Genetics of Prostate Cancer: An Overview

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Urology Clinics of North Texas – Medical City Dallas / Baylor Plano

Symposium – North Texas Prostate Cancer Coalition

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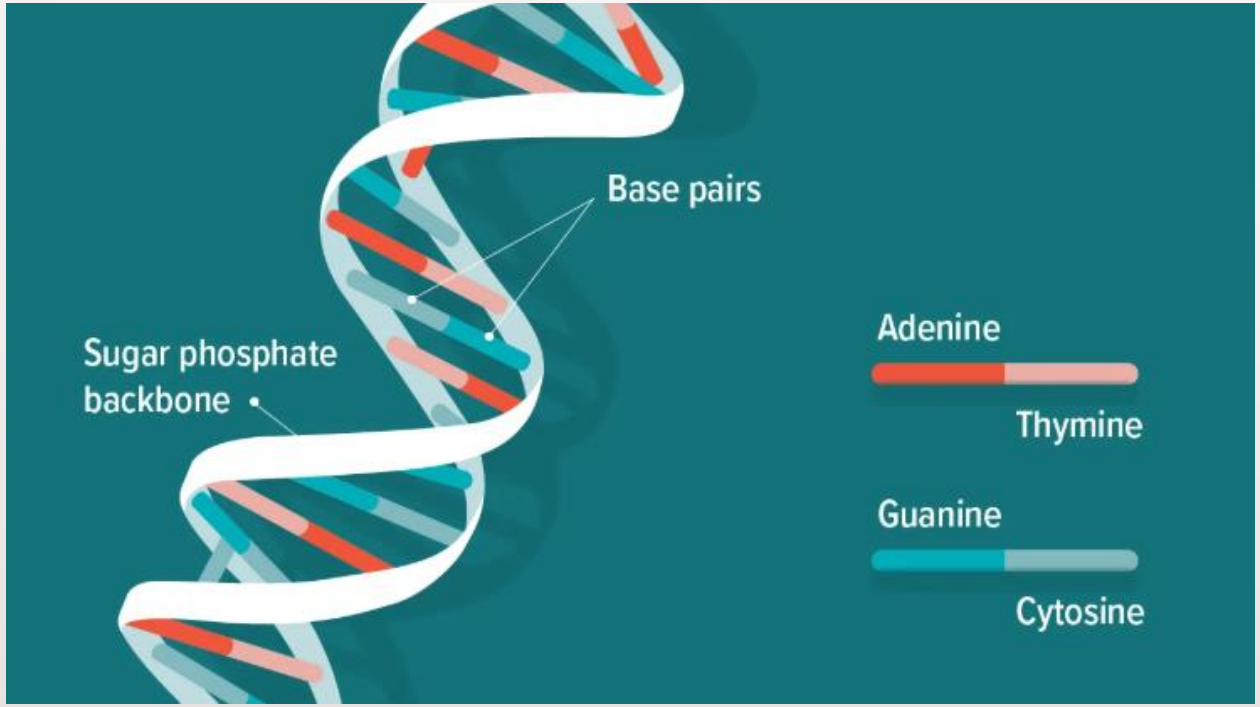
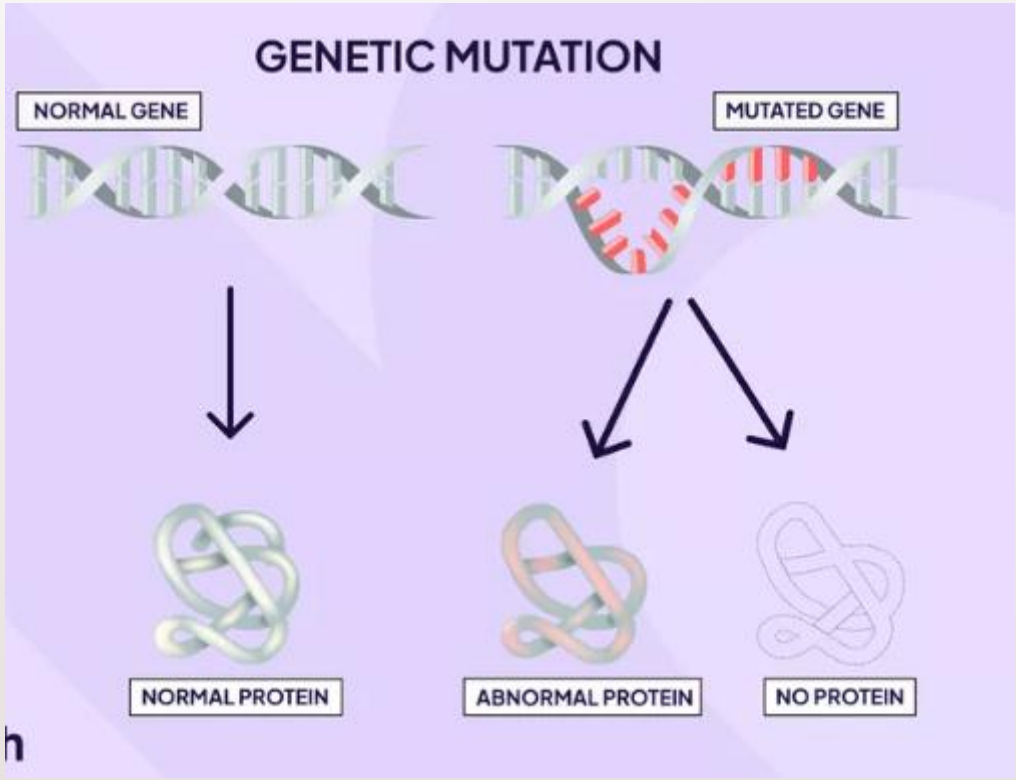
Let's start with the basics….

