

A decorative graphic in the top left corner consisting of a cluster of dots in various shades of blue, orange, and grey, arranged in a roughly circular pattern.

The Connection Between Genetics and Prostate Cancer: Focus on BRCA Gene Mutations

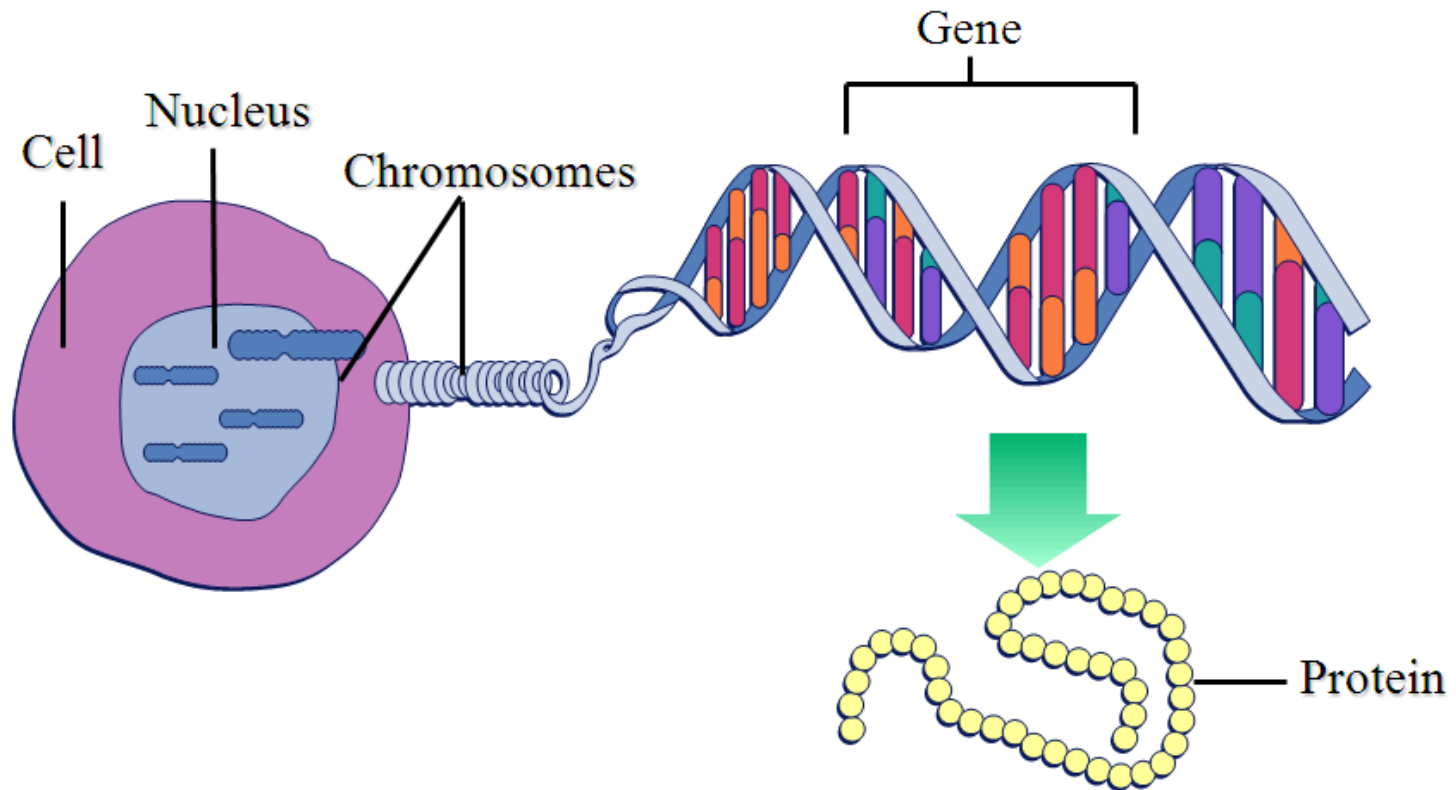
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Medical Science Liaison – Urology
Myriad Genetics Laboratories



