Adolescent & Young Adult Cancer Survivors: Hereditary Considerations

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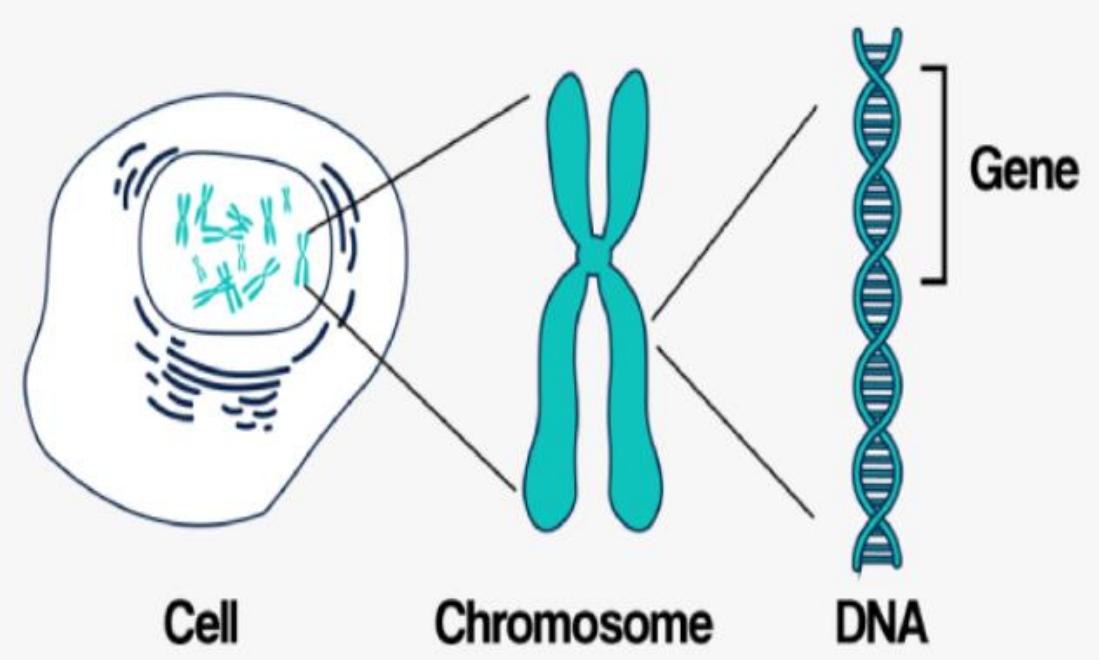
- None