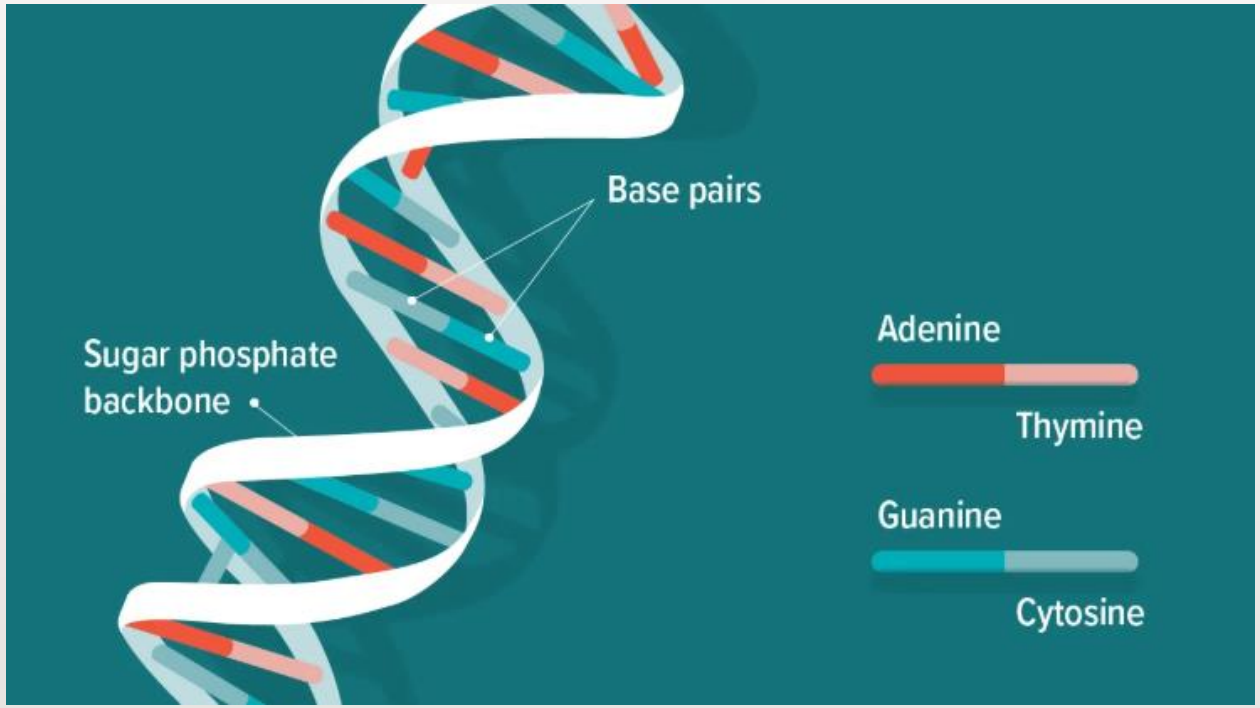
What is DNA?



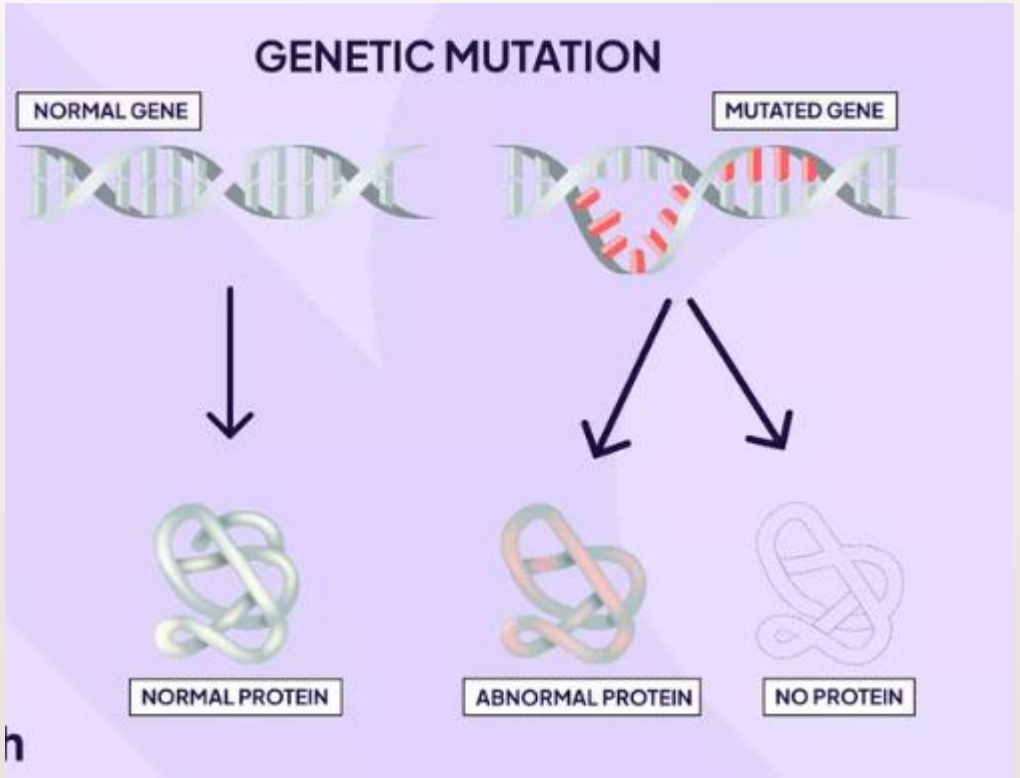
What is a mutation?