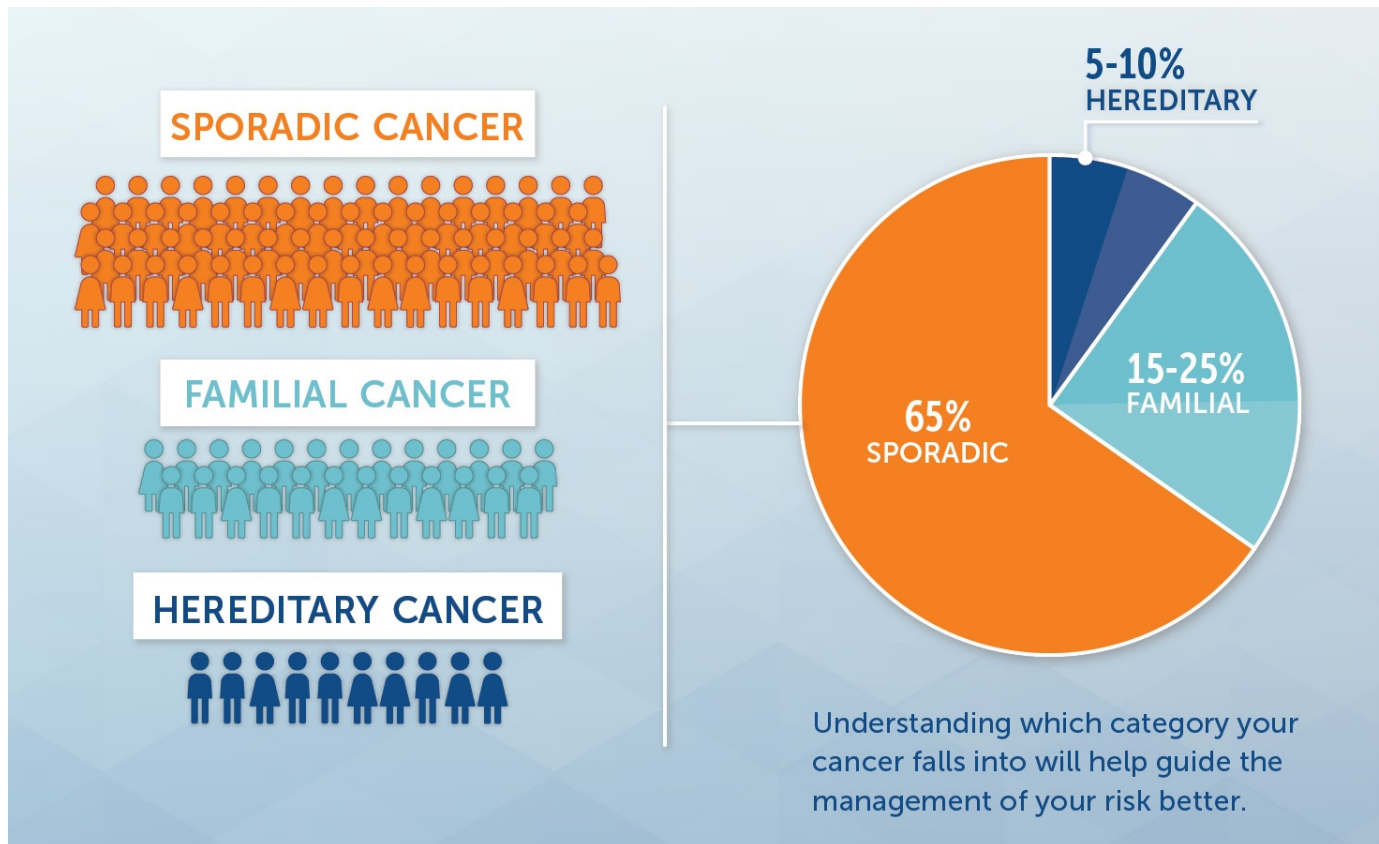
Agenda

- Genes overview
- Genetic mutations
- Personalized treatment decisions
- Indicators for genetic testing
- Importance of genetic testing

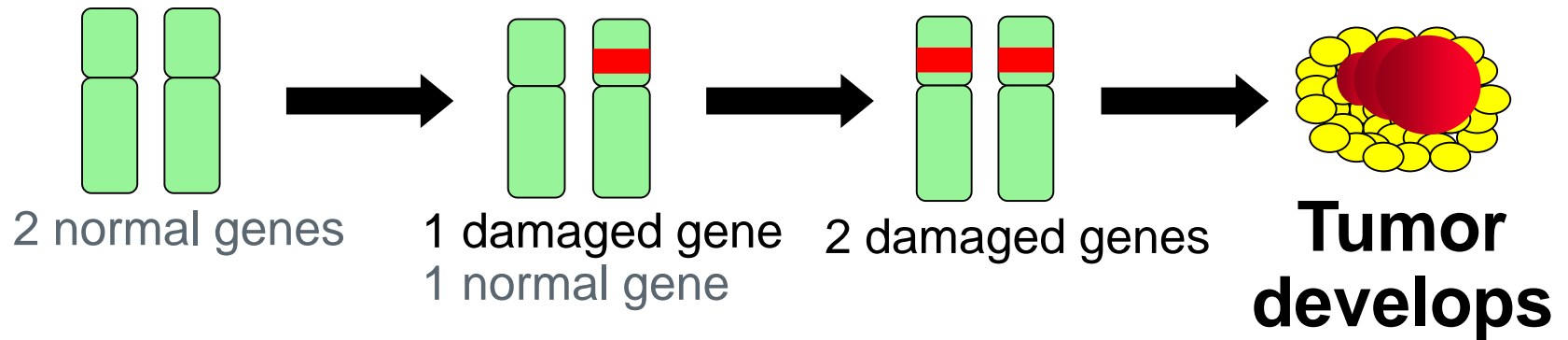
Genes Contain Instructions for Making Proteins



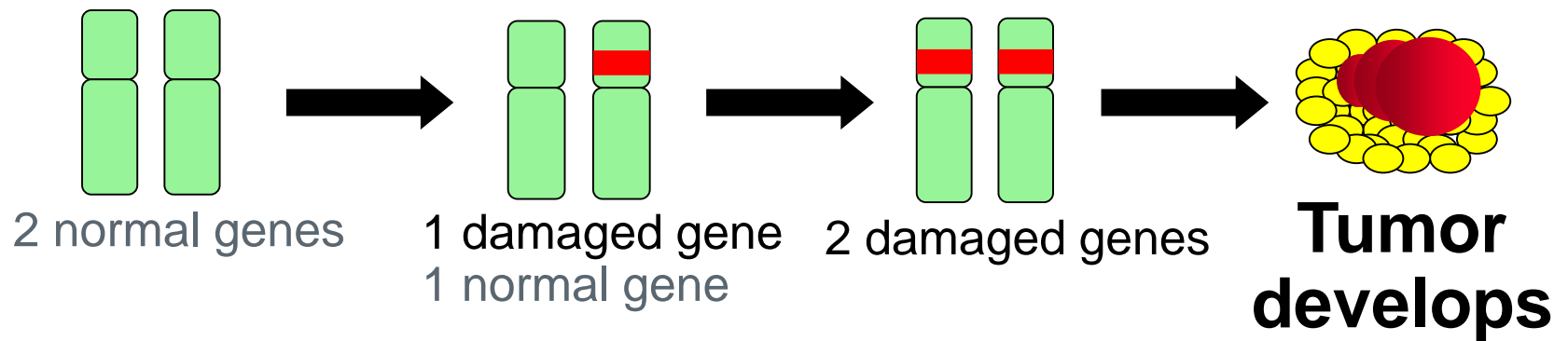
Cancer can be Hereditary, Familial or Sporadic



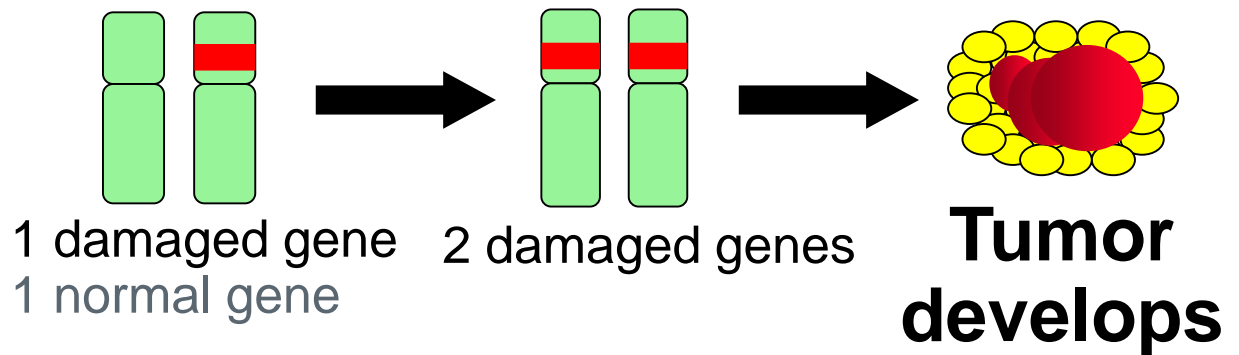
Development of Sporadic and Hereditary Cancer



