Genetic Testing Update for Cancer Survivors

Ann M. Maguire, MD, MPH, FACP

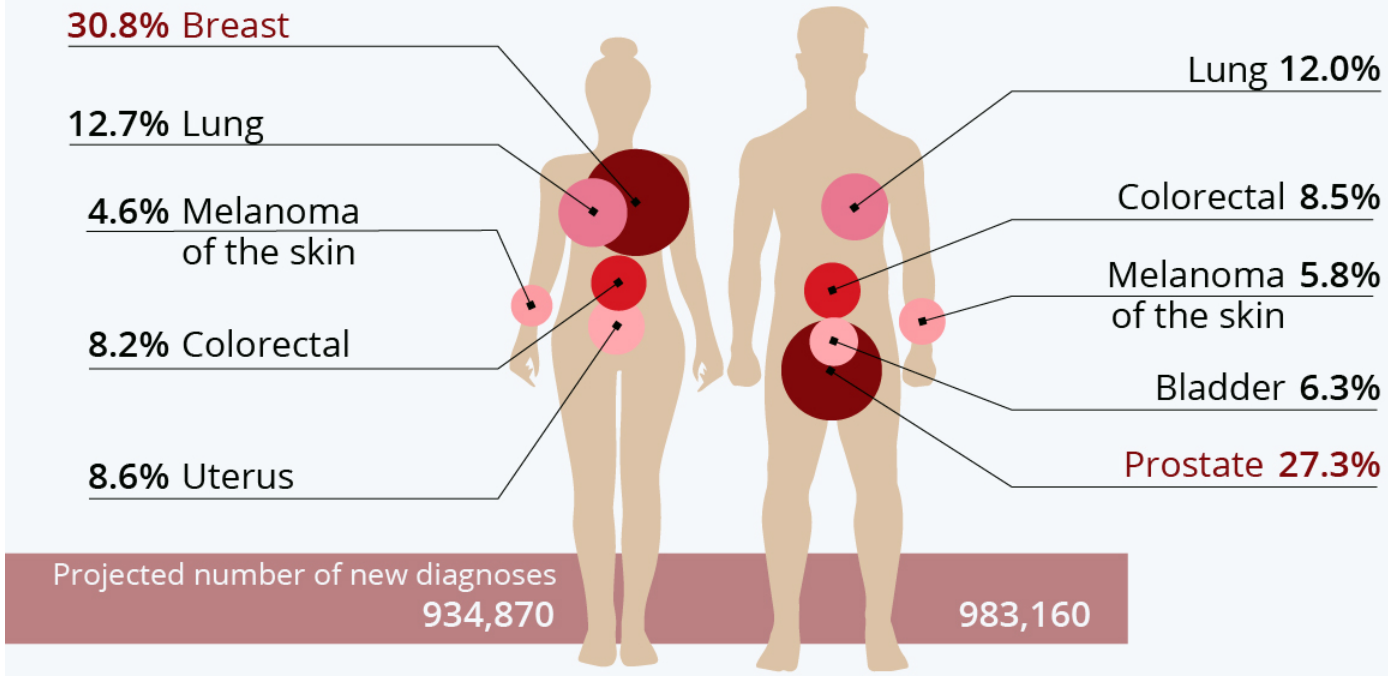
Questions

- How is cancer risk and treatment influenced by genetic factors?
- When is genetic testing appropriate for survivors with a family history of cancer?
- How do I order testing for hereditary cancer risk assessment?
- How should I advise patients choosing direct-access genetic testing?
- What is“cell free DNA” testing?

How is cancer risk and treatment influenced by genetic factors?

The Most Common Types of Cancer in the U.S.

Projected share of new cancer diagnoses in the U.S. in 2022, by gender



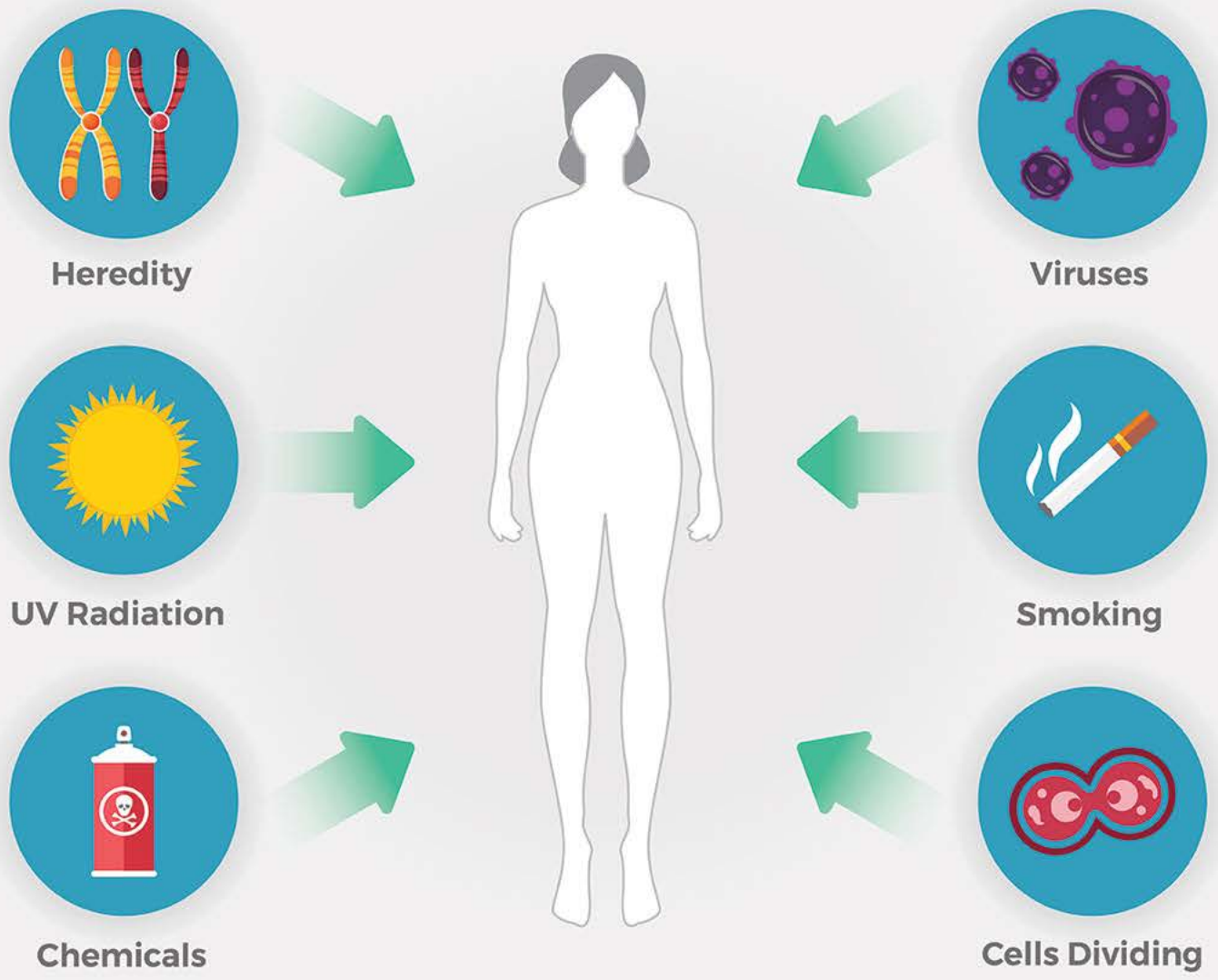
Source: American Cancer Society


THE
ANGELINA
EFFECT
Angelina Jolie's double mastectomy puts genetic testing in the spotlight. What her choice reveals about calculating risk, cost and peace of mind
BY JEFFREY KLUGER & ALICE PARK