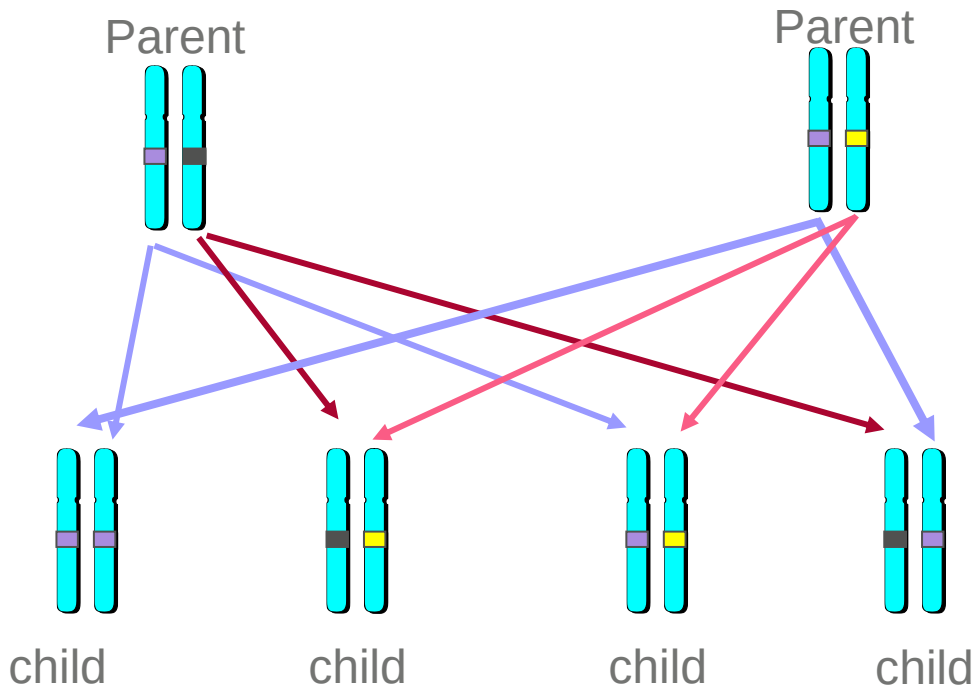
Learning objectives

- Review background information on hereditary cancer genetics
- Review utility of testing on different samples
- Review specific considerations for AYAs with a hereditary cancer syndrome

Background



Children inherit half of their genes from each parent*



*except for the genes on the X and Y chromosomes

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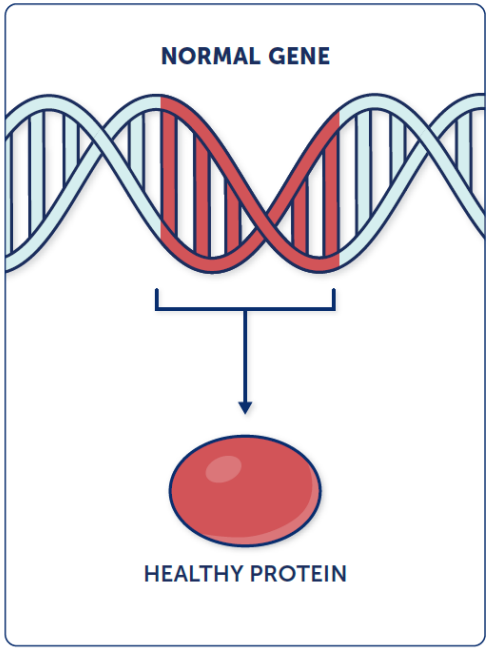
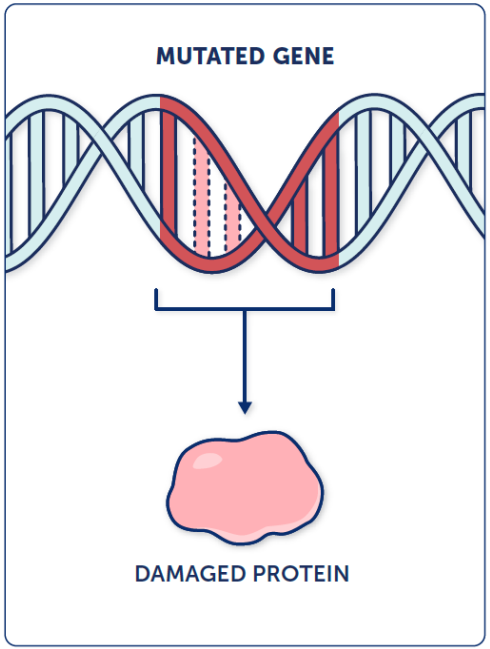
WHAT HAPPENS WHEN THERE IS A GENETIC MUTATION?





DNA analysis may be performed on different types of tissue.