DNA = RECIPE FOR LIFE

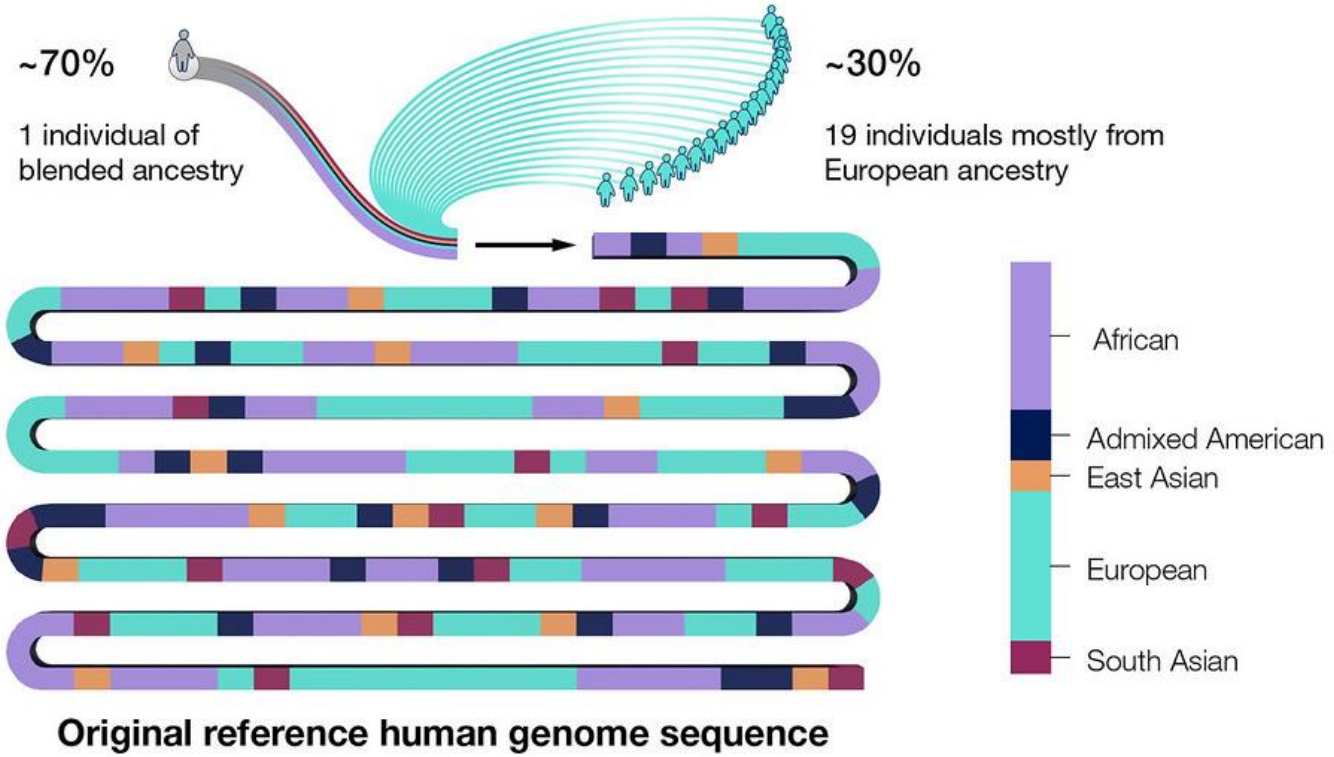


MUTATION = MISTAKE IN THE RECIPE



THE HUMAN GENOME PROJECT: where it all began[1]

Whose genome was sequenced by the Human Genome Project?



The human genome sequence generated by the Human Genome Project was actually a patchwork of multiple people whose identities were intentionally made anonymous to protect their privacy.

Role of Genetics in Prostate Cancer

- Prostate cancer has a strong genetic component.
- **5-15%** of prostate cancer is attributable to **hereditary** factors. [1]
- **15 to 20%** of prostate cancer can be **familial**, with some features of hereditary cancer present, but no detectable mutation is identified. [2]
- **70-80%** of prostate cancer is **sporadic**.

How to alter PSA screening for those at increased (genetic) risk for prostate cancer?

Early Detection of Prostate Cancer: AUA/SUO Guideline (2023)

5. Clinicians should offer prostate cancer screening beginning at age 40 to 45 years for people at increased risk of developing prostate cancer based on the following factors: Black ancestry, germline mutations, strong family history of prostate cancer. (*Strong Recommendation; Evidence Level: Grade B*)

BUT WHAT ABOUT A GENETIC EVALUATION?