Development of Sporadic and Hereditary Cancer

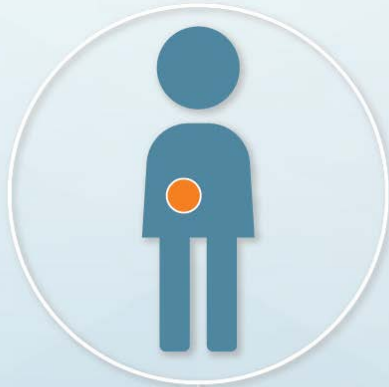


In hereditary cancer, one damaged gene is inherited.





Genetics: Somatic vs Germline Mutations



SOMATIC MUTATION

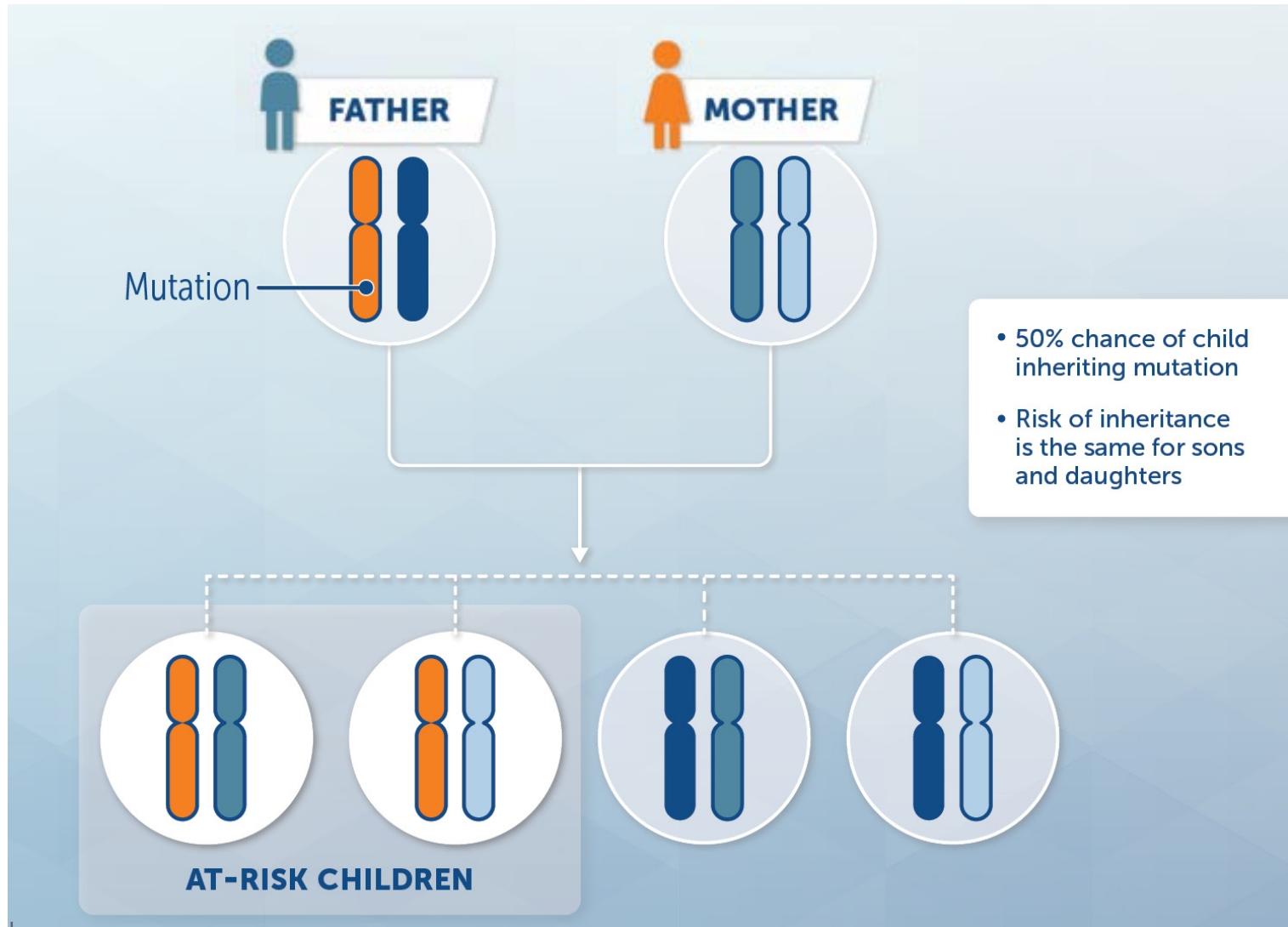
- Every cancer has many somatic mutations.
- A **somatic mutation** is a change in the gene that arose in the tumor and is confined to the tumor.
- Most cancer is sporadic (i.e., it happened by chance).



GERMLINE MUTATION

- A **germline mutation** is a change in the gene that was inherited and therefore causes an increased risk for cancer.
- This is also known as **hereditary cancer**.
- Only around 10% of cancer is hereditary.

Inheritance of Hereditary Cancer Risk





Familial and Hereditary Prostate Cancer

- Prostate cancer is rarely diagnosed in men <50 years old, but then increases rapidly
- Other than age, the strongest risk factor for prostate cancer is a family history of prostate cancer
 - Suggests importance of genetic factors in disease development
- Genes currently associated with an increased risk for prostate cancer
 - *BRCA1/BRCA2*
 - MMR genes (Lynch syndrome)
 - *ATM*
 - *CHEK2*
 - *TP53*
 - *NBN*
 - *HOXB13*
 - Several others



Background on BRCA Genes

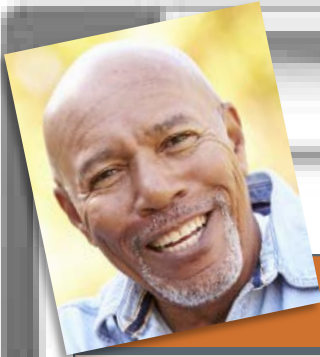
- Myriad discovered the *BRCA1* and *BRCA2* genes in the early 2000s
- The BRCA genes, along with other genes, are very important in helping to repair damaged DNA
- When these genes are altered (have a mutation) DNA damage may not be repaired properly
- Additional genetic mutations continue to build up which can lead to cancer

Why is Genetic Testing Important to You?