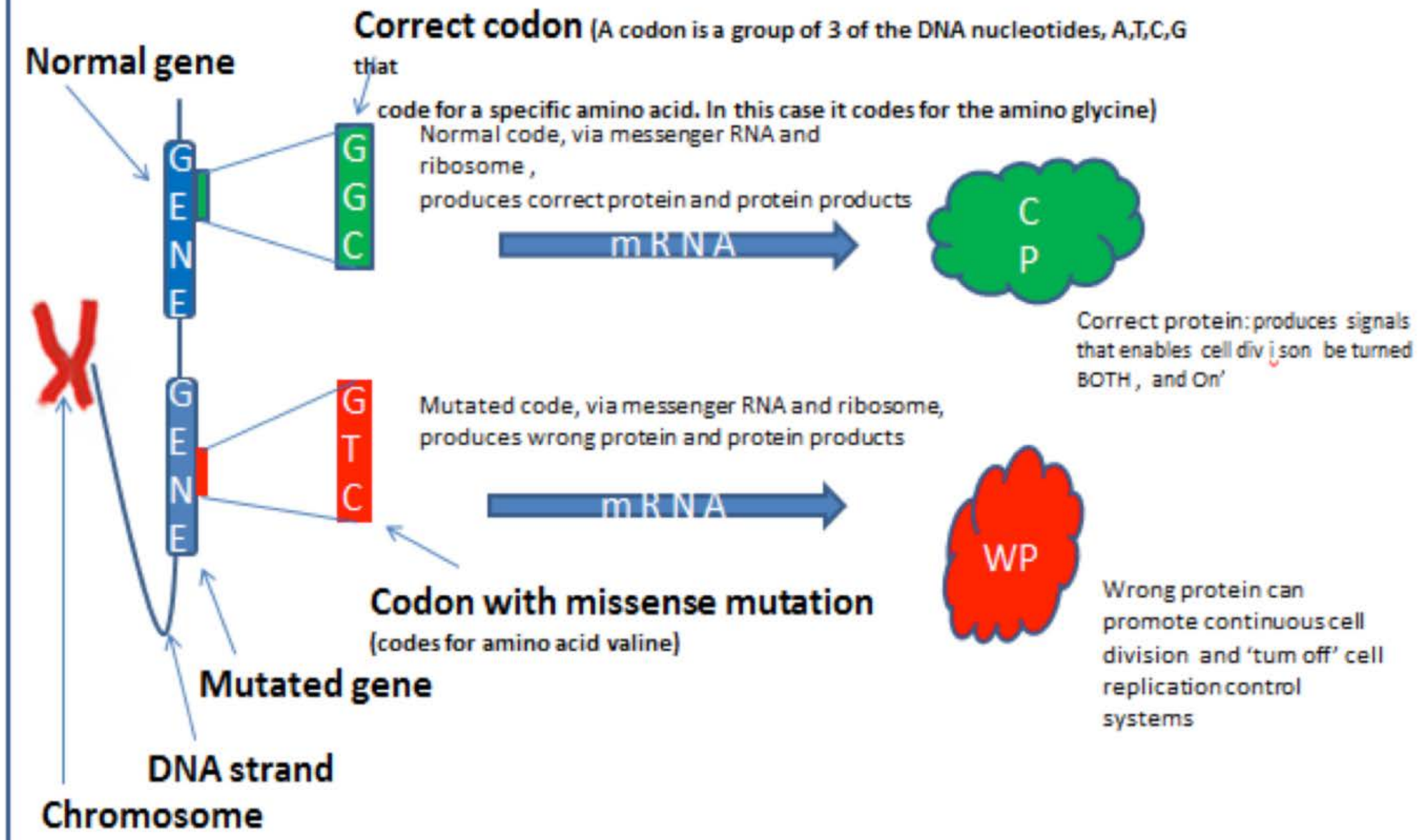
The Human Genome and Cancer

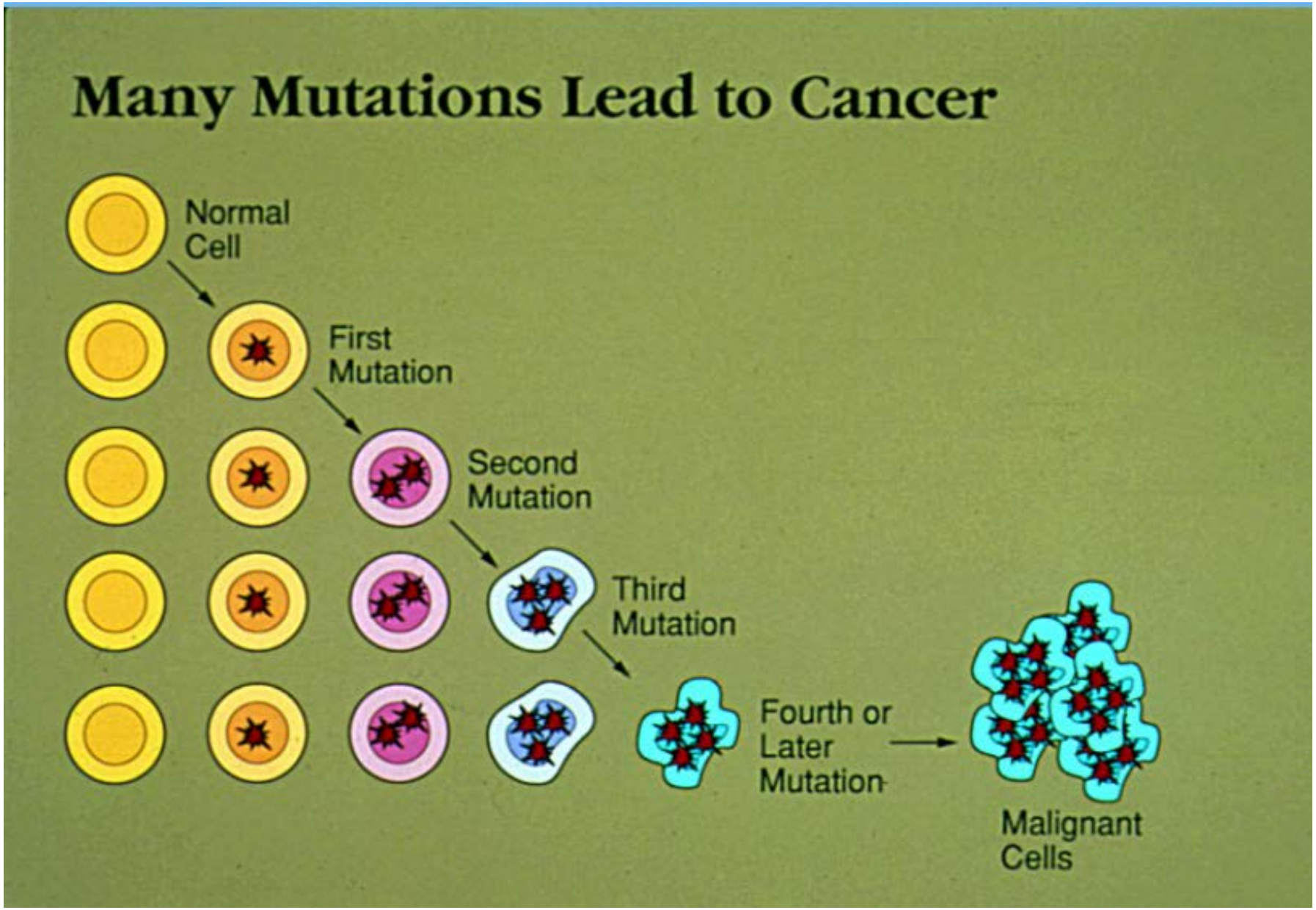
- All cancers arise from genetic alterations
- Not all genetic changes are inherited!
- About 5-10% of cancer is hereditary
- The Human Genome Project is catalyzing the discovery of cancer genes and the development of :
  - Predictive tests to identify genetic predisposition
