

October 2018

"Prostate Cancer Genetics 100"

Leonard G. Gomella, MD
Chairman
Department of Urology
Sidney Kimmel Cancer Center
Philadelphia, PA



Jefferson
HEALTH IS



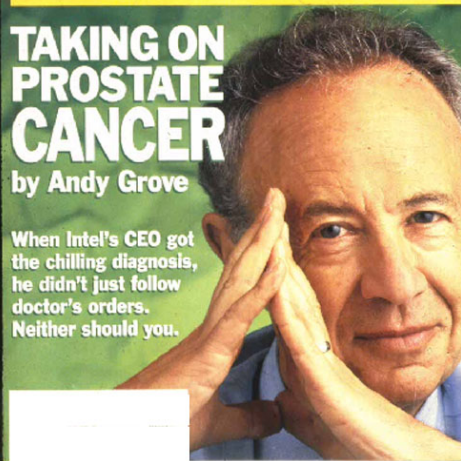
MAY 13, 1996 \$4.50

FORTUNE

TAKING ON PROSTATE CANCER

by Andy Grove

When Intel's CEO got the chilling diagnosis, he didn't just follow doctor's orders. Neither should you.

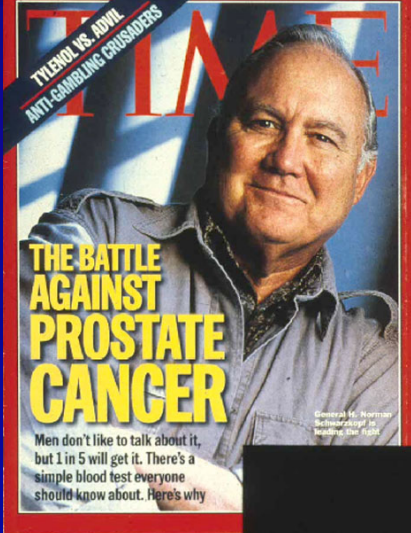
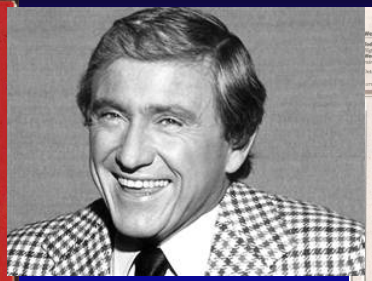


TYLENOL VS. ADVIL
ANTI-CAMBRIDGE CROSSBREDERS

TIME

THE BATTLE AGAINST PROSTATE CANCER

Men don't like to talk about it, but 1 in 5 will get it. There's a simple blood test everyone should know about. Here's why

The Washington Post

Powell Has Surgery for Prostate Cancer

Doctors Predict Complete Recovery

By GLENN KESSLER
Washington Post Staff Writer

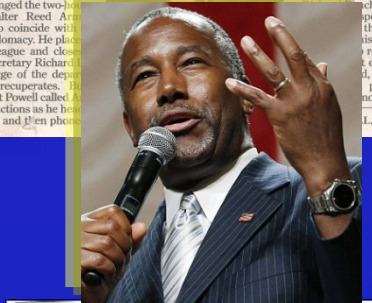
Secretary of State Colin L. Powell underwent surgery yesterday morning to remove a cancerous prostate gland and is expected to make a full recovery, the State Department said.

Powell, 66, arranged the two-hour procedure at Walter Reed Army Medical Center to coincide with a slow period in diplomacy. He plus his longtime colleague and close aide, Richard Armitage, were in charge of the department's operations. Powell called Armitage to get instructions as he headed to the hospital, and given photos of the successful procedure from which most men quickly recover.

The surgery, while not an emergency, appears certain to revive speculation about how long Powell will continue as secretary of state, though talk of his leaving was quickly rejected by his aides. Powell has indicated to aides he intends to serve only in Bush's current term, but has given no sign of an even earlier departure.

State Department spokesman Richard Muir told reporters that Powell will spend several days recuperating at the hospital before returning home in McLean. "I report that he is out of everything went fine," he said, saying doctors found no prostate cancer and no complications.

L.A. 116, Col. 4

Health and behavior

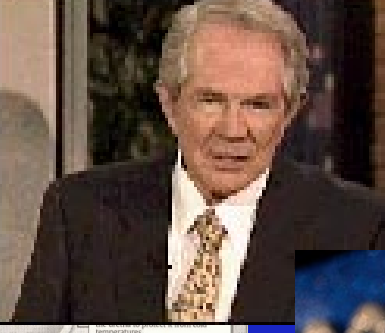
Tutu tries to melt silence on prostate cancer

By Anita Manning
USA TODAY


Archbishop Desmond Tutu, who has spoken publicly about his struggle with prostate cancer since his diagnosis in 1996, got some bad news in the fall.

Despite radiation therapy, his PSA level — the measure of prostate-specific antigen that signals the presence of cancer cells in the prostate — was increasing. Tutu had been given all the radiation his body could take, and his options were limited.

