Dr. Dattoli on Genetic Testing for Prostate Cancer

What's in Your Genes?

Understanding Genetics, Family Risk, and Precision Medicine in Prostate Cancer Care

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The genes we inherit cannot be changed—but understanding them can change the course of our health and, perhaps, the health of future generations. For many years, physicians have recognized that prostate cancer often "runs in families." Today, remarkable advances in genetics have helped us understand why.

We now know that some men inherit genetic mutations that increase their lifetime risk of developing prostate cancer, while other genetic changes develop only within the cancer itself. Understanding the difference between these two types of mutations has become one of the most important advances in modern prostate cancer care.

Welcome to the era of precision medicine, where treatment decisions are increasingly guided by the unique genetic makeup of both the patient and the cancer.

Germline Mutations: The Genes You Were Born With

Every cell in your body contains DNA inherited from your parents. When a mutation is present from birth and exists in every cell, it is called a germline mutation. These inherited mutations can be passed from one generation to the next.

Approximately 5% to 10% of prostate cancers are directly related to inherited germline mutations. While this percentage may seem small, these cancers warrant special attention as they often develop at younger ages and are more likely to behave aggressively.

The best-known inherited mutations involve the BRCA1 and BRCA2 genes. While these genes are commonly associated with breast and ovarian cancer, they also play an important role in prostate cancer.

Men with a BRCA2 mutation have a substantially increased lifetime risk of developing prostate cancer, and these cancers are more likely to spread beyond the prostate and require aggressive treatment. BRCA1 mutations also increase prostate cancer risk, although generally to a lesser degree.

Other important inherited genes include:

- ATM
- CHEK2
- PALB2
- HOXB13
- RAD51C and RAD51D
- The Lynch syndrome genes (MLH1, MSH2, MSH6, and PMS2)

These genes function as part of the body's DNA damage repair system. When these repair mechanisms fail, damaged DNA accumulates, increasing the likelihood that cancer will develop.

Family History: Looking Beyond Prostate Cancer

Your family history remains one of the strongest predictors of prostate cancer risk.

You should discuss genetic counseling with your physician if your family includes:

- Prostate cancer in your father, brother, son, or multiple close relatives.
- Breast cancer (men or women), especially at a young age.
- Ovarian cancer.
- Pancreatic cancer.
- Colorectal or certain uterine cancers associated with Lynch syndrome.
- Melanoma, particularly when it occurs with other cancers in the family.

Recent research has shown that inherited defects in DNA repair genes—particularly BRCA2, ATM, CHEK2, and related genes—may increase susceptibility to several different cancers, including prostate, breast, ovarian, pancreatic and melanoma. These genes are not "prostate cancer genes" or "melanoma genes." Rather, they are DNA repair genes that help protect cells throughout the body. When one of these genes is altered, the increased cancer risk may appear in different organs among different family members.

This is why physicians today evaluate the entire family cancer history rather than focusing only on prostate cancer.

Somatic Mutations: The Genetics of the Cancer Itself

Not all genetic mutations are inherited, e.g. as prostate cancer develops, it acquires additional mutations that are present only within the cancer cells. These are called somatic mutations because they occur during a person's lifetime and cannot be passed on to children.

These acquired mutations help explain why one man's prostate cancer behaves very differently from another's. Some tumors remain slow growing for years, while others become aggressive or resistant to treatment.

Understanding these mutations has become a central theme in modern prostate cancer care.

Next-Generation Sequencing (NGS): Reading Your Genetic Blueprint

Most modern genetic testing uses a technology known as Next-Generation Sequencing (NGS).

Unlike older laboratory methods that examined one gene at a time, NGS can analyze dozens—or even hundreds—of genes simultaneously using a single specimen.

This allows physicians to identify inherited mutations, characterize the molecular fingerprint of an individual's cancer, and select therapies based on the unique biology of that tumor.

NGS has transformed prostate cancer from a disease treated primarily according to stage and grade into one increasingly managed according to its genetic profile.

Two Different Types of Genetic Testing

Although both use NGS technology, they answer very different questions.