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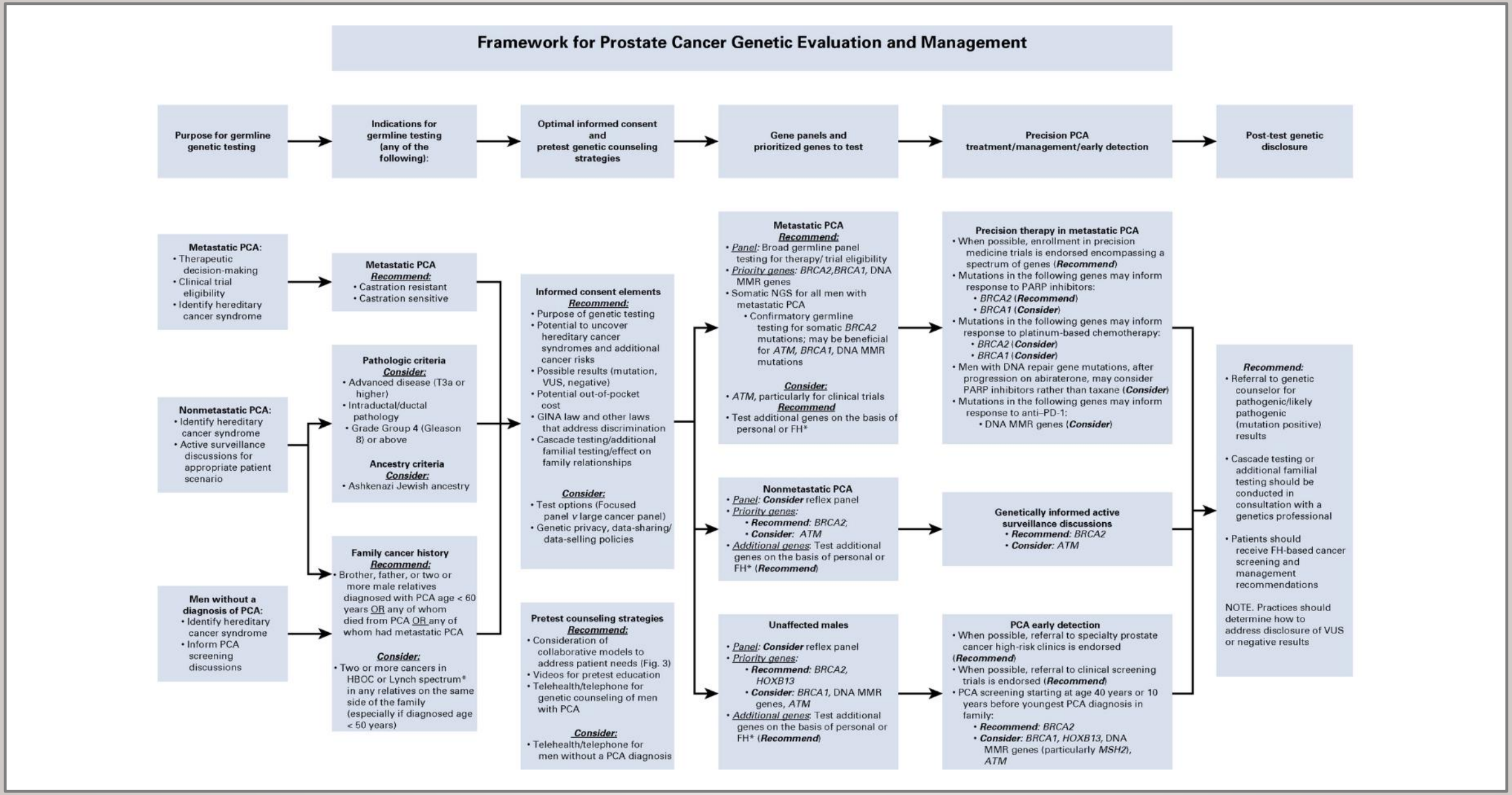
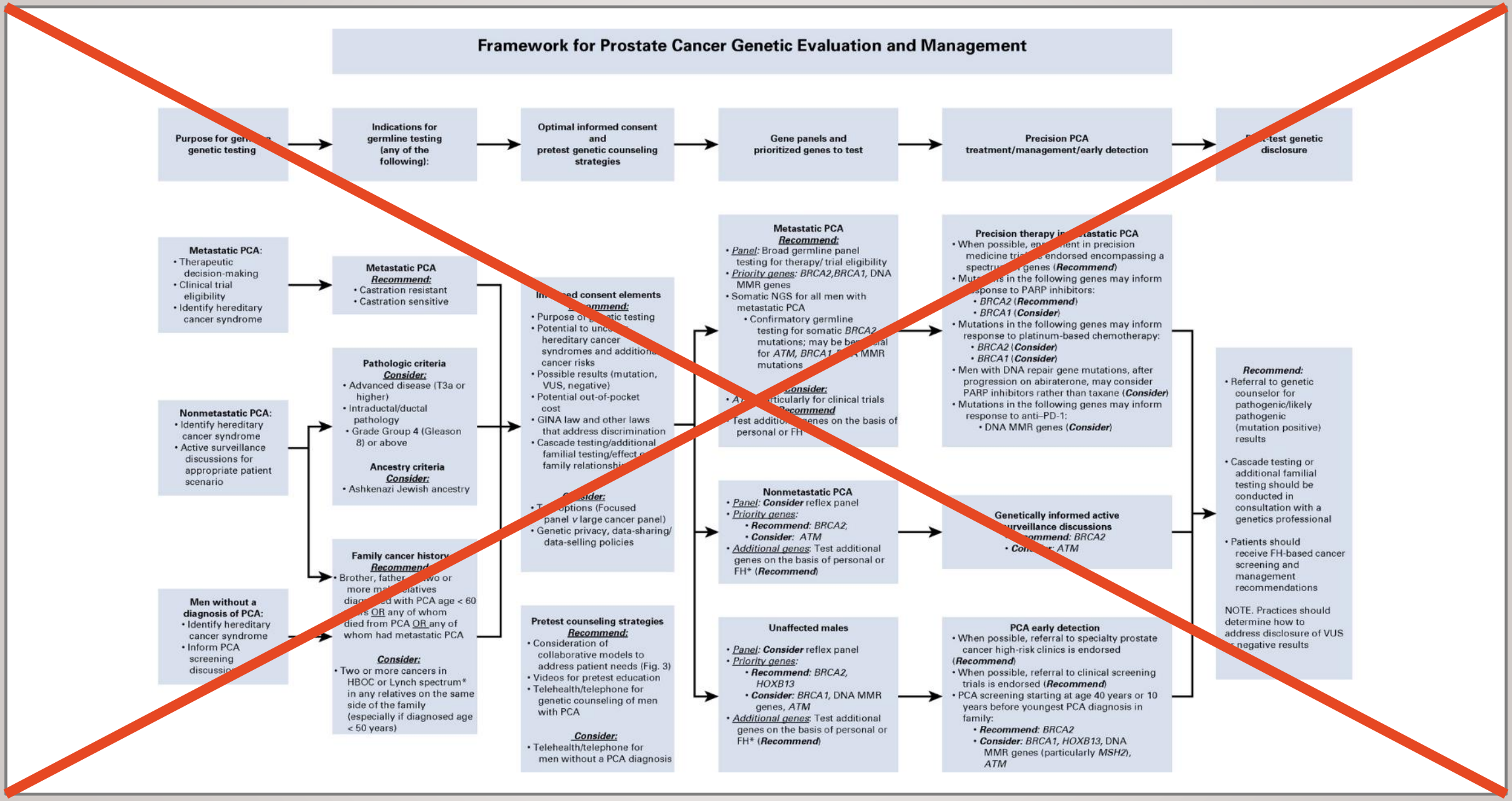
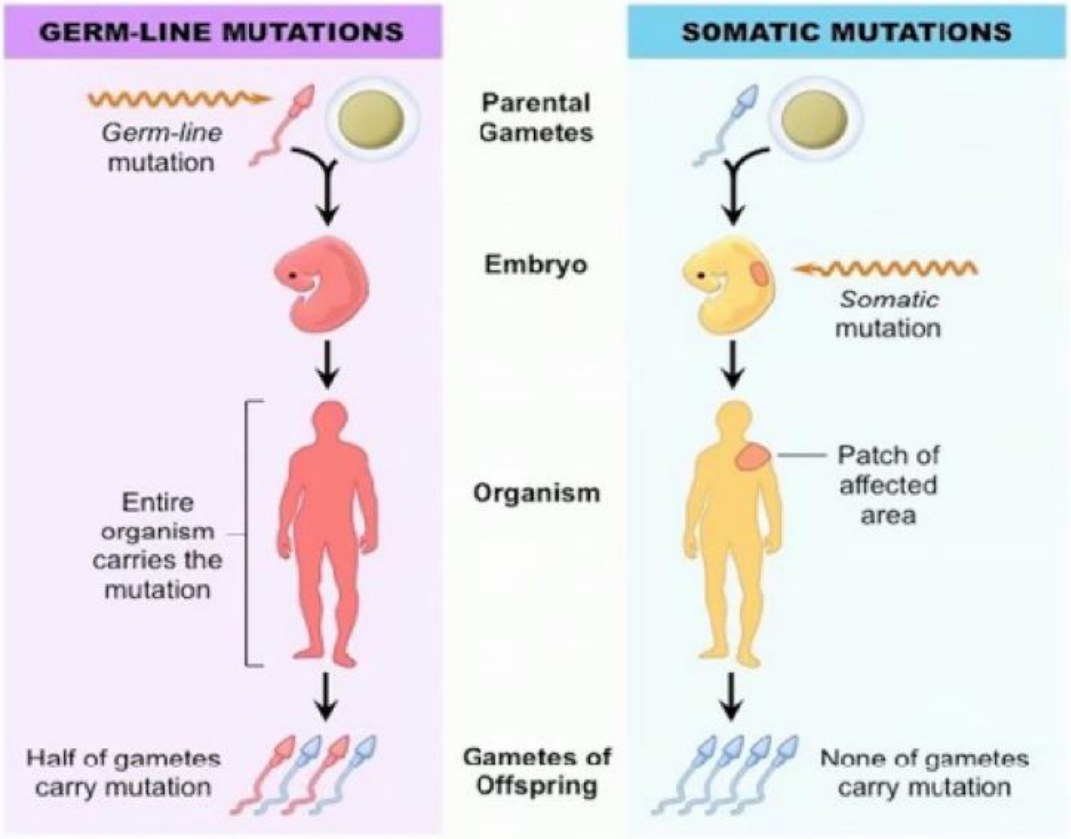