  - Diagnostic tests to detect cancer in its earliest stages
  - Therapies that target gene abnormalities in cancer cells

What Causes Genetic Changes?

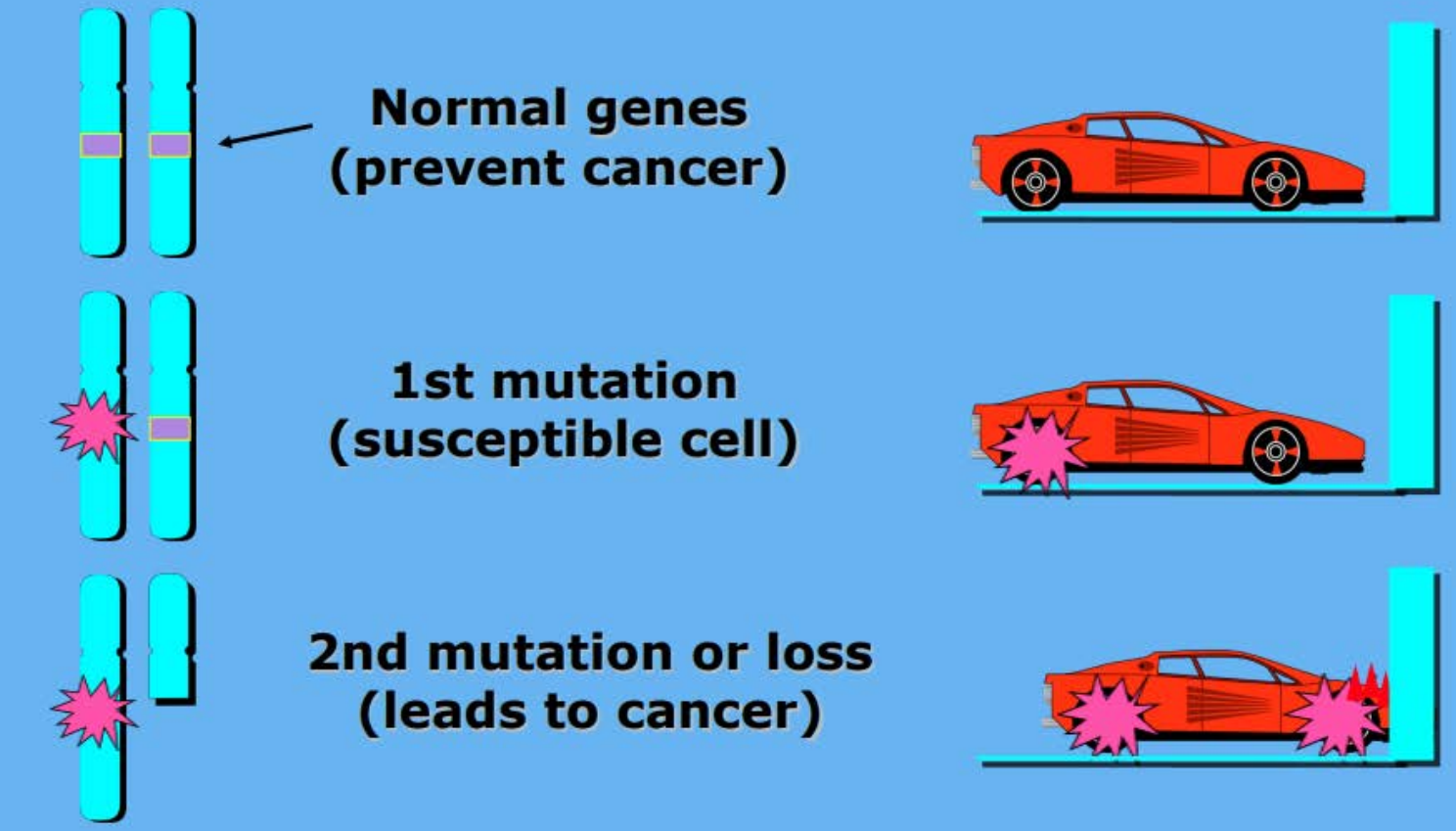


Graphic 2: a mutated gene can cause the production of a problematic protein

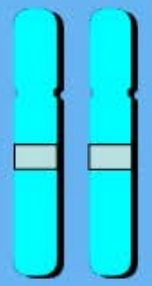



Many Mutations Lead to Cancer
Normal Cell
First Mutation
Second Mutation
Third Mutation
Fourth or Later Mutation
Malignant Cells