- Impact on treatment decisions for current prostate cancer
- Identify second cancer risks and management strategies
- Identify family members at hereditary risk



How does genetic testing impact Gene?



Gene

Patient Age: 67

Clinical Stage: T1c

PSA prior to Biopsy: 6.3

Gleason Score: 3 + 4 = 7

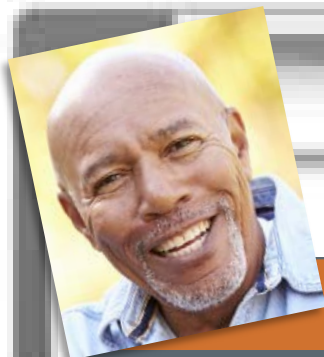
AUA Risk Classification:
Favorable Intermediate

Family History

Relative	Cancer Site	Age of DX
Father	Prostate	63
Sister	Breast	49

Gene has a Gleason Score of 3+4 and could consider a radical prostatectomy. However, Gene is also a candidate for active surveillance and is interested in this option.

The urologist also notes that Gene has a family history of cancer and orders hereditary cancer testing....



Gene

Patient Age: 67

Clinical Stage: T1c

PSA prior to Biopsy: 6.3

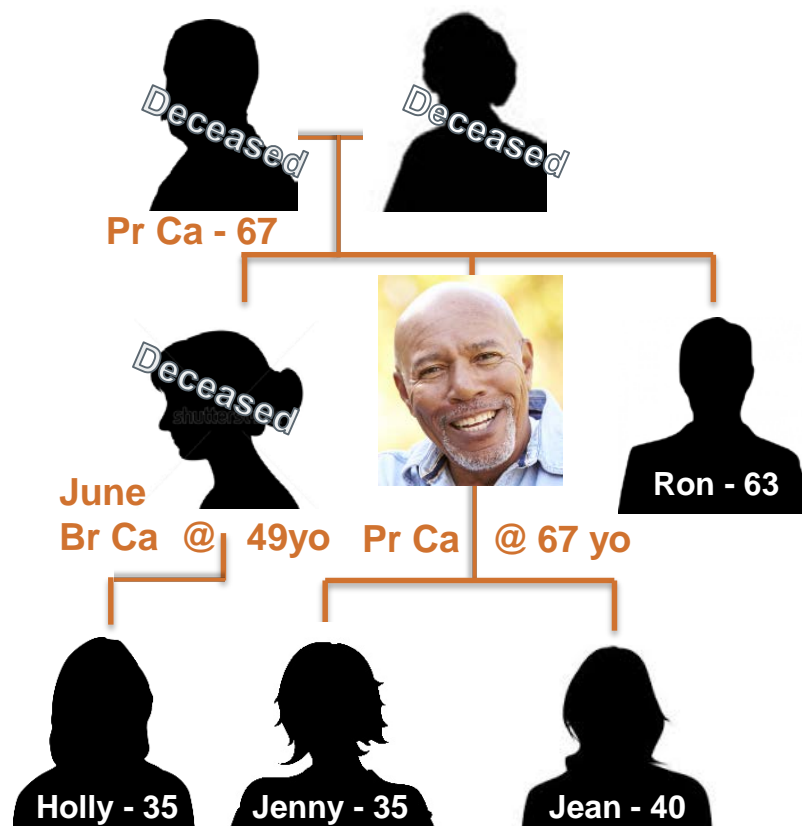
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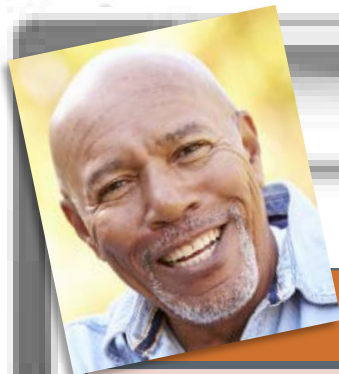
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Based on recent studies and Gene's family history, the urologist orders a multi-gene hereditary cancer test





Gene

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Gene has a mutation in the *BRCA2* gene

- Treatment Impact: Based on studies that *BRCA*-associated prostate cancers are more likely to be lethal, active surveillance may not be the best choice for Gene
 - Gene and his urologist agree on a radical prostatectomy
 - On the small chance Gene progresses to metastatic cancer, targeted therapies may be available based on his *BRCA2* status



BRCA-Related Prostate Cancer is more Aggressive

Clinicopathologic Features	BRCA carriers	Non-carriers
Gleason ≥ 8	35%	15%
T3/T4	37%	28%
Nodal Involvement	15%	5%
Metastatic	18%	9%

Outcome	BRCA carriers	Non-carriers
Disease Specific Survival	8.6 years	15.7 years
Overall Survival	8.1 years	12.9 years
Localized PCa 5 year DSM	18%	4%
Localized PCa 5 year Metastasis	23%	7%



Personalized Prostate Cancer Treatment

- Patients with germline **BRCA mutations** may respond much better to **platinum-based chemotherapy** for metastatic disease
 - Trials underway in prostate cancer
- Patients with germline mutations in **Lynch syndrome genes** (mismatch repair) respond to certain **immunotherapy drugs**
 - Trials underway in prostate cancer
- Patients with germline mutations in **TP53 gene** should **avoid therapeutic radiation** unless no other option for treatment¹
- Other DNA repair genes being evaluated for response to PARP inhibitors

¹NCCN Clinical Practice Guidelines in Oncology – Genetic/Familial High-Risk Assessment: Breast and Ovarian (V.1.2018)

