The Patrick C. Walsh
Hereditary Prostate Cancer Program

Celebrating Progress and Discovery

Patrick C. Walsh, M.D.
University Distinguished Service
Professor Emeritus of Urology

Message of Thanks

In the late 1980s, I saw a 49-year-old man with prostate cancer who asked me an important question that I could not answer: "Is prostate cancer hereditary?"

When I asked why he wanted to know, he said, "Because my father, my father's three brothers, and my grandfather all died from prostate cancer." But when I posed the question to my colleagues, they said "How can it be hereditary if every man eventually develops it?" No one seemed to recognize this as an important problem, and no one seemed to be working on it. Since that time and for more than 40 years, in partnership with colleagues across departments within Johns Hopkins and others around the world, I have focused my steadfast efforts to answer this question and uncover the genetic factors underlying prostate cancer.

In February 2018, in honor of my 80th birthday, thanks to your shared passion for discovery and generous support, we created the Patrick C. Walsh Hereditary Prostate Cancer Program to advance scientific research on this topic. It is my pleasure, and my honor, to share this update on the incredible progress our team has made over the last five years towards meeting our ambitious goals.

Our work offers the opportunity to identify men and their family members who are at the highest risk of developing aggressive forms of prostate cancer at a time when cure is still possible. Armed with this knowledge, they can begin PSA testing at an earlier age and let the information of their increased risk help inform their course of care.

As we move past the fifth anniversary of the establishment of the Patrick C. Walsh Hereditary Prostate Cancer Program, I am once again reminded that none of our work would be possible without you, our devoted patients, families, and philanthropic partners. Thank you.

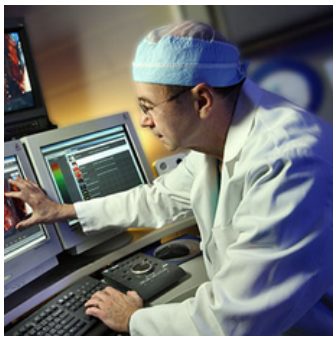
With sincerest gratitude,

Pat

Patrick C. Walsh, M.D.

TIMELINE OF DISCOVERY

Our team's journey to uncover and understand the heritability of prostate cancer began more than 40 years ago. Today, the Patrick C. Walsh Hereditary Prostate Cancer Program provides sustaining resources to build on this progress and to support the ambitious pursuit of scientific discovery.



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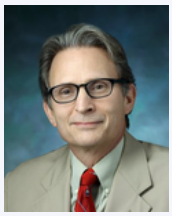

WILLIAM ISAACS, PH.D. JOINS THE BRADY FACULTY WITH A FOCUS ON THE GENOMICS OF PROSTATE CANCER.

1992

BRADY INVESTIGATORS ARE THE FIRST TO CHARACTERIZE AND DEFINE HEREDITARY PROSTATE CANCER.

2008

ADVANCES IN **NEXT-GENERATION GENETIC SEQUENCING** MAKE IT POSSIBLE TO IDENTIFY MULTIPLE, RARE GENETIC VARIANTS CONTRIBUTING TO PROSTATE CANCER.

2008

DR. ISAACS AND COLLEAGUES IDENTIFY SINGLE-NUCLEOTIDE POLYMORPHISMS 'SNPS' IN FIVE CHROMOSOMAL REGIONS WHICH, ALONG WITH A FAMILY HISTORY OF PROSTATE CANCER, HAVE A SIGNIFICANT ASSOCIATION WITH PROSTATE CANCER - AT ANY AGE.

2012

HOXB13 G84E IS IDENTIFIED AS THE FIRST VALIDATED PROSTATE CANCER SUSCEPTIBILITY GENE.

2016

A STUDY AT JOHNS HOPKINS DETERMINES THAT OF MEN WHO DIED FROM PROSTATE CANCER PRIOR TO AGE 65, **10 TO 12%** CARRIED GERMLINE MUTATIONS IN ***BRCA2/BRCA1*** AND ***ATM***.