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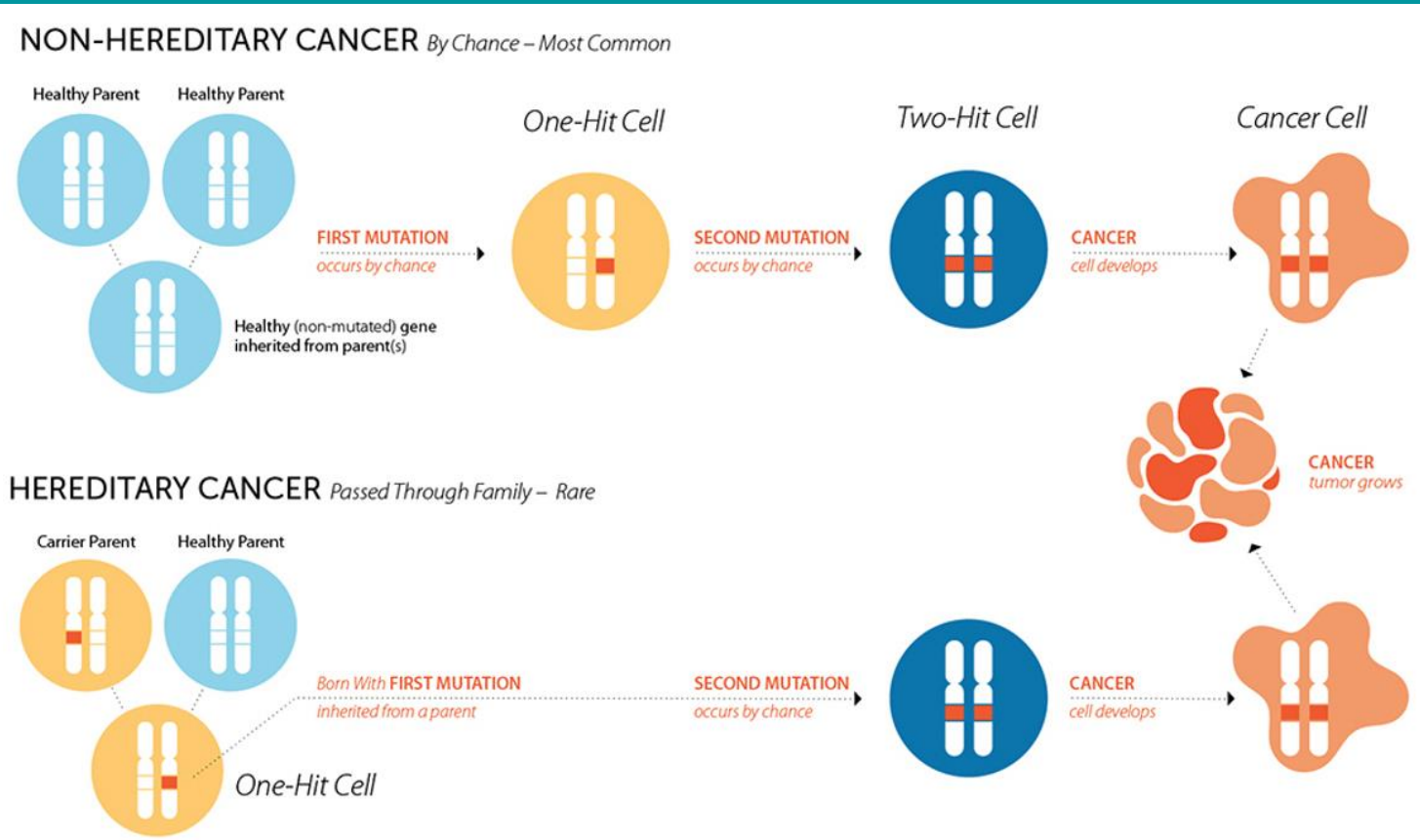