Clinical Trials Around BRCA Mutations

- New class of drug known as PARP inhibitors
 - Only effective or most effective in patients with germline BRCA mutations
 - Already FDA-approved in metastatic breast and ovarian cancer patients
 - Shown to improve progression-free survival, improved response to other chemotherapy
 - Numerous trials underway in metastatic prostate cancer
- Consideration of early use of platinum-based therapies if cancer progresses

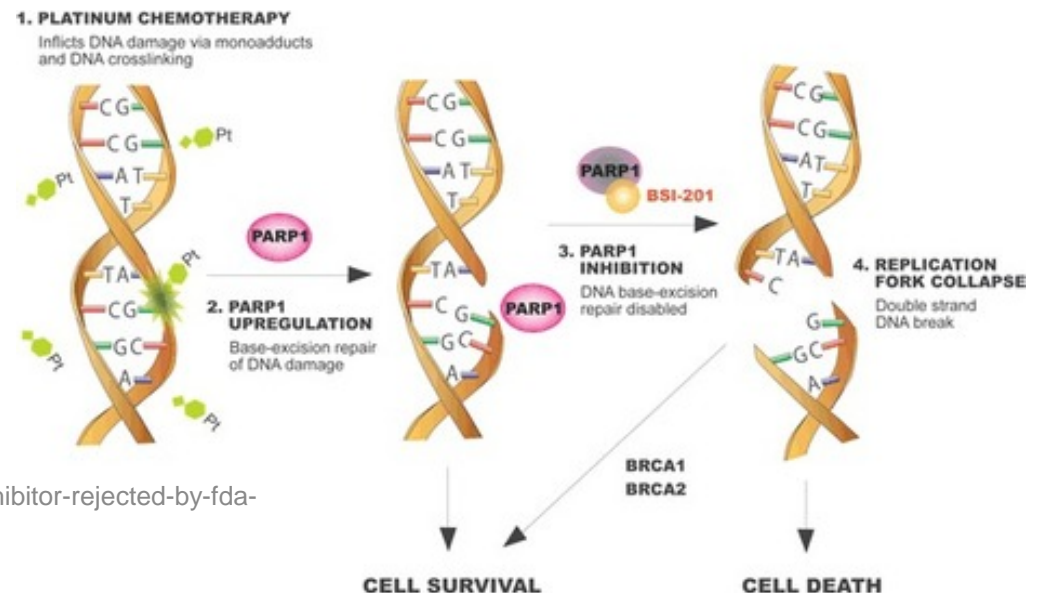


Image source: <https://blogs.shu.edu/cancer/2014/06/26/parp-inhibitor-rejected-by-fda-advisory-committee/>



Gene

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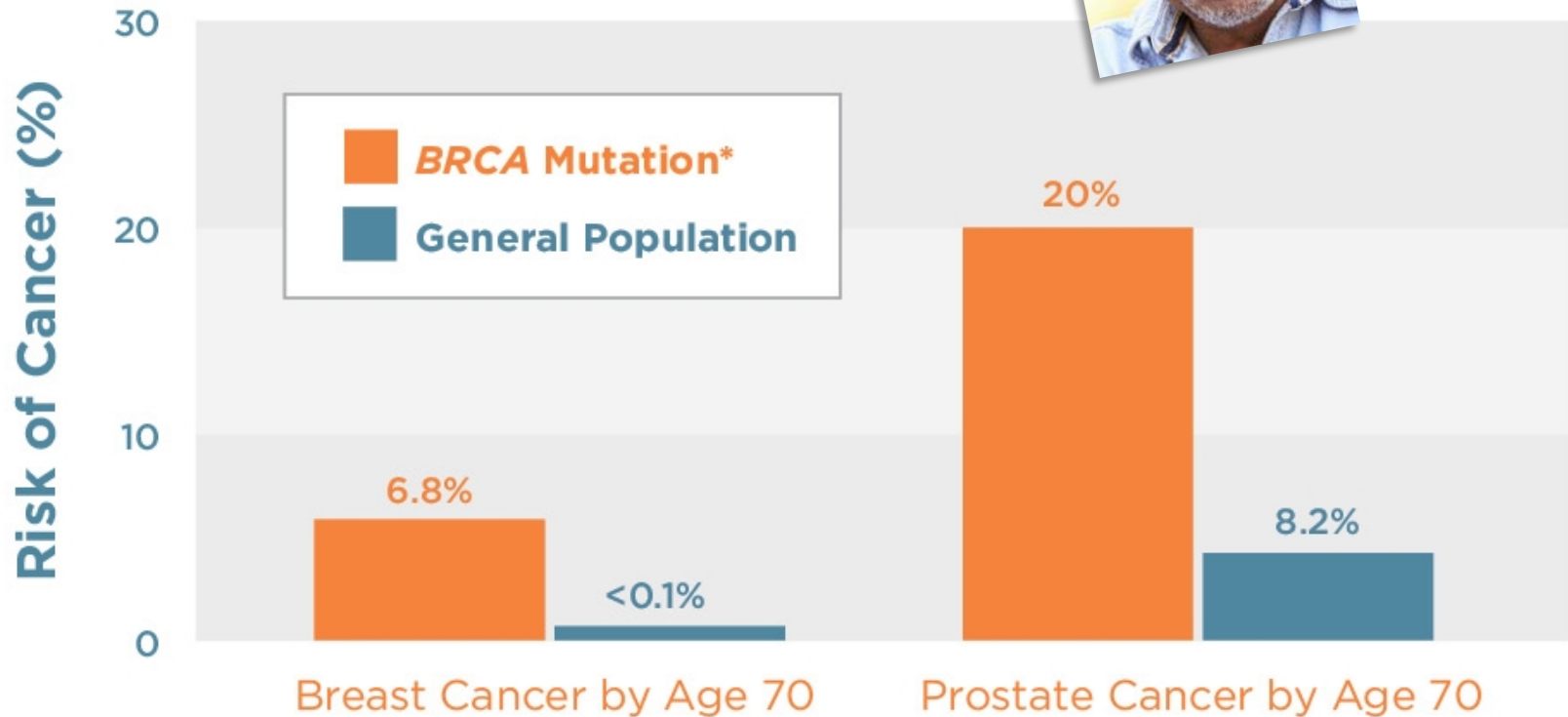
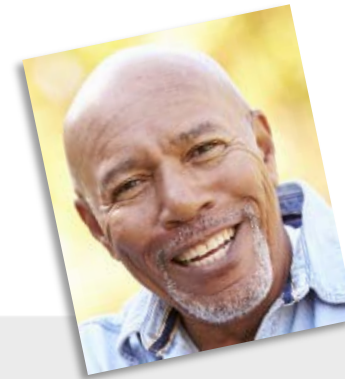
Family History