BUT WHAT ABOUT AN ACTUAL GENETIC EVALUATION?



- Important to know the difference between **germline** and **somatic** mutations.
- **Germline mutations:** What you inherit from your parents (found in every cell of the body).
- **Somatic mutations:** Changes in the DNA of body cells that occur during your lifetime (not inherited).

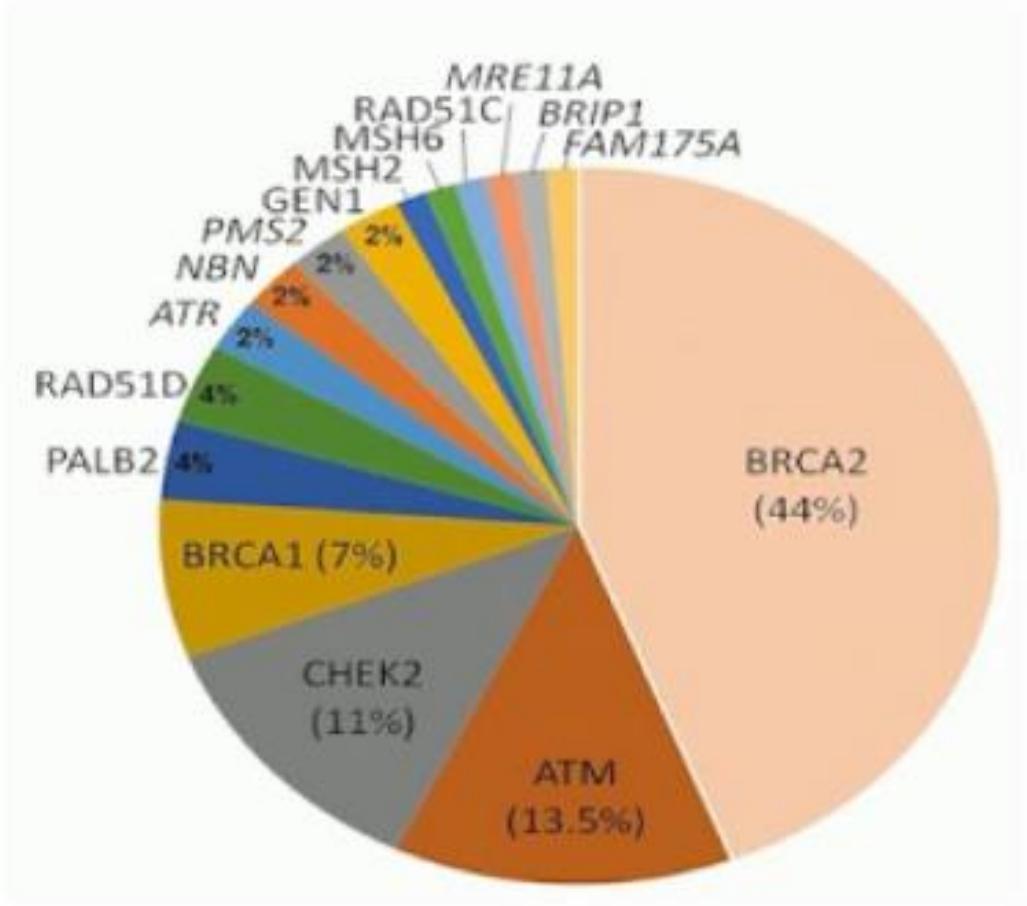
Figure 1 – Germline and somatic genetic mutations:



What does testing involve?

