.9%.
10 year population risk is 0.6%.
Lifetime risk is 16.9%.
Lifetime population risk is 11.2%.
Probability of a BRCA1 gene is 0%.
Probability of a BRCA2 gene is 0%.





Does testing, BRCA2 mutation found

- With a positive genetic result, risk and management based on mutation-specific data
- No risk modeling done

RESULT: POSITIVE

One Pathogenic variant identified in BRCA2. BRCA2 is associated with autosomal dominant hereditary breast and ovarian cancer syndrome and autosomal recessive Fanconi anemia.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BRCA2	c.3744_3747del (p.Ser1248Argfs*10)	heterozygous	PATHOGENIC

NCCN guidelines for BRCA2 female

BRCA2		
Cancer risk	**Associated cancer management**	**Age to begin management**
Breast cancer 55-70% in females	Annual breast MRI and clinical exam Annual mammogram (alternating with MRI) Discuss option of risk-reducing bilateral mastectomy	Age 25 Age 30
Ovarian cancer 13-29%	Surgery to remove ovaries and fallopian tubes, consider hysterectomy	Age 40-45
Pancreatic cancer 5-10%	Annual screening only recommended with family history of pancreatic cancer, consider if no family history of pancreatic cancer	Age 50 (or 10 years younger than relative)

Other Sources of Genetic Results

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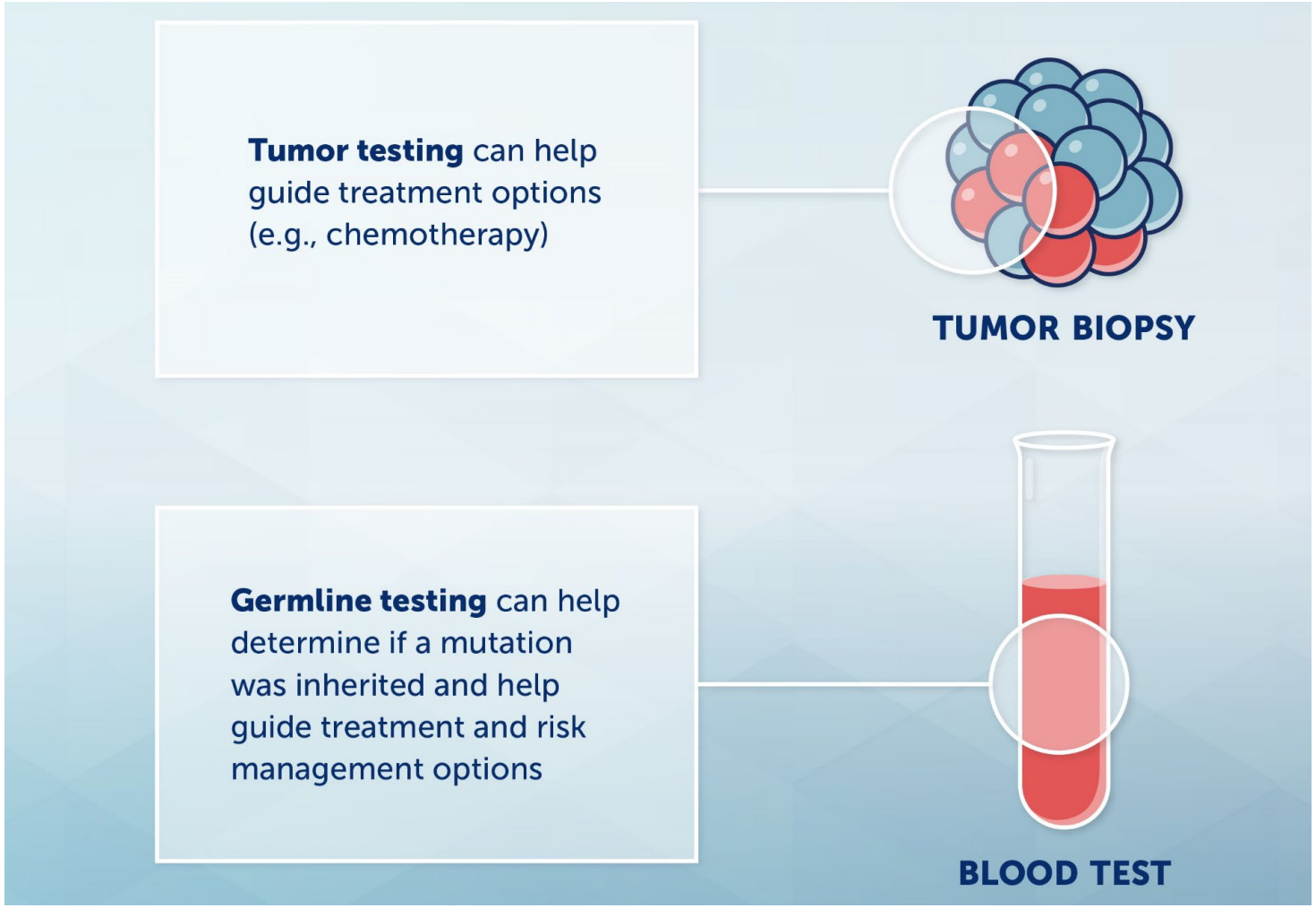
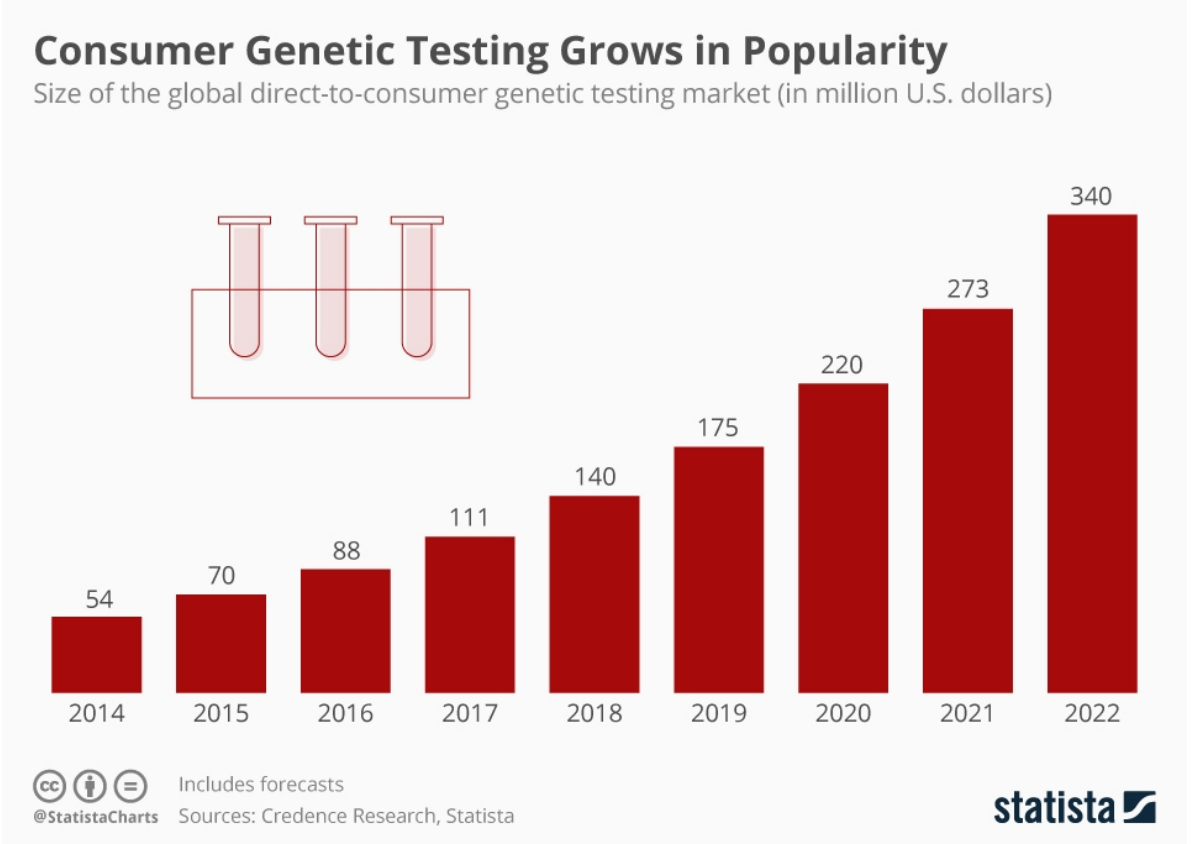
Germline vs Somatic