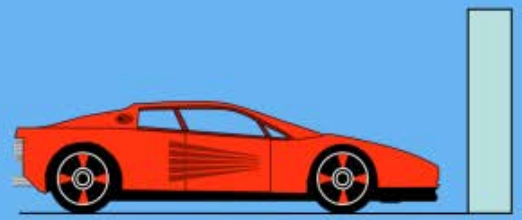
Tumor Suppressor Genes



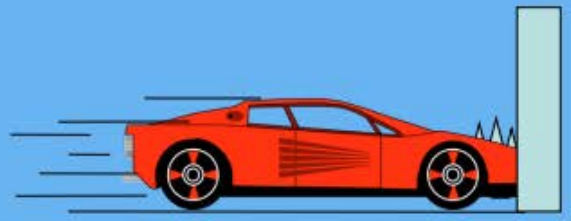
Oncogenes



Normal genes
(proto-oncogenes - regulate cell growth)



1st mutation
(oncogene - leads to accelerated cell division)

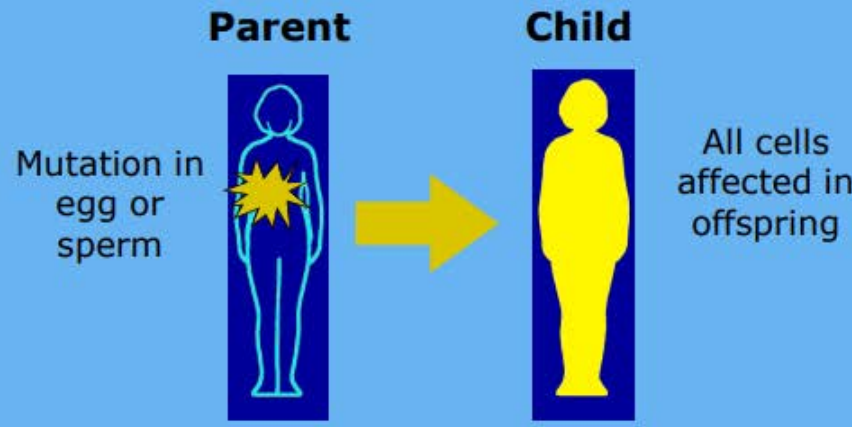


1 mutation sufficient for role in cancer development

What is the difference between Germline and Somatic genetic mutations? When should we test for each?

Cancer Arises From Gene Mutations

Germline mutations



- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Somatic mutations

- Occur in nongermline tissues
- Are nonheritable

Clinical Applications of Genomic Sequencing

Indication	Implications	Examples
Risk (Classically Germline)	Predisposition to develop future cancers	Testing for hereditary cancer syndrome pathogenic mutations
Diagnostic	Help with diagnosis of a given syndrome or cancer	Germline: *PTEN* mutations to diagnose Cowden syndrome Somatic: KRAS mutations in Cologuard colon cancer screening kits
Prognostication (Classically Somatic)	Favorable or unfavorable prognosis	Gene expression profiles that anticipate recurrence in early-stage, hormone-receptor positive breast cancer
Prediction	Response to therapy	Germline: *BRCA1/2* mutations and PARP inhibitor therapy Somatic: *BCR-ABL* fusion gene and Imatinib therapy in chronic myelogenous leukemia

When is genetic testing appropriate for survivors with a family history of cancer?

Case

- 59 year old female who was diagnosed with right invasive breast cancer at age 45.
- She was treated with a right mastectomy and prophylactic bilateral salphingo oophorectomy for preventive purposes.
- She stated that she has begun the genetic counseling process many times and “chickened out”
- She is now interested in genetic testing because she has a 25 yo daughter and is concerned about her daughter’s risk.

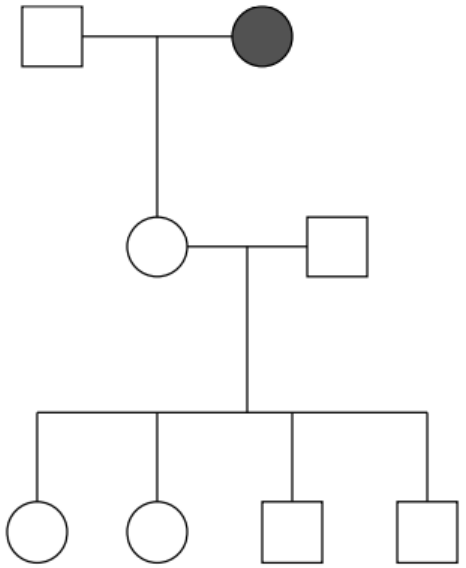
Case continued

Family History is significant as below:

• Ovarian Cancer	Mother age 50
• Pancreatic Cancer	Mother age 73
• Pancreatic Cancer	Maternal Grandfather
• Lung Cancer	Paternal Uncle
• Melanoma	Paternal Uncle

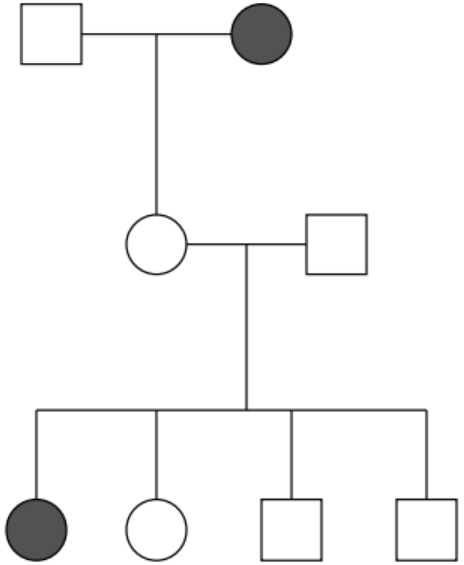
How do you advise this patient?

SPORADIC



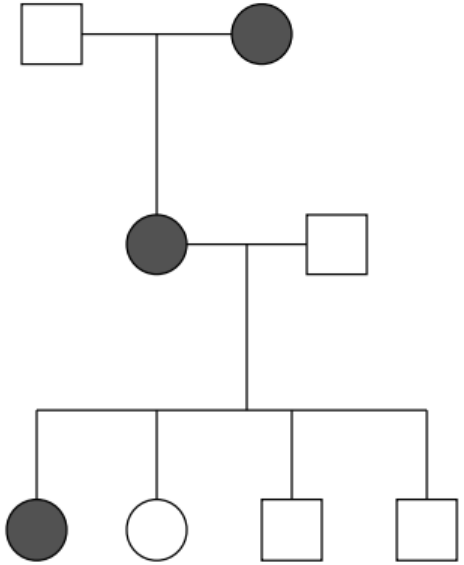
Features
Few affected family members
Caused by an accumulation of mutations throughout life
Not hereditary

FAMILIAL



Features
Clusters of cancer in a family
Genetic predisposition is not evident in the family history