Germline Genetic Testing

Germline testing determines whether you inherited a mutation associated with hereditary cancer.

Because your inherited DNA is present in every cell of your body, testing can usually be performed using:

- Blood
- Saliva
- Occasionally a cheek (buccal) swab

Companies offering hereditary cancer testing include:

- Invitae
- Myriad Genetics
- Ambry Genetics
- Tempus Germline
- Foundation Medicine (FoundationOne Germline)
- Fulgent Genetics
- Northstar Genomics
- Natera
- GeneDx
- Color Health

These multigene panels commonly evaluate BRCA1, BRCA2, ATM, CHEK2, PALB2, HOXB13, Lynch syndrome genes, and numerous other hereditary cancer genes.

Somatic (Tumor) Genomic Testing

Somatic testing—also known as somatic tumor genomic testing, comprehensive genomic profiling (CGP), or molecular profiling—examines the DNA of the cancer itself rather than the DNA you inherited.

Its purpose is to identify genetic alterations that developed as the tumor grew and that may influence prognosis, response to treatment, eligibility for targeted therapies, immunotherapy, or participation in clinical trials.

Testing may be performed using:

- Tissue from the original prostate biopsy.
- Tissue removed during radical prostatectomy.
- Tissue from a metastatic site (especially lymph nodes or bone).
- Circulating tumor DNA obtained from a blood sample (often called a liquid biopsy).

Leading laboratories offering comprehensive tumor genomic profiling include:

- FoundationOne CDx
- FoundationOne Liquid CDx
- Tempus xT
- Tempus xF
- Caris Molecular Intelligence
- NeoGenomics
- Guardant360
- Northstar Genomics

These assays evaluate hundreds of genes and may identify alterations involving DNA damage repair pathways, homologous recombination repair (HRR), microsatellite instability (MSI), tumor mutational burden (TMB), PTEN loss, gene fusions, and many other biomarkers that may guide individualized treatment.

Why Some Patients Need Both Tests

Patients often ask why both germline and somatic tumor testing are recommended.

The answer is simple.

Germline testing asks:

"Did I inherit a mutation that increases my risk of cancer and that could affect my family?"

Somatic (tumor) genomic testing asks:

"What genetic changes has my cancer acquired, and how can they help determine the best treatment?"

These tests provide complementary information.

Another important distinction is that germline testing generally needs to be performed only once during a person's lifetime because inherited DNA does not change.

Somatic (tumor) genomic testing, however, may be repeated as the cancer evolves. As prostate cancer progresses, new mutations may develop that influence treatment decisions.

Why This Matters

Genetic testing is no longer simply an academic exercise.

Today, the results may influence:

- Cancer screening recommendations.
- Prognosis.
- Family counseling.
- Selection of targeted therapies such as PARP inhibitors.
- Eligibility for immunotherapy.
- Enrollment in clinical trials.

Perhaps most importantly, identifying an inherited germline mutation allows children, siblings, and other family members to undergo testing themselves. Earlier screening and preventive care may detect cancer sooner—or even prevent it.

The Bottom Line

Our understanding of prostate cancer has changed dramatically over the past decade.

We now recognize that every prostate cancer has its own unique molecular fingerprint, and every patient has his own inherited genetic blueprint.

Current national guidelines from organizations such as the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend germline and somatic genomic testing for many men with high-risk, recurrent, and metastatic prostate cancer because the information directly influences treatment decisions and provides valuable information for family members.

Knowledge truly is power. Understanding your genes may help determine not only your own treatment, but also protect future generations of your family.

If you have prostate cancer—or a family history of prostate, breast, ovarian, pancreatic, colorectal cancer, or melanoma—ask your physician whether genetic counseling and genetic testing are appropriate. The answers may change not only your treatment, but your family's future.

Suggested References (2024–2025, plus landmark studies)

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5. Pritchard CC, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. New England Journal of Medicine. 2016;375:443-453. (Landmark study establishing the prevalence and significance of germline DNA repair mutations.)
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First published by the Dattoli Cancer Foundation in the quarterly newsletter, Journey Express, Autumn/Winter 2026