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Gene has a mutation in *BRCA2* gene

- General Practitioner: Regular clinical male breast exams
- Dermatologist: Annual skin checks

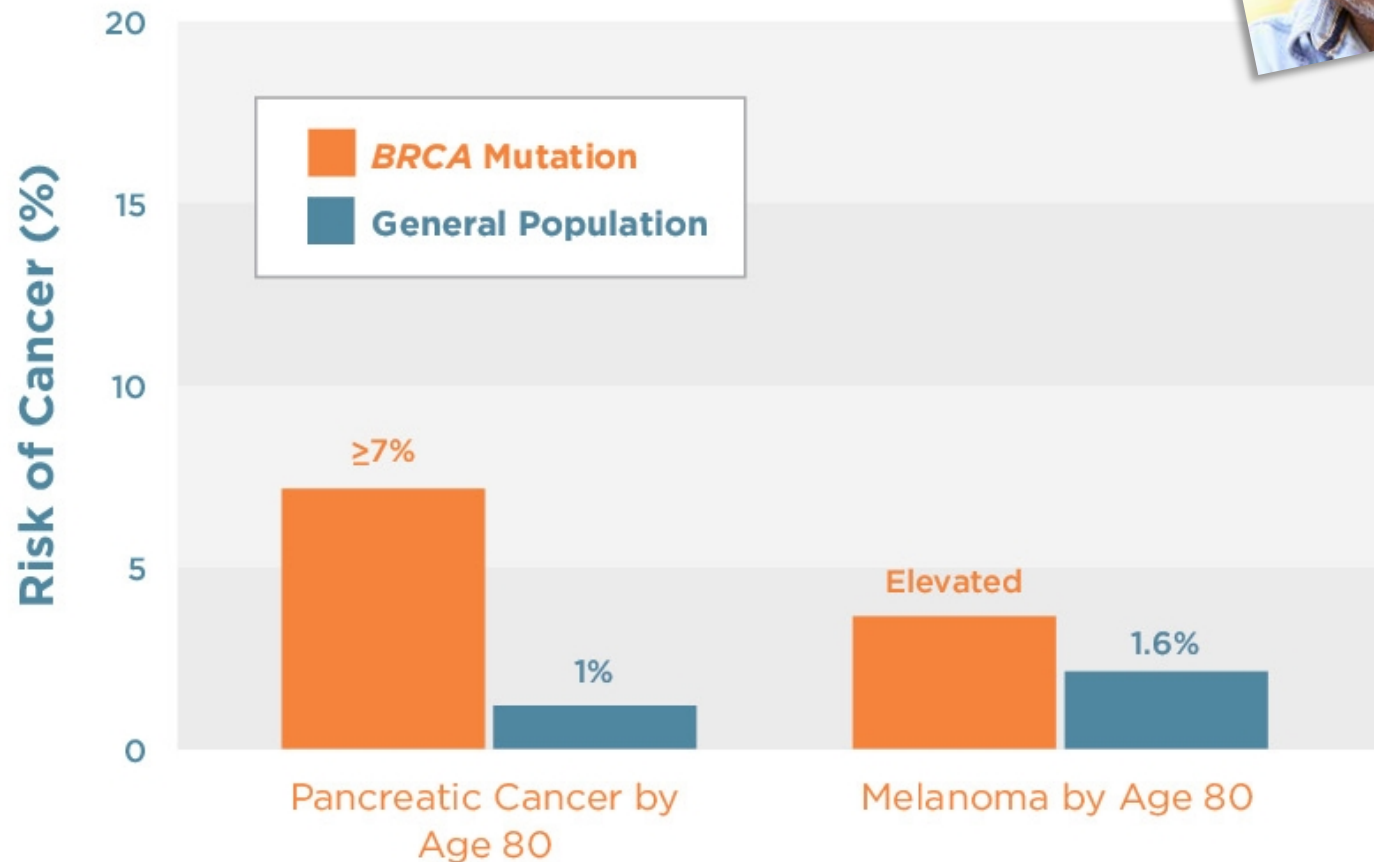
BRCA Mutation Risks in Men



**Risks refer to BRCA2 mutation carriers.
Risks for male BRCA1 mutation carriers are less characterized.*

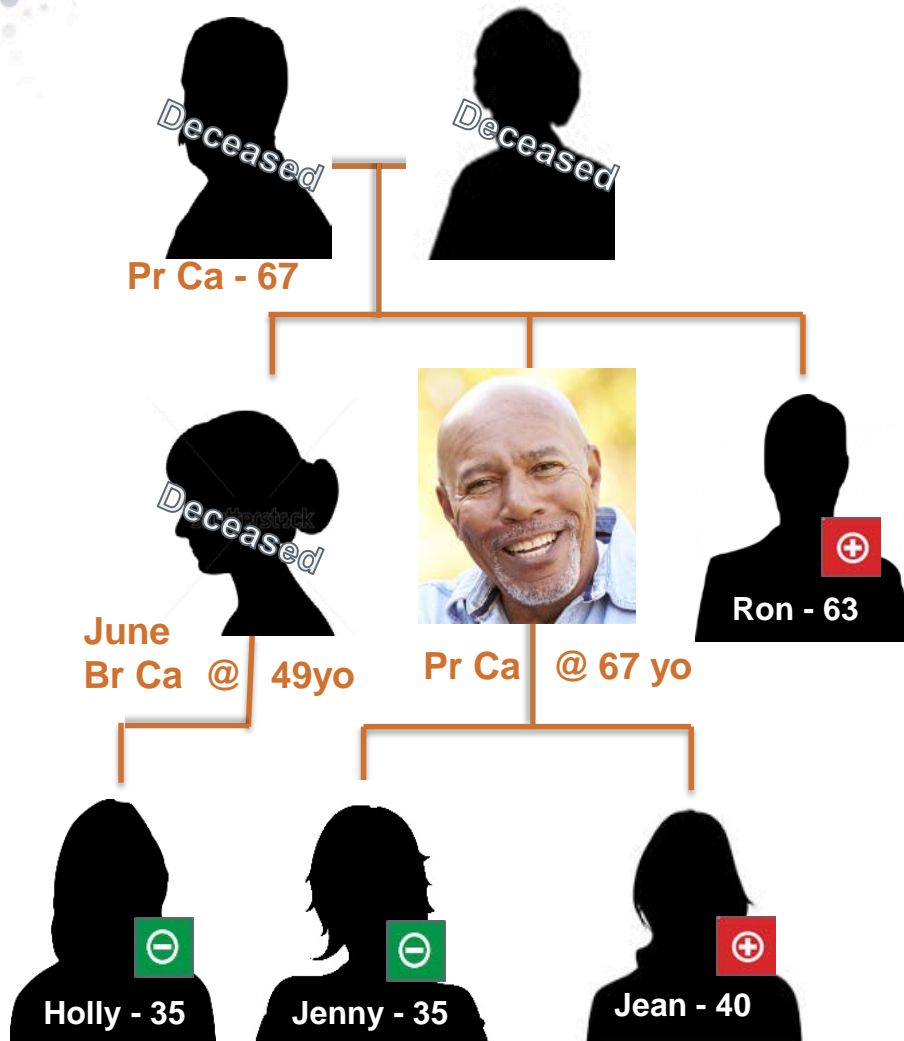
May account for ~15% of all male breast cancer