- **Germline** → Usually blood or saliva.
- **Somatic**→ Usually samples primary tumor or metastatic tissue.

Figure 2 – Germline mutations in metastatic prostate cancer patients:



These mutations are linked with:

- **younger age of cancer onset**
- **aggressive clinical course**
- **increased cancer mortality**

WHAT GENES SHOULD BE TESTED?

Table 4. Purpose of genetic testing and choice of genes.

Source Test	NCCN	ESMO	Philadelphia PCCC	AUA/ASTRO	EAU-EANM-ESTRO...
Germline	Increased risk PCa: HRR genes; *EPCAM*, MMR genes; Increased risk & early onset familial PCa: *HOXB13*; Early onset, aggressive phenotype, reduced survival: *BRCA2*; High risk HBOC syndrome: *BRCA1, BRCA2* pathogenic or likely pathogenic, *ATM*.	*BRCA1, BRCA2*, other DDR genes (e.g., *ATM, MSH2, FANCA, MLH1, RAD51B, RAD51C, CDK12, FANCD2*)	**No PCa**: High-risk for early detection: *BRCA2(r), HOXB13(r), BRCA1(c), ATM(c)*, MMR genes (particularly MSH2)(c);[a] **Non-mPCa**: Active surveillance: BRCA2(r), ATM(c);[a] **mPCa**: post somatic confirmatory testing for PCa disposition & cascade testing: *BRCA1, BRCA2, ATM*, MMR genes;[a] precision therapy or clinical trial: broad germline testing *BRCA2, BRCA1, ATM* MMR genes[a].	**Non-mPCa**: *ATM, BRCA1, BRCA2, CHEK2, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, TP53*;[b] **mPCa**: *BRCA2, ATM, CHEK2, BRCA1, RAD51D, PALB2*;[b] **mCRPCa**: *ATM, BRCA1, BRCA2, PALB2*;[b] inform prognosis, precision therapy and counselling re family risk MMR genes	*BRCA1, BRCA2, ATM, CHEK2, HOXB13*, MMR *genes*; High-risk: *BRCA2, ATM*, MMR genes (particularly MSH2).
Somatic	precision therapy or clinical trial for: **mPCa:** *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, CDK12*; **mCRPCa**: MMR genes	HRR genes, MMR genes	**mPCa**: NGS testing; **mCRPCa**: Precision therapy-PARP inhibitors *BRCA2(r), BRCA1(c)*; Platinum-based chemotherapy *BRCA1(c), BRCA2(c)*; Anti-PD1 MMR genes(c)	**mCRPCa**: inform prognosis, precision therapy and counselling re family risk MMR genes	**mPCa**: HRR genes; MMR genes (followed by germline for BRCA1, BRCA2, ATM, MMR genes); **mCRPCa**: somatic and/or germline as above

PCa prostate cancer, *HRR* (homologous recombination repair) genes *BRCA1, BRCA2, ATM, PALB2, CHEK2*; MMR (mismatch repair) genes *MLH1, MSH2, MSH6, PMS2*, *mPC* metastatic castrate resistant prostate cancer, *NGS* next generation sequencing (comprehensive genetic testing), (*r*) recommend, (*c*) consider.

[a]Test additional genes on basis of personal or family history(r).

[b]none specified, PCa associated genes identified only.

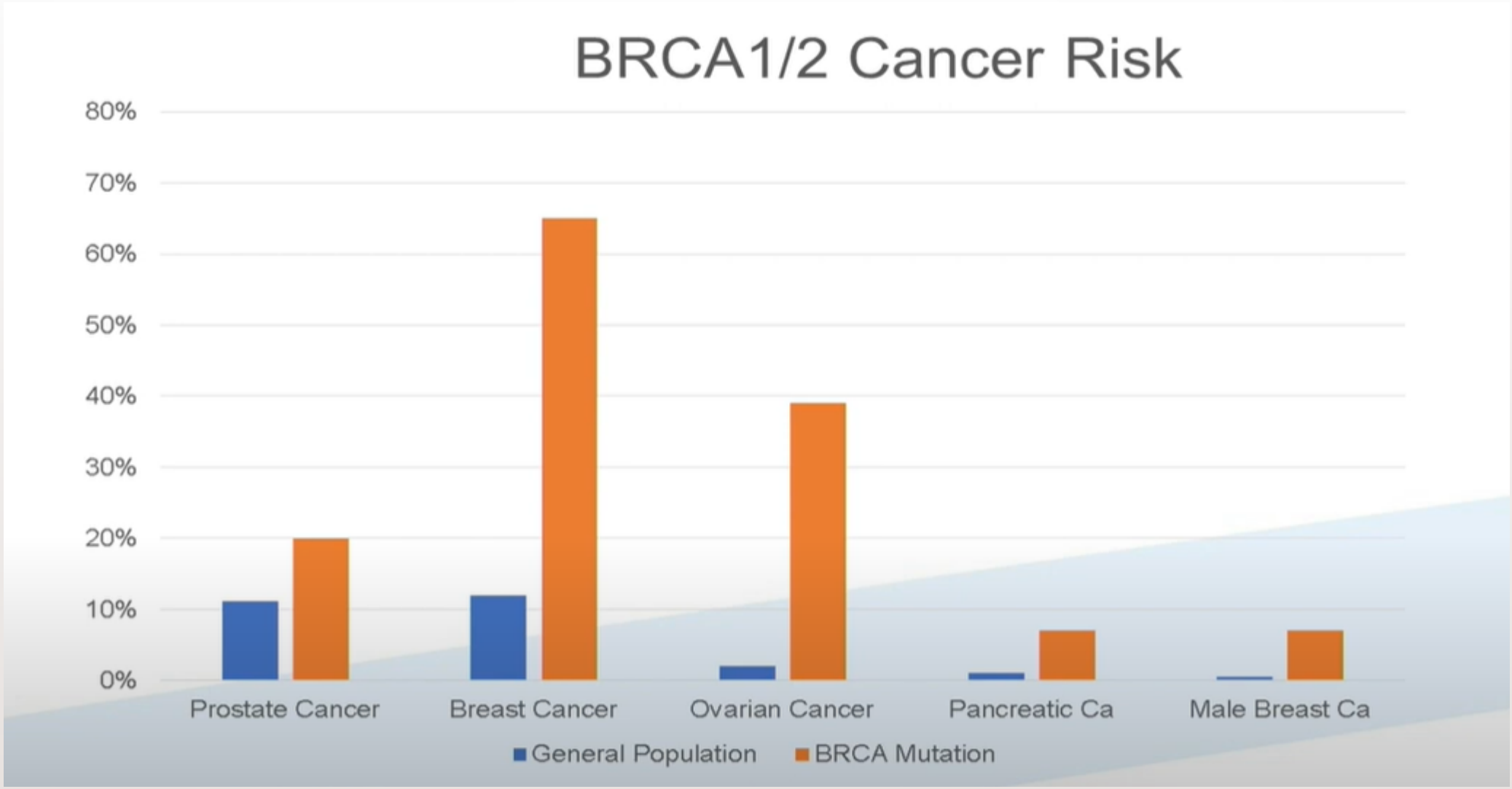
[c]no consensus regarding type of germline testing.