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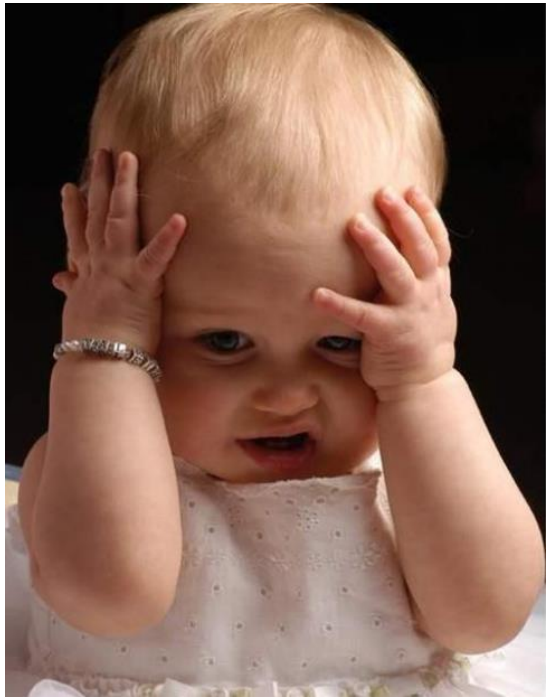
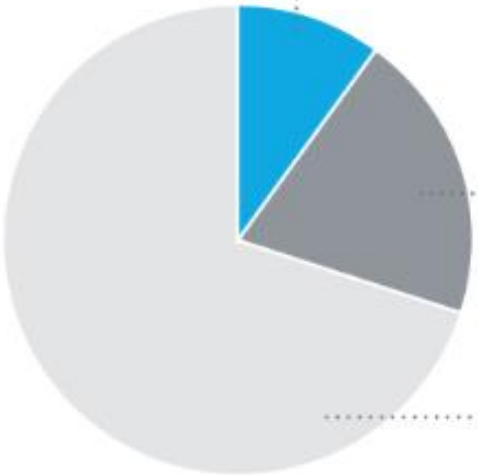


So, not all DNA mutations come from my parents?

Key Point #1

- The information gained from testing on tumor versus blood/saliva may aid in the care of the patient in different ways.

Categories of Cancer According to Cause



HEREDITARY CANCER

A clustering of cancer in a family due to inherited gene changes (mutations), which can be passed from parent to child

FAMILIAL CANCER

A clustering of cancer in a family that may be due to genes and/or other shared factors, such as environment and lifestyle