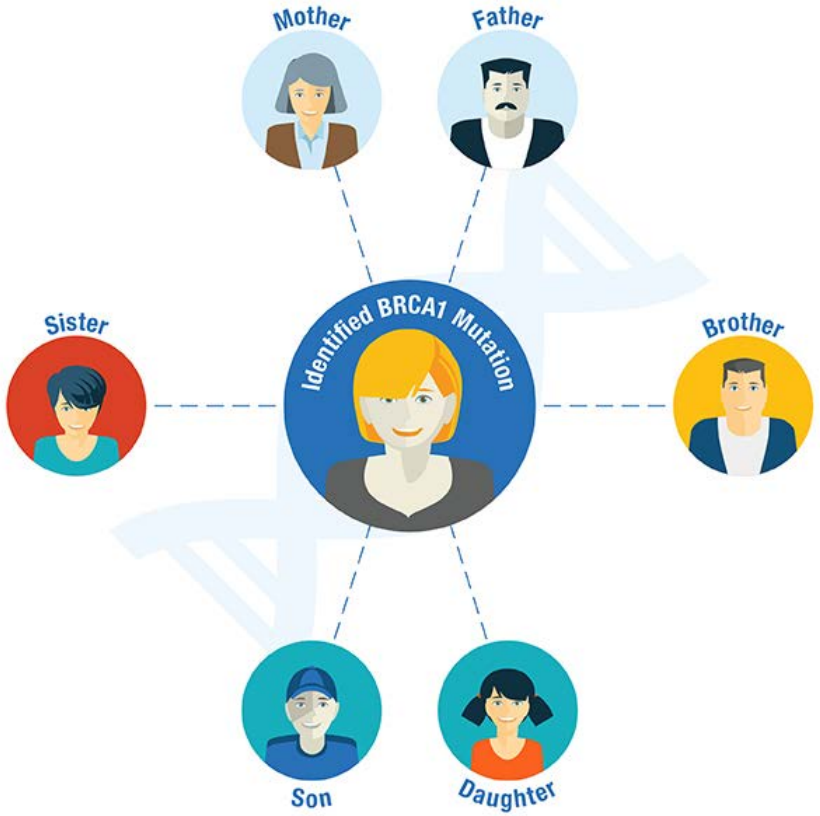
HEREDITARY



Features
Cancer in more than 2 generations
Caused by mutations in genes
Bilateral breast cancer
Multiple related cancers

Hereditary Cancer: The Importance of Family

5-10% of cancer cases are caused by genetic mutations inherited from a parent and run in families.



Parents, siblings and children have a **50% risk** to carry the same mutation.

When to suspect hereditary cancer

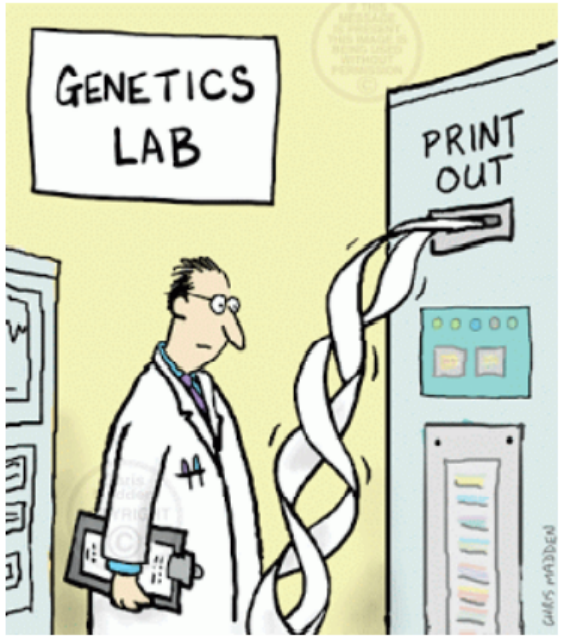
- Earlier age at diagnosis than expected
- Multiple generations with cancer
- Multiple cancers in one generation
- Rare types of cancer
- Bilaterality
- Constellation of tumors characteristic of a specific syndrome

When should genetic testing be offered?

- When there is a reasonable likelihood of identifying a cancer predisposing mutation
- When there is a genetic test available that can be adequately interpreted
- When the results will influence the patient

and/or their family's healthcare

- Patient wants information (empowerment)



ASCO, 2003; NCCN, 2021

https://www.samahope.org/dont-dna-test-just-buy-scale/

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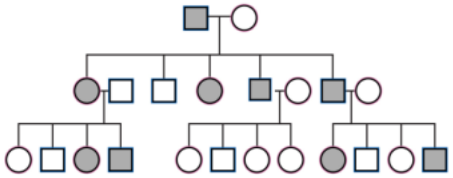
How do I order testing for hereditary cancer risk assessment?

Key Components of Genetic Cancer Risk Assessment

While models vary based on practice setting and resources, comprehensive GCRA will entail one or more consultative sessions:

Pre-test consultation



Results disclosure

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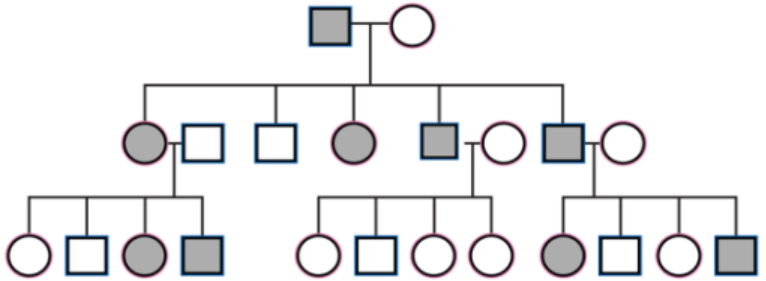
Key Components of the Pre-Test Consultation

- Engage patient & assess concerns/motivations
- Document patient and family cancer history
- Explain principles of heredity and cancer genetics
- Facilitate informed consent; initiate testing

Credit: NSGC www.findageneticcounselor.com



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Key Components of Results Disclosure

- Interpret/communicate genetic test results
- Provide personalized risk management recommendations and resources
- Facilitate adaptation and coping with impact of result
- Assist patient with plan for communication of results/recommendations with at-risk family members