2018

THE PATRICK C. WALSH HEREDITARY PROSTATE CANCER PROGRAM IS ESTABLISHED TO HONOR DR. WALSH ON HIS **80TH BIRTHDAY** AND ENABLE THE CONTINUED PURSUIT OF SCIENTIFIC DISCOVERY.

2020

BRADY ADVISORY BOARD MEMBERS **ROSS AND BETH MYERS** CREATE A MATCHING OPPORTUNITY FOR SUPPORTERS, RAISING MORE THAN $4 MILLION FOR HEREDITARY PROSTATE CANCER RESEARCH.

"If this will help prevent my sons and grandsons from walking in my shoes, I will help." - Ross Myers

2021

JUN LUO, PH.D., PLAYS A CRUCIAL ROLE IN THE DISCOVERY OF ***X285K***, A NOVEL VARIANT OF ***HOXB13*** WHICH IS SHOWN TO PREDISPOSE MEN OF AFRICAN DESCENT TO DEVELOPING LETHAL PROSTATE CANCER.

2023

DR. LUO, THE ALAN W. PARTIN, M.D., PH.D. PROFESSOR OF UROLOGY, IS NAMED CO-DIRECTOR OF THE PATRICK C. WALSH HEREDITARY PROSTATE CANCER PROGRAM.

WHAT IS THE DIFFERENCE BETWEEN GENETIC AND HEREDITARY?

Because all cancers arise from damage to DNA, all cancers can be considered to have a genetic basis. Hereditary cancer is caused by alterations in the genetic material transmitted from parents to children, otherwise known as germline changes. It affects every cell in the body, has the potential to cause cancer in multiple organs, and is inherited by future family members. Hereditary cancer is rare and affects about 5% of all prostate cancer patients.

5-YEAR PROGRESS UPDATE

8,000
Individual DNA samples sequenced

50+
Scholarly publications since 2018

20,000
Samples collected from prostate cancer patients in the Brady biorepository

14+
Faculty collaborators

3,000
Family DNA samples sequenced

FINDINGS

Men with *BRCA/ATM* are at increased risk of disease progression

BRCA2 is the most important gene in the entire genome in terms of its frequency of pathogenic mutations and the association of these mutations with the risk for lethal disease. Although it took the prostate cancer research community a long time to realize it, *BRCA2* is just as important in prostate cancer as it is in breast and ovarian cancer risk. *ATM* is a gene that is similar to *BRCA2* in this respect. If carried, this mutation gives women an estimated 20-60% increased risk for breast cancer. Men with *BRCA2/ATM* mutations on prostate cancer active surveillance are at increased risk of disease progression and should be under increased scrutiny. Men with Gleason Pattern 5 prostate cancer, the most lethal form of primary prostate cancer, are much more likely to carry a germline mutation in either *BRCA2* or *ATM*.

Are there more prostate cancer susceptibility genes to be found?

Analysis of whole exome sequence data from men with prostate cancer reveals that the most important genes that confer inherited risk of lethal prostate cancer are a small set of 4 genes, all involved in DNA repair: *BRCA2*, *ATM*, as discussed above, *PALB2*, and *MSH2*. In men of African descent this list includes *HOXB13 X285K*. A major question looms: are there genes other than *BRCA2*, *ATM*, *PALB2*, *MSH2*, and *HOXB13* that can be identified and shown to have diagnostic and, ideally, prognostic abilities? To address this question we are examining whole exome sequences, from as many prostate cancer patients as possible, to identify novel, candidate prostate cancer susceptibility genes.

We have recently identified two candidate risk genes, *GPCRC5C* and *IGF1R*, both in men of African descent, that have mutations that are significantly more common in cases than in the general population. While we are excited about these finding, the frequency of these mutations overall is very low, necessitating the need for additional data before we can determine if they play a significant role in inherited prostate cancer susceptibility.