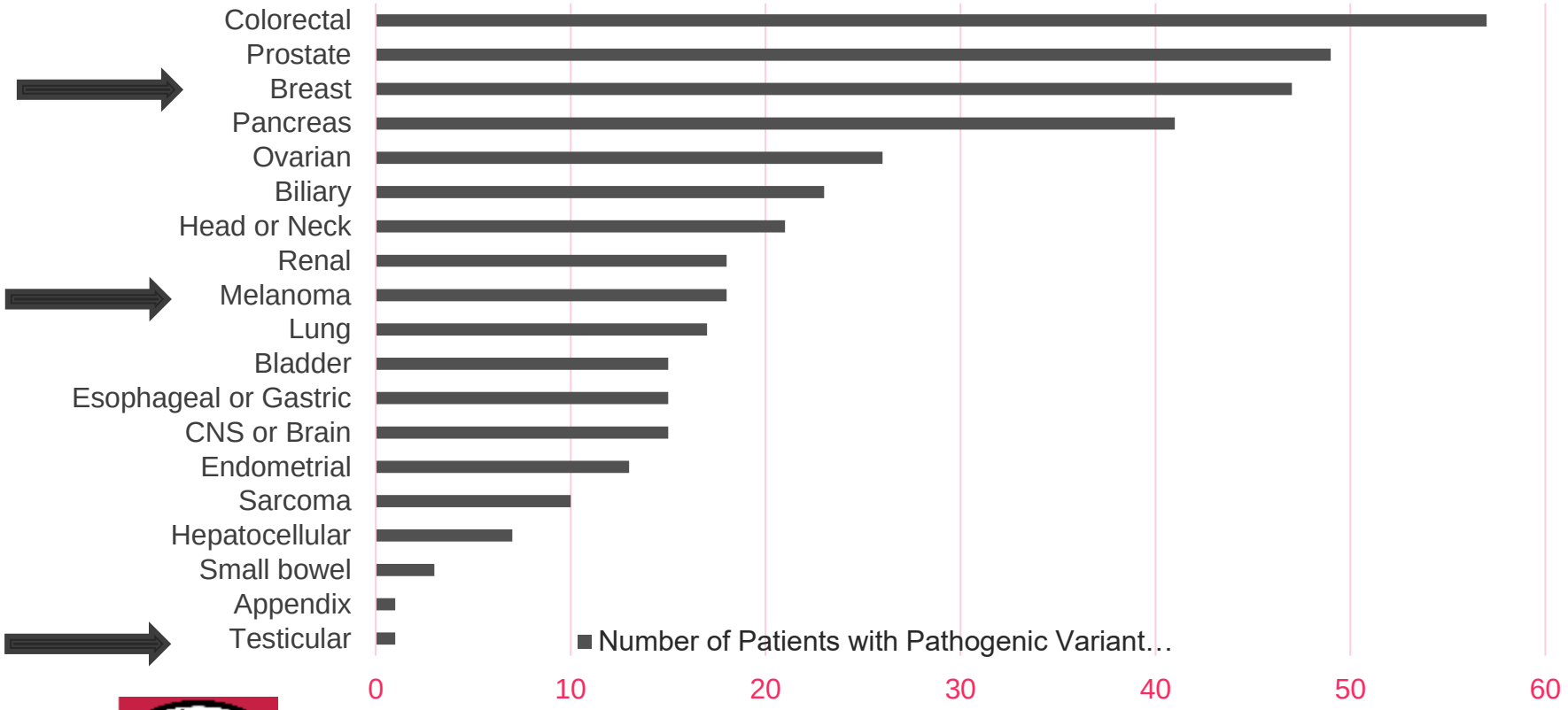
SPORADIC CANCER

Happens by chance in one or two related family members, typically at older ages

- An estimated 84,100 adolescents and young adults (AYAs) between the ages of 15 to 39 will be diagnosed with cancer in the United States in 2024. This accounts for about 4.2% of all cancer diagnoses.

- The most common cancers in adolescents and young adults (ages 15-39 years) are:
  - Breast cancer
  - Thyroid cancer
  - Testicular cancer
  - Melanoma
  - Other cancer in AYA include brain and other CNS tumors, cervical cancer, colorectal cancer, leukemia, lymphoma, and sarcomas.

Germline Pathogenic Variants Detected by Cancer Type



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Samadder NJ, Riegert-Johnson D, Boardman L, et al. *JAMA Oncol.* 2021;7(2):230–237. doi:10.1001/jamaoncol.2020.6252

Key Point #2

- A young age of diagnosis is one the possible signs of a hereditary cancer syndrome; however, cancer type must be taken into consideration.

- 1507 AYA patients with solid tumors diagnosed <29 years
- 12% had a germline pathogenic/likely pathogenic variant
- Other studies showed a 7-8% rate
- Adrenocortical carcinoma and high-grade gliomas had the highest percentage of solid tumors

Nat Commun **11**, 2206 (2020). https://doi.org/10.1038/s41467-020-16067-1

Key Point #3

- 10-15% of solid tumors have a hereditary etiology

Risk of subsequent neoplasm

- Higher risk of a second primary neoplasm
- “It is now confirmed, as well, that there is a remarkably elevated risk of secondary primary neoplasms in AYA cancer survivors who carry a germline P/LP mutation in cancer-predisposing genes compared to those who do not.”