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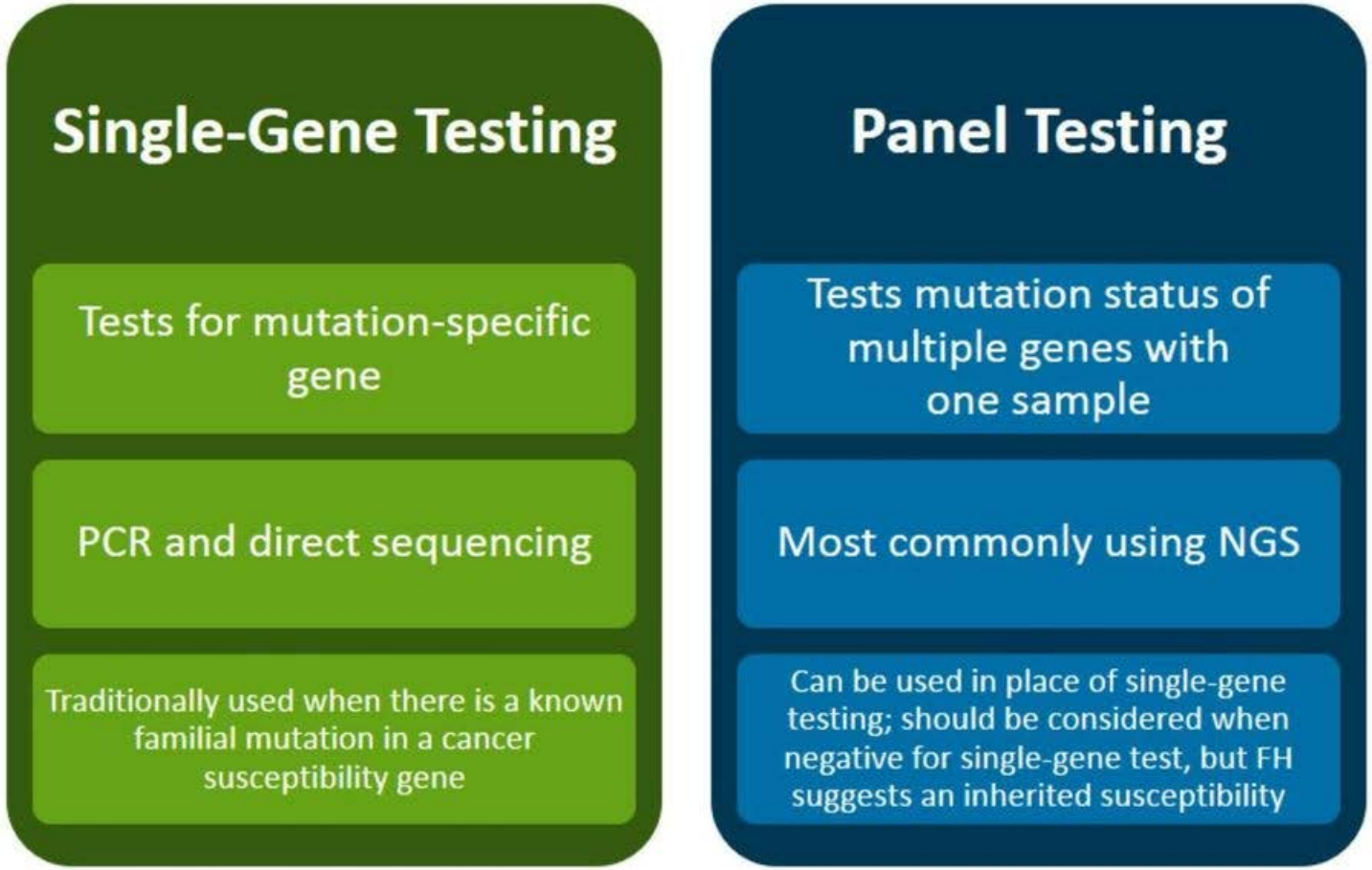
Single-Gene vs Multigene (Panel) Testing



NCCN Guidelines®. Genetic/familial high-risk assessment: breast and ovarian. Version 2.2017.

Germline Testing Panels

Testing Option	When to Use	Pros/Cons
Single Site	• Tests for specific mutation previously identified in family	• PRO: Definitive Y/N answer for family • CON: Misses potential additional mutations in family members
Single Gene(s)	• Test 1-2 genes for mutations • Tests for a single hereditary cancer syndrome	• CON: Inefficient given NGS • CON: Can be exome-based and not capture splice variants depending on testing company • CON: Misses potential additional mutations in family
Founder Mutation Panel	• Tests for specific sites commonly mutated in certain high risk populations (ex. Ashkenazi Jewish 3-site *BRCA1/2* panel)	• PRO: Population-level screening possible with fewer resources • CON: Cannot confirm true negatives w/o additional testing
Multi-gene Panel	• Test multiple genes at the same time for mutations (typically ~20 for cancer-specific, 80-100 genes for pan-cancer) • Tests for multiple hereditary cancer syndromes	• PRO: Efficient + limit retesting given NGS • CON: Panels can include/exclude genes based on their assays + the literature + ??? -> **need to actually review what is included** • PRO/CON: Variants of uncertain significance (VUS) and off-syndrome results
Whole-exome sequencing / Whole-genome sequencing	• Broadest testing available	• PRO: Most comprehensive, best for challenging cases • CON: Comparatively more expensive, long time delay, difficult to interpret results

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Germline Testing Results

Positive — *Pathogenic mutation identified* → Increased cancer risk

Negative — *No mutations identified (benign variants/polymorphisms typically not reported)* → Cancer risk based on personal/family history

VUS — *80-90% will be re-classified as benign*
No action taken → Cancer risk not yet known

Labs continue follow-up and re-contact providers
-> reach out to patients

Slide courtesy of Sarah Nielsen, Feighanne Hathaway

NCCN Guidelines

Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Guidelines

NCCN Guidelines Version 2.2022

- Additional Genetic Mutations
- BRCA-Related Breast and/or Ovarian Cancer Syndrome
- Breast and/or Ovarian Genetic Assessment
- Cowden Syndrome/PHTS
- Genetic/Familial High-Risk Assessment: Breast and Ovarian
- Hereditary Breast and/or Ovarian Cancer Syndrome
- Li-Fraumeni Syndrome
- Multi-Gene Testing

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
BRCA1	• **Absolute risk:** >60%[21-25] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence:** Very strong (with predisposition to triple-negative disease)	• **Absolute risk:** 39%–58%[26] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence:** Very strong	**Pancreatic cancer** • **Absolute risk:** ≤5% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A. • **Strength of evidence:** Strong **Prostate cancer** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: There have been a few case reports of Fanconi-like conditions in individuals with two *BRCA1* pathogenic variants.[27,28]		
BRCA2	• **Absolute risk:** >60%[21-25] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence:** Very strong (with predisposition to ER+ disease)	• **Absolute risk:** 13%–29%[26] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence:** Very strong	**Pancreatic cancer** • **Absolute risk:** 5%–10% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A. • **Strength of evidence:** Very strong **Prostate cancer and melanoma** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: Counsel for risk of autosomal recessive condition in offspring.		
BRIP1	• **Absolute risk:** Insufficient data to define • **Management:** Insufficient data; managed based on family history • **Strength of evidence:** Limited; potential increase in female breast cancer (including triple negative)[19]	• **Absolute risk:** >10%[5-7] • **Management:** ▸ Risk reduction: Consider RRSO at 45–50 y • **Strength of evidence:** Strong	**Other cancers** • Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *BRIP1* appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset of ovarian cancer.		

Footnotes on GENE-A 7 of 9 **References on GENE-A 8 of 9 and GENE-A 9 of 9**

Continued

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.