BRCA Mutations and Other Cancers



JNCI 1999;15:1310-16
JNCI 2002;15:1365-72
J Med Genet 2005;42(9):711-9
NCI (SEER) 2012

Importance to Gene's Family:



Ron - Brother : **BRCA2**

- Urologist: Earlier and more frequent prostate cancer screening
- General Practitioner: Regular clinical male breast exams
- Dermatologist: Annual skin checks.

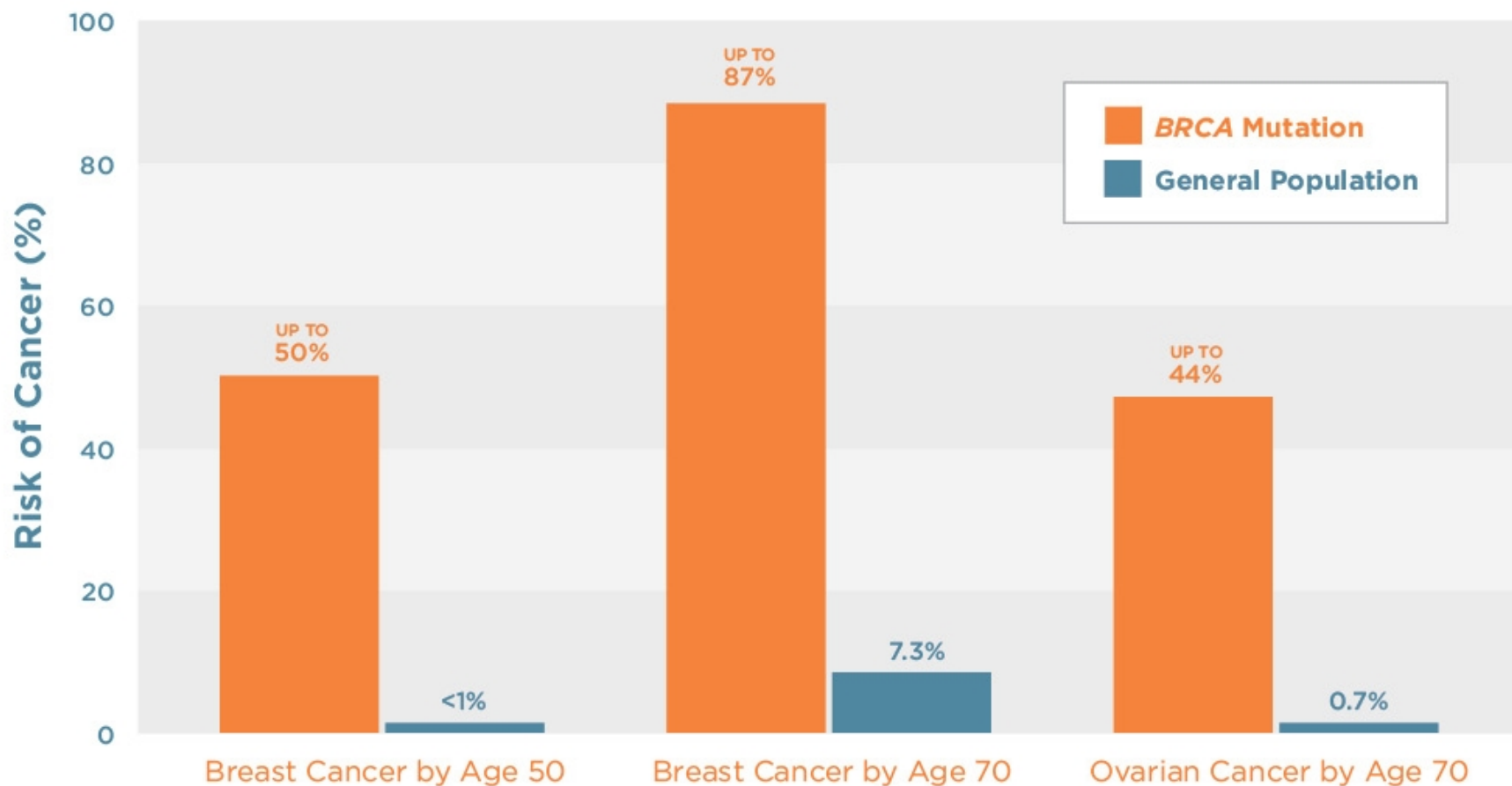
Jean – Daughter: **BRCA2**

- Breast Specialist: Consider risk reducing double mastectomy with reconstruction
- Gynecologic Oncologist: Consider oophorectomy after she is finished having children
- Dermatologist: Annual skin checks