J. Clin. Oncol. 36, 2078–2087 (2018)

Key Point #4

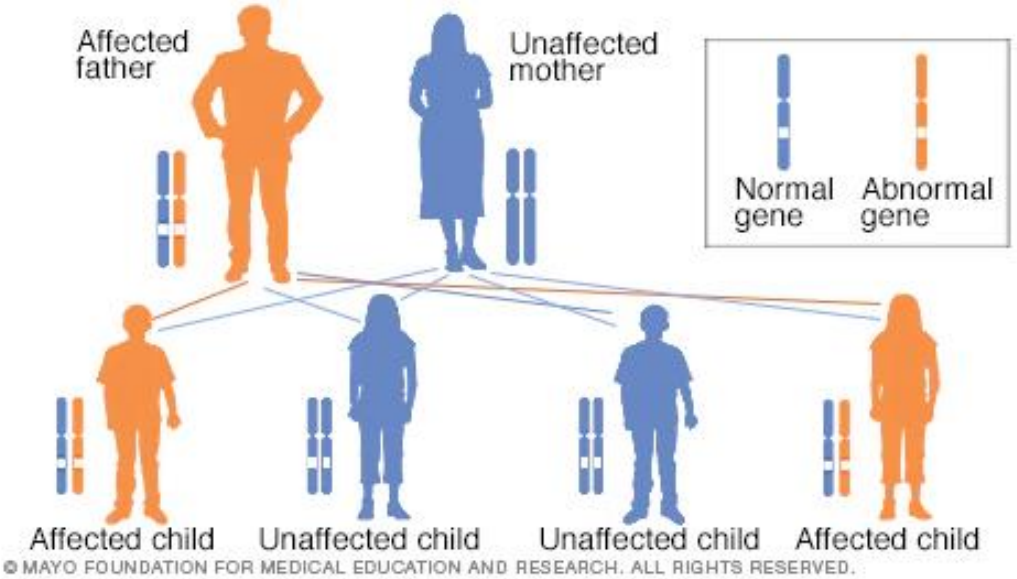
- There is a higher risk for a subsequent neoplasm for AYAs with a hereditary cancer syndrome

Considerations for AYA with hereditary cancer syndrome

- Risk of subsequent neoplasm
- Need for personalized long-term surveillance
- Potential reproductive implications
- Cascade testing of at-risk family members

Inheritance - Dominant

50% chance to pass on the mutation



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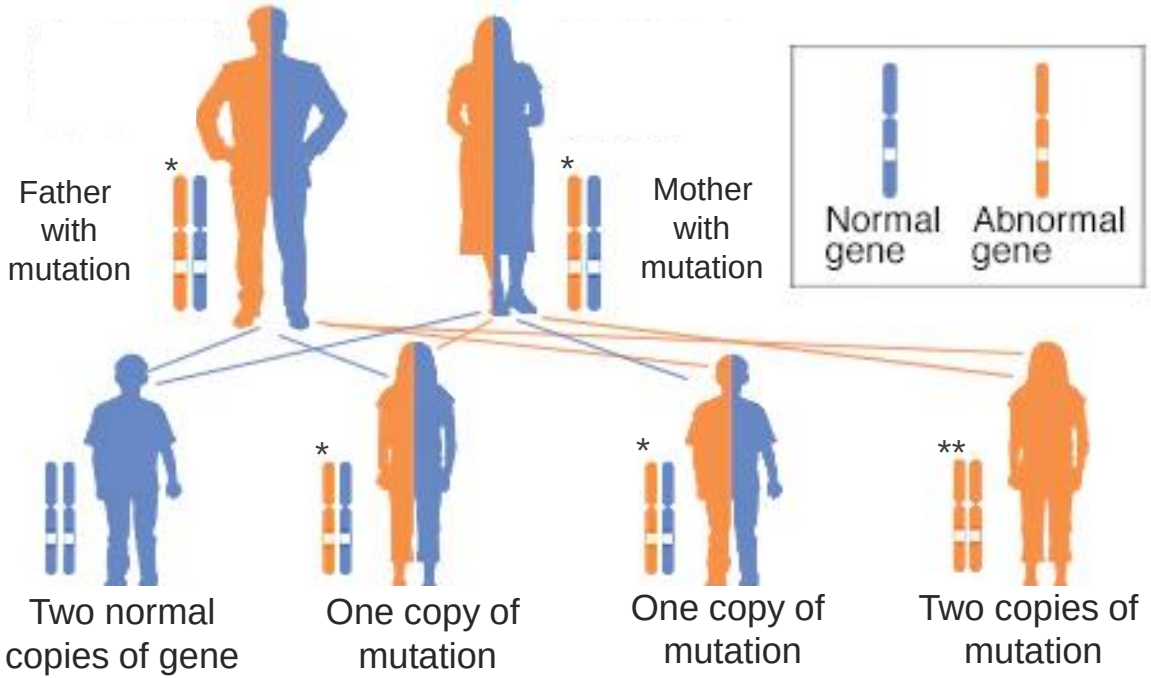
Inheritance - recessive