Case continued – Test results

- Our patient was tested using a multi gene panel that included all high and moderate risk Breast cancer genes.
- **The patient tested positive for a CHEK2 mutation.**
- CHEK2 is a Tumor Suppressor gene which regulates cell growth by controlling cell mitosis/ division.
- Mutations in CHEK2 lead to loss of control of cell division and ultimately can lead to cancer.
- CHEK2 is considered a “moderate risk” Breast cancer gene that also predisposes patients to other cancers.

Case continued - Surveillance

Cancer screening recommendations for this patient include:

- High risk Breast Cancer screening with mammography and Breast MRI (Strong Evidence – CHEK2)
- Colorectal Cancer screening with colonoscopy(Evidence not well established – CHEK2)
- Thyroid Cancer screening with ultrasound (CHEK2 related increased risk).
- Pancreatic Cancer screening with MRI/MRCP and Endoscopic Ultrasound based on 2 relatives with Pancreatic Cancer (1st degree and 2nd degree)

How should I advise patients choosing direct-access genetic testing?

Case

48 yo African American woman presents to establish care

Family history includes:

- Breast cancer in her sister, age 38.
- Her father died of Prostate Cancer
- Her paternal grandmother was diagnosed with Ovarian Cancer
- Her Paternal great aunt died of Pancreatic cancer after being treated for Breast Cancer.
- None of her relatives pursued genetic testing.

She received a 23&Me test kit for Christmas and was relieved to learn that she tested negative for breast cancer genes.

What do you say to this patient?

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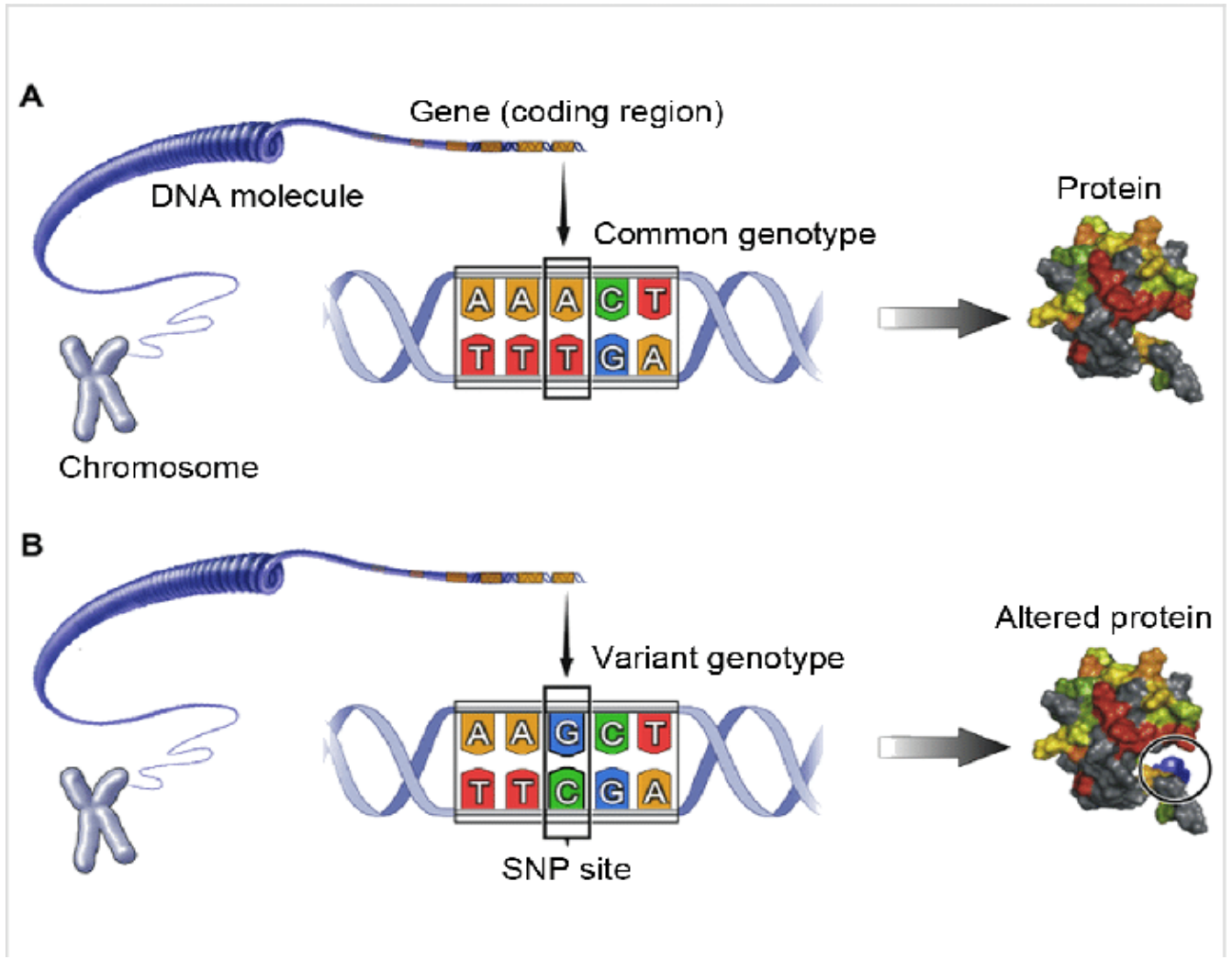
- Plus new reports and features as more discoveries are made

Direct Access Genetic Testing

- Customers send a sample and receive results directly from a secure website or in a written report
- May not involve a healthcare provider or insurance company.
- Patients can opt-in or opt-out of pre and post test genetic counseling.
- “Polygenic risk scores” allow companies to use participant data and self-reported medical history to predict risk.
- May not be generalizable to all populations
- Many vendors have “commercial partners” including pharmaceutical industry and companies that recruit for clinical trials.

Single Nucleotide Polymorphism



Problems with Direct Access testing

False positives

- Significance of VUS may be overstated

False negatives

- Many companies only test for common SNPs NOT representative of all cancer causing mutations.

  eg: Some Breast Cancer tests only screen for the 3 BRCA mutations found in Ashkenazi women

Lack of proper pre and post test counseling

- Many patients do not discuss results with their physicians.
- Testing may not change screening behaviors or outcomes.