Jenny and Holly – Daughter and Niece: **BRCA2**

- Primary Care/ Gynecologist: Evaluate for general population screening

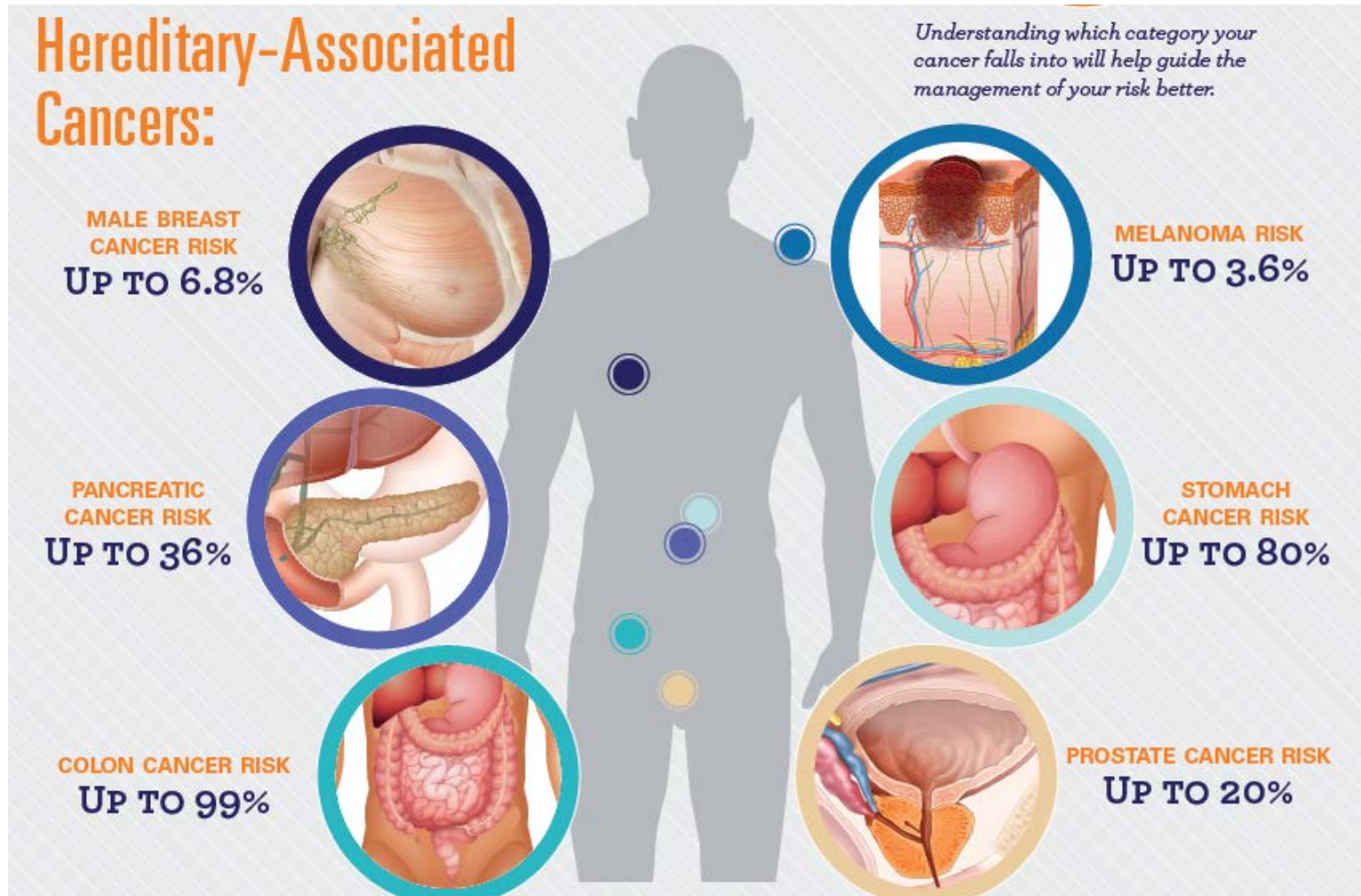
BRCA Mutations Increase Breast and Ovarian Cancer Risks



NEJM 1997;336:1401-8
AJHG 2003;72:117-30
JNCI 1999;15:1310-6
JCO 2007;25(11):1329-33

Science 2003;643-6
JCO 2005;23(8):1656-63
NCI (SEER) 2012

Patients with Hereditary Cancer Syndromes have elevated risk for multiple cancers





Criteria for Genetic Testing of Prostate Cancer

Hereditary cancer testing is recommended for patients with prostate cancer who meet the following criteria:

- ☐ **Patient with metastatic prostate cancer**
- ☐ Patient with prostate cancer with a Gleason Score of 7+ **AND** they have 1+ family members with **ANY** of the following:
 - ◆ 1+ family member with Breast Cancer ≤50 years, **or**
 - ◆ 1+ family member with Ovarian Cancer at any age, **or**
 - ◆ 2+ family members with Breast, Pancreatic, or Prostate (**Gleason 7+ or metastatic**) cancer at any age

*Close blood relatives include parents, children, siblings, grandparents, aunts/uncles, nieces/nephews, great-grandparents, and first cousins.

Indicators Of Hereditary Cancer

An individual with a personal or family history of any one of the following:

	MULTIPLE 2 or more	YOUNG age 50 or younger	RARE any age
Breast	●	●	†
Prostate	●		
Melanoma	●		
Ovarian	●		●
Pancreatic	●		
Colorectal	●	●	†
Endometrial	●	●	†
Gastric	●		
Other**	●		

● Hereditary Breast and Ovarian Cancer (HBOC)-associated cancers[§]
 ● Lynch-associated cancers[^]

†Abnormal MSI/IHC or histology.

#Male breast cancer, triple negative breast cancer.

**Other Lynch syndrome-associated cancers, 10 or more gastrointestinal adenomatous polyps.

§HBOC syndrome-associated cancers include breast (including ductal carcinoma in situ [DCIS]), ovarian, pancreatic, and aggressive prostate cancers.

^ Lynch syndrome-associated cancers include colon/rectal, uterine/endometrial, ovarian, stomach/gastric, kidney/urinary tract, biliary tract, small bowel, pancreas, brain, and sebaceous adenoma cancers.



Identifying if you might be a candidate for testing



www.hereditarycancerquiz.com/phen



Keys to Genetic Testing

- Know your personal and family history
 - Men with metastatic prostate cancer
 - Family history of prostate, breast, ovarian, pancreatic cancer
- Complete Hereditary Cancer Quiz
- If you may be an appropriate candidate for genetic testing, talk to your urologist or health care provider
- Panel testing (multiple genes associated with hereditary cancer risk) is considered the best option
- Education and informed consent
- Results generally available in 2-3 weeks

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Thank you for this wonderful
opportunity to talk with you!!

Questions ???