AUTOSOMAL RECESSIVE RISK IN CANCER GENES – MULTI-GENE PANEL TESTING

GENE and CONDITION	DESCRIPTION
ATM – Ataxia-Telangiectasia (AT)	AT is characterized by progressive cerebellar ataxia, telangiectasias, immune defects, and a predisposition to malignancy. Cells of individuals with AT are abnormally sensitive to ionizing radiation and resistant to inhibition of DNA synthesis by ionizing radiation.
BRCA1 – Fanconi anemia complementation group S (FANCS)	There are rare reports of compound heterozygous or biallelic *BRCA1* P/LP variants causing FANCS. FANCS is characterized by developmental delay apparent from infancy, short stature, microcephaly, and coarse dysmorphic features. It is associated with defective DNA repair and increased chromosomal breakage.
BRCA2 – Fanconi anemia complementation group D1	FA is characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. Bone marrow failure with pancytopenia often presents in the first decade of life. Adults with biallelic *BRCA2* (one allele hypomorphic) are reported. Biallelic PVs in *BRCA2* are associated with early-onset acute leukemia and solid tumors.
BRIP1 – Fanconi anemia complementation group J (FANCJ)	FA is characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. Bone marrow failure with pancytopenia often presents in the first decade of life.
MLH1, *MSH2*, *MSH6*, *PMS2*, *EPCAM* – CMMRD	CMMRD is a childhood cancer predisposition syndrome characterized by hematologic malignancies, brain/CNS tumors, colorectal tumors and multiple intestinal polyps, and other malignancies including embryonic tumors and rhabdomyosarcoma.
PALB2 – Fanconi anemia complementation group N (FANCN)	FA is characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and an increased lifetime risk of cancer. Bone marrow failure with pancytopenia often presents in the first decade of life. Biallelic PVs in *PALB2* are associated with solid tumors, such as medulloblastomas and Wilms tumors.
RAD51C – Fanconi anemia complementation group O	FA is characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. Bone marrow failure with pancytopenia often presents in the first decade of life.

Reproductive implications

- Patients of reproductive age should also be advised about prenatal diagnosis and assisted reproduction and partners should be tested in case of identification of PV/LPV in genes associated with rare autosomal recessive conditions, such as Fanconi anemia

Key Point #5

- Patients of reproductive age should be advised of the modes of inheritance (AD, AR), risk to offspring, partner testing, and prenatal/preimplantation testing options.

Emotional distress

- May be influenced by
  - Disease characteristics
  - Prenatal/preimplantation testing options
  - Discrimination
  - Social support
  - Coping mechanisms
  - Perception of risk
  - History of cancer in the family

Predictive testing in minors

- Traditionally deferred if there is no preventative or therapeutic measures
- When possible, obtain assent of minor
- Discuss how/when patient will be informed of test results
- Consider maturity of adolescent and their desire to know/not know
- Discuss perceived challenges and benefits of cancer screening

- The family's experiences with a hereditary cancer syndrome has been shown to be an important predictor of one's personal risk perception.
- The opportunity to receive accurate, updated medical information at regular intervals is important, particularly as adolescents reach an age when they will assume responsibility for their own health

Key point #6

- Predictive testing in minors is a detailed pre-test conversation which addresses not only the scientific facts but also the psychosocial components. This conversation also includes a discussion of the long-term plan.

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