Direct to Consumer Tests

- **Who:**
  - AncestryDNA, FamilyTreeDNA, etc.
- **What:**
  - Tests for a selection of SNPs, think of these like flags or markers (lost key analogy)
  - Related to inherited conditions, health risks, drug responses, inherited traits, ancestry
  - Can link to family members who also did testing
- **Limitations**
  - Most risks are multifactorial
  - Clinician involvement not required
  - Unexpected results (APOE-4, 44-site BRCA1/2)
  - Overly reassured by results (44-site *BRCA1/2*)
  - Privacy concerns
  - Eurocentric data



Population-based screening

What:

- Build genetic databases for research
- Same tech as clinical testing, more limited gene panels reported out
- Can provide non-comprehensive genetic screening to patients upon request
  - Familial hypercholesterolemia (FH), hereditary breast and ovarian cancer (HBOC), and Lynch syndrome
  - Some with pharmacogenomic results reported

Who:

- Tapestry Study at Mayo Clinic
- Helix Study at HealthPartners
- All of Us Research Program at NIH

Limitations:

- Patients may require more comprehensive testing

Cell-free DNA (cfDNA) cancer screening

- **Who:**
  - Galleri
- **What:**
  - Screening test and does not diagnose cancer
  - Looks for a unique “fingerprint” of cancer by analyzing methylation patterns of cell-free DNA
  - If detected, the test predicts the most likely origin of the cancer signal, to help guide the diagnostic workup
  - Not yet FDA approved or offered by GC
- **Limitations**
  - Low sensitivity in early-stage cancers
  - Potential for false positives and negatives
  - Challenges in distinguishing cancer-derived DNA from background noise
  - Cost

Galleri®
Multi-cancer early detection

Summary

- Genetic testing for hereditary cancer is a complex, ever-evolving field
- Identifying a hereditary cause for cancer in a family can aid prevention/screening for the patient and family members
- Different types of genetic tests have different applications
- Genetic counselors are here to help!

References

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Thank You!

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