Mutation may be the link to aggressive cancer in Black Men

It is well established that men of African descent in the United States suffer disproportionately from prostate cancer, being more likely to be diagnosed than European Americans and at least twice as likely to die from this cancer. The role of genetic factors in this disparity is an intense area of investigation. Recently, a novel germline mutation, *X285K* in *HOXB13*, the only prostate cancer-specific susceptibility gene discovered to date, was reported to occur in men of African descent. Dr. Isaacs' research team was the first to show that this mutation is associated with increased risk for more aggressive disease in men of African descent. Subsequent studies from other investigators worldwide rapidly confirmed that this mutation is a strong predictor of poor outcomes in men of African descent, being found at higher frequency in men with lethal, metastatic disease. The molecular mechanism of this increased risk has now been described by Dr. Jun Luo's group, a finding with strong prognostic and therapeutic implications.

Leveraging SNP data

SNPs (pronounced "snips") are single nucleotide polymorphisms that are small variations in one's inherited DNA sequence. For each of our patients we determine the presence of SNP variations at over 10,000 positions across the genome. Having this genome-wide SNP data makes it possible to search for associations of genetic variants with other characteristics of our patient population and their cancers. For example, while ancestry self-report is typically quite robust, we can use these SNP data to provide a genetic basis for ancestry that is less subjective. A particularly exciting application of the SNP data is its use in understanding inherited genetic programming of gene expression for key genes like the master oncogene, *MYC*, which has been shown to be essentially required for prostate cancer formation. The role of genetics in determining or modifying any characteristics or traits in patients and/or their tumors in our study population can be examined by using patient SNP profiles that we have now generated. This finding has important implications for targeting personalized screening programs for genetically at-risk men, using a GRS, or genetic risk score approach, to quantify inherited disease risk.

LOOKING AHEAD

STUDYING *HOXB13 X285K*

Black Men have an increased risk of developing lethal prostate cancer. Jun Luo, Ph.D. played a crucial role in the recent discovery of *HOXB13 X285K*, which has been linked to a risk of aggressive prostate cancer in men of African ancestry. Dr. Luo, together with Dr. Arthur Burnett, recently traveled to the University of the West Indies in Jamaica to establish a collaborative project studying the clinical correlates of the *HOXB13 X285K* founder mutation in the Jamaican population.

FEDERAL GRANTS

Dr. Luo, along with epidemiologist Elizabeth A. Platz, Sc.D., M.P.H. of the Bloomberg School of Public Health, and Tamara Lotan, M.D., Professor of Pathology, received a three-year grant (2023-2026) from the Department of Defense to advance their research into the role of the *HOXB13* variant, *X285K*, and its associated risk of lethal prostate cancer in men of African ancestry.

THE NEXT SUSCEPTIBILITY GENES?

We have about 20 candidate genes that we are interrogating for functional properties by looking at the effects of gene under- or overexpression on the behavior of either normal prostate epithelial cells or malignant prostate cancer cells. This behavior includes tumor characteristics such as growth rate and invasion of prostate cells grown in culture.

DATA SHARING AND COLLABORATION

Our research teams were the first to characterize many of the genes that play a role in prostate cancer thanks to the critical access to tumor tissue samples from radical prostatectomies performed at the Brady. The goal is to develop an data sharing system so that this information can be made available to qualified prostate cancer investigators around the world. Our current collaborators include Dr. Shawn Lupold and Research Technologist Daniel Rabizadeh at the Brady; Drs. Jun Wei, Jianfeng Xu, and Lilly Zheng at NorthShore Research Institute in Chicago; and, Dr. Kathleen Cooney, Chair, Department of Medicine, Duke University School of Medicine.

WAYS TO SUPPORT

secure.jhu.edu/form/urology

BradyDevelopment@jhmi.edu

The Brady Urological Institute
Development Office
600 North Wolfe Street, CMSC 130
Baltimore, MD 21287

410-955-8434