BRCA2 best studied for potential screening and treatment.

Germline mutations in **11.8% of metastatic disease** and **4.6% of localized disease**.

Source Test	NCCN
Germline	Increased risk PCa: HRR genes; *EPCAM*, MMR genes; Increased risk & early onset familial PCa: *HOXB13*; Early onset, aggressive phenotype, reduced survival: *BRCA2;* High risk HBOC syndrome: *BRCA1, BRCA2* pathogenic or likely pathogenic, *ATM*.
Somatic	precision therapy or clinical trial for: **mPCa:** *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, CDK12;* **mCRPCa**: MMR genes


TIME
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



https://auau.auanet.org/node/38240

BRCA 1/2 Mutations and PCa

- DNA damage response (DDR) genes
- 2-6 fold ↑ lifetime risk (BRCA2 > BRCA1)
- 8.6-fold ↑ risk by age 65 (BRCA2)
- PCa: Likely to be aggressive: Gleason 8 or higher, node +, mets, poor survival
- ↑ self and family risk for other hereditary cancers: breast, ovarian, melanoma, pancreatic, Lynch Syndrome, colon, gastric
- Direct screening and mCRPC therapy (e.g., PARP inhibitors)

https://auau.auanet.org/node/38240

Who should be tested? (NCCN)

- Men with **metastatic prostate cancer** (germline and/or somatic)
- Men with **high or very high risk localized cancer**
- Men with **family history of prostate cancer < 60yrs of age or prostate cancer-related death**

Who should be tested?

- Men with **personal history of breast cancer**
- Men with **family history** of early onset breast, colorectal or endometrial cancer (< 50 yrs old)
- Men with **family history** of ovarian, exocrine or pancreatic cancer (any age)
- Family history of **lynch-syndrome related cancer**
- **Ashkenazi Jewish ancestry**

Who should be tested?

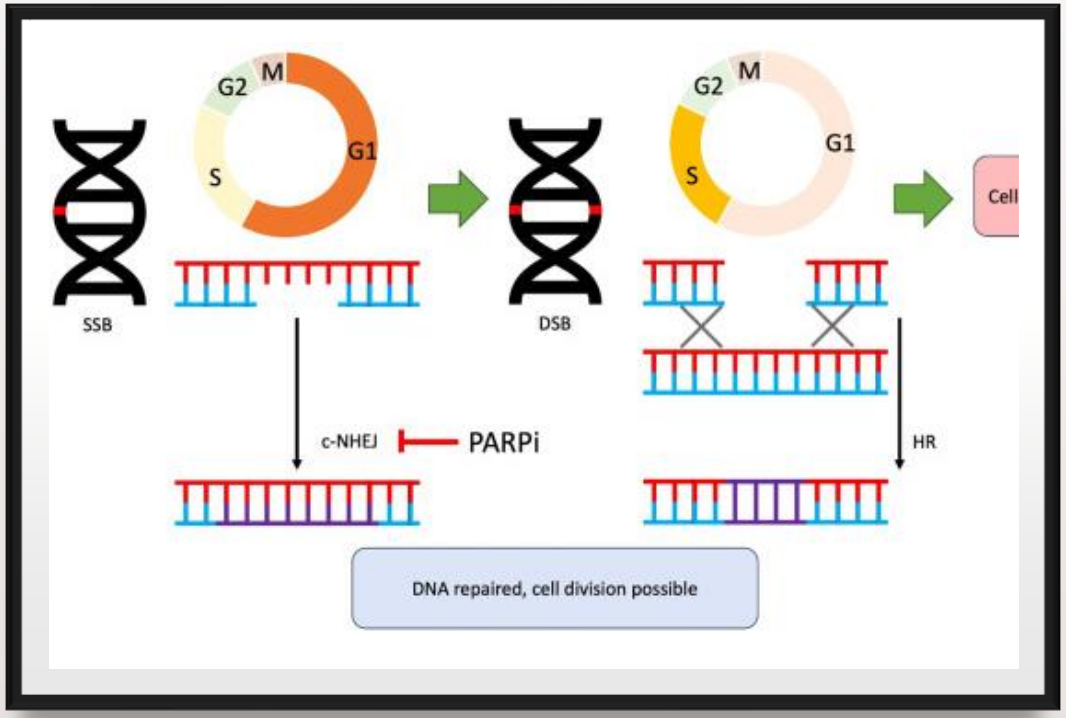
- For those without a prostate cancer diagnosis:
  - **Family history "suggestive"** of hereditary prostate cancer or hereditary breast and ovarian cancer or colon cancer syndromes (NCCN)

How does this impact treatment?