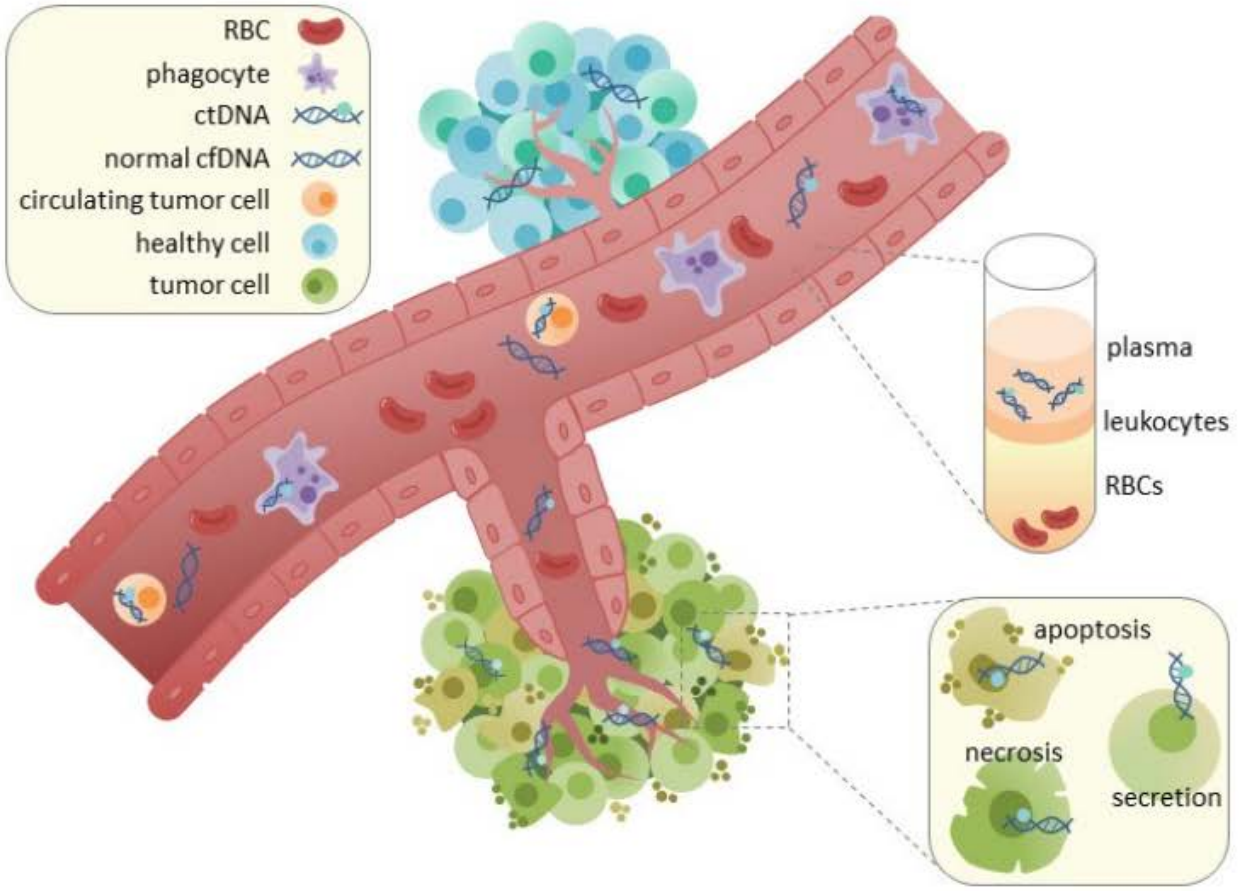
What is “cell free DNA” testing?

Case

- 54yo university professor sends a Mychart message requesting that PCP order a “blood test for breast cancer screening”.
- Multiple prior mammograms describe dense breasts and patient is concerned about the sensitivity of mammography to detect cancer
- Her Google search came up with a paper published as a “poster abstract” in a minor clinical journal recommending a commercial test for breast cancer screening.

What do you say to your patient?

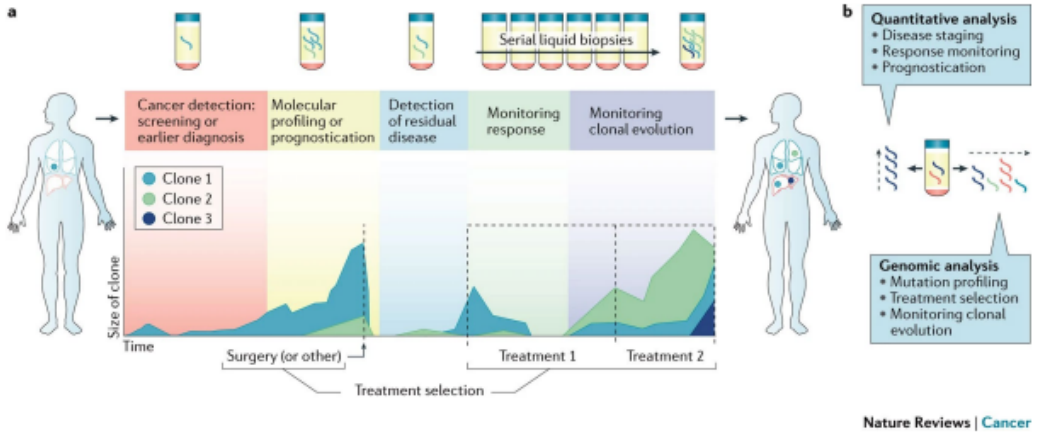
Sources of circulating DNA
Clonal hematopoiesis and ctDNA/metastatic disease



https://upload.wikimedia.org/wikipedia/commons/0/0f/CtDNA_in_circulation.png

Circulating Tumor DNA: Definition

- **Circulating tumor DNA (ctDNA):** Fragmented cell-free DNA *derived from tumor cells* in the bloodstream
  - Released material from apoptosis/necrosis of tumor cells
- Incidental capture depends on availability of tumor genome DNA
  - Most likely with large burden of metastatic disease
  - Higher sensitivity from germline testing platform



Wan et al. *Nature Reviews Cancer* 2017

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https://www.syantra.com/for-patients

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Information for patients

With a cancer diagnosis, early detection means better outcomes. It means hope. But when it comes to breast cancer, a significant portion of women have reduced opportunity for an early, life-saving diagnosis.

That's why we developed Syantra DX | Breast Cancer. A screening blood test for breast cancer that's easy, convenient, and accurate.

because every woman deserves to be sure

What is Syantra DX | Breast Cancer?

Syantra DX | Breast Cancer is an advanced, innovative precision medicine test. It measures a suite of breast cancer gene expression biomarkers from whole blood and uses algorithms developed with machine learning. It can identify invasive breast cancer at early stages, before it spreads.

A different approach to detection

Syantra DX | Breast Cancer is a screening blood test for the detection of the presence of breast cancer. The test's efficacy is rooted in three primary, innovative elements: the novel biomarker signature, unique PCR reagents and protocols, and a proprietary artificial intelligence-informed software platform.

The Syantra DX | Breast Cancer process

Learn about the Syantra DX | Breast Cancer clinical studies

Summary

- All cancers arise from genetic alterations, BUT not all of these mutations are inherited.
- Have a low threshold for referring cancer survivors who are interested in testing to a genetic counselor.
- Genetic counselors can help identify the most appropriate testing for your patient.
- Be wary of results from commercial direct access genetic testing labs.
- Use caution when ordering cell-free DNA testing – this exciting technology may not be appropriate for screening in common cancers.


Thank
you!