Somatic Mutation Testing in Prostate Cancer

- Identify "**actionable**" mutations.
  - HRD genes: e.g. *BRCA1, BRCA2, PALB2*
  - → PARP inhibitors
    - Up to 20-25% of cases
  - MMR (mismatch repair) genes: e.g. *MLH1, MSH2, MSH6 Or MSH high*
  - → Pembrolizumab
    - 3-5% of cases

Targeted Drug Therapy [5]



- PARP inhibitors
  - Simply put – these drugs block the PARP enzyme, which helps repair DNA damage, and this prevents cancer cells from repairing their damage and leading to cell death.

Targeted Drug Therapy/Precision Medicine [5]

- **PARP inhibitors**
  - **Taken as pills or capsules, typically 1-2x per day.**
  - **Typically used in metastatic castration-resistant prostate cancer (mCRPC) with BRCA mutations.**
    - Rucaparib (Rubraca): mCRPC after taxane therapy, BRCA mutation
    - Olaparib (Lynparza): mCRPC with abiraterone, BRCA mutation OR by itself after failing enzalutamide or abiraterone (BRCA or HHR mutation)
    - Niraparib + Abiraterone (Akeega): mCRPC with BRCA mutation
    - Talazoparib (Talzenna): mCRPC, HRR mutation

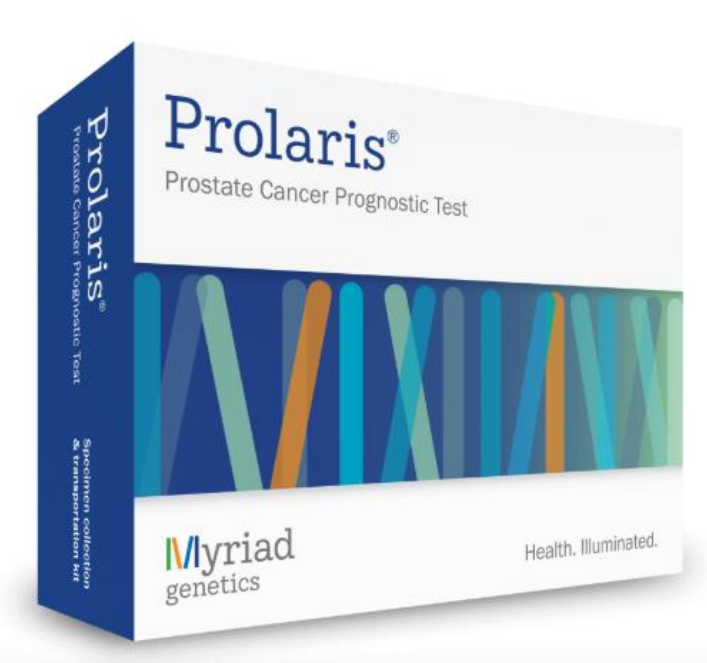
Targeted Drug Therapy [5]

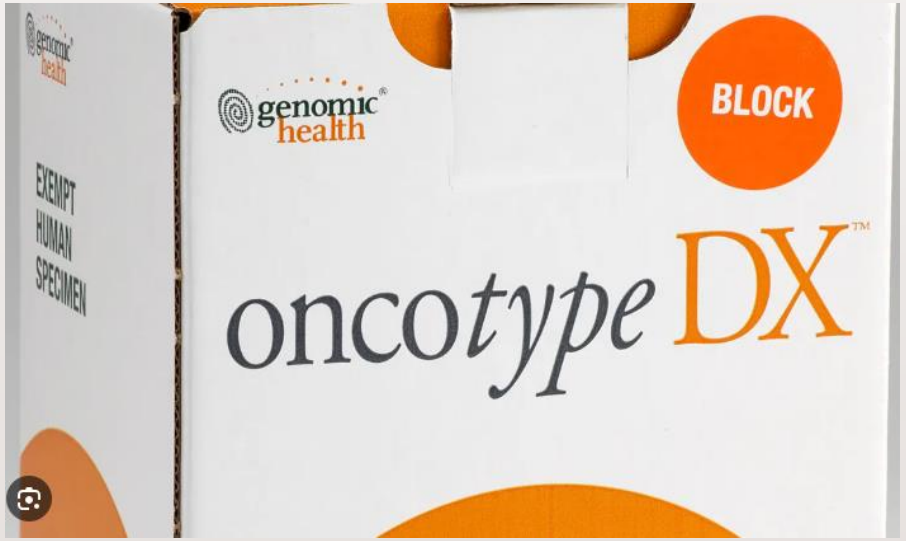
- PARP inhibitors
  - **Adverse effects:** Nausea, vomiting, diarrhea, fatigue, loss of appetite, anemia, constipation, skin rash, abnormal liver tests, low platelets, cough, shortness of breath.
  - **Rare:** myelodysplastic syndrome or AML.

Genomic Testing

Decipher®

PROSTATE BIOPSY GENOMIC CLASSIFIER





Genomic testing

- Tissue based biopsies
- Molecular signatures
- Used to make treatment and management decisions
- NOT used in advanced or metastatic prostate cancer

Conclusions

- Prostate cancer has a strong genetic component.
- We have identified several “actionable mutations” but this is just the “tip of the iceberg”….
- Ask your urologist about whether a genetic evaluation would be appropriate, especially if you have high risk or metastatic disease OR a strong family history.

References

1. https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genome-project

2. Tuffaha et al. "Guidelines for genetic testing in prostate cancer: a scoping review". Prostate Cancer and Prostate Diseases. *Nature*, 2024.

3. AUA 2020: Panel Discussion – Genetic Testing: What the Urologist Needs to Know. https://www.urotoday.com/conference-highlights/aua-2020/aua-2020-prostate-cancer/122593-aua-2020-panel-discussion-genetic-testing-what-the-urologist-needs-to-know.html

4. Wei JT, Barocas D, Carlsson S, et al. Early detection of prostate cancer: AUA/SUO guideline part I: prostate cancer screening. J Urol. 2023;210(1):45-53.

5. Targeted Drug Therapy for Prostate Cancer. American Cancer Society. https://www.cancer.org/cancer/types/prostate-cancer/treating/targeted-therapy.html.

Questions?