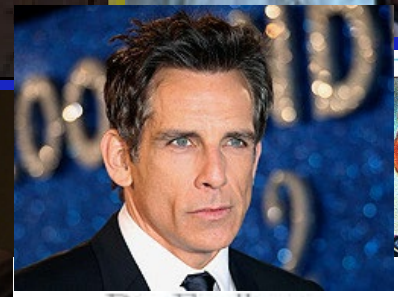
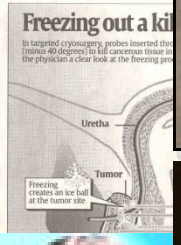
"It is imperative that (men) have regular examinations. We ought to be behaving the way women behave over breast

Palmer to need radiation



ASSOCIATED PRESS



Prostate cancer's high profile

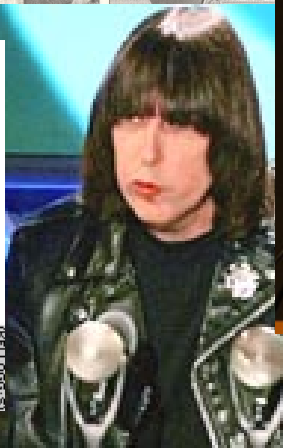
Actor Robert De Niro




Kellogg's
FROSTED FLAKES
OF CORN

THEY'RE GRR-REAL!

TONY



Dan Fogelberg




The Innocent Age

opportunity to co-writing of my thing my normal rather difficult."

Palmer under January 1997 at in Rochester, M to competition months later.

"We are pro follow-up because blood



got prostate cancer?

Let's not give their kids less milk. Now, some of their sons have prostate cancer. The risk of prostate cancer is rising. Studies show that dairy consumption may reduce your risk of prostate cancer. Instead, maybe that's why Henry Clinton's campaign headquarters kept sending out those free ice cream sandwiches.

www.MilkSucks.com

PETA

Prostate Cancer Celebrities

Same disease, different stories in the news.....

- **Senators Dole & Kerry, Colin Powell, Ben Carson Ben Stiller**
 - PSA screening, then surgery
- **General Schwarzkopf; Len Dawson**
 - Rectal exam abnormal, then surgery
- **Mayor Giuliani**
 - Hormones + seeds + external beam radiation
- **Ian McKellan (Gandalf & Magneto): Active surveillance**
- **Arnold Palmer**
 - Surgery, rising PSA, radiation
- **Archbishop Tutu**
 - Radiation, rising PSA, cryotherapy
- **Pat Robertson, Ben Stiller, Chris Matthews**
 - Laparoscopic/robotic prostatectomy
- **Johnny Ramone, Jerry Orbach, Thurl Ravenscroft, Merv Griffin, Dan Fogelberg, Dennis Hopper**
 - Died from prostate cancer

Lecture Overview

- Basic principles of genetics and genomics
- Prostate cancer genes
- Practical genetic testing for prostate cancer



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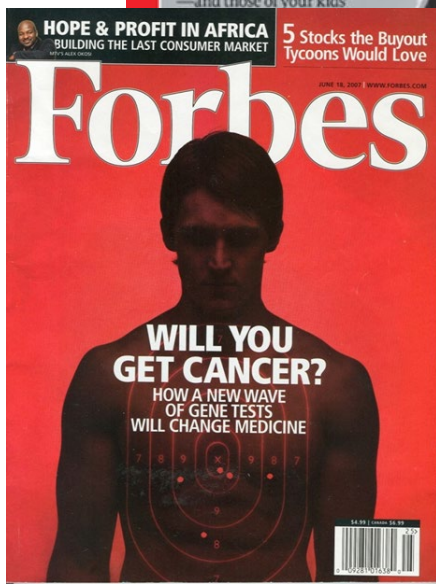
Background

- Approximately 5-15% of prostate cancers are due to an inherited predisposition.
- Genetic counseling and genetic testing may benefit patients by identifying the genetic basis leading to cancers in their family.
- This can help with decisions for cancer screening, treatment options, cancer risk reduction, and other preventive measures.



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CANCER AWARENESS

Genomics, studies try to uncover prostate cancer

By Paul Jablow
FOR THE INQUIRER

For researchers, physicians — and patients — prostate cancer has always been among the most maddening and elusive of foes.

The third-most common cancer in the United States, behind breast and lung cancers, its course is less

one cancer from another. Now researchers at Thomas Jefferson University and elsewhere think they are coming closer to solving it through increasingly sophisticated genetic studies.

The payoff would be in saving lives, and also in avoiding the overuse of surgery, radiation, and other treatments that have debilitating

FDA to Finalize LDT Guidance Amid Uncertainty on Number of Genetic Tests Impacted

Feb 04, 2016 | [Turna Ray](#)

60,000 Genetic Tests!!!

NEW YORK (GenomeWeb) – An analysis conducted by Tennessee-based healthcare IT firm NextGxDx suggests there may be around 60,000 genetic testing products currently on the market, comprising more than half of the US laboratory-developed test market.

Moreover, depending on the criteria used, NextGxDx has projected that around 7,600 of these genetic testing products could be deemed high risk by the US Food and Drug Administration, for which labs may have to meet premarket review requirements. Since the agency intends to finalize its draft oversight plan for LDTs this year, it's critical that the FDA and industry players have an accurate estimate of currently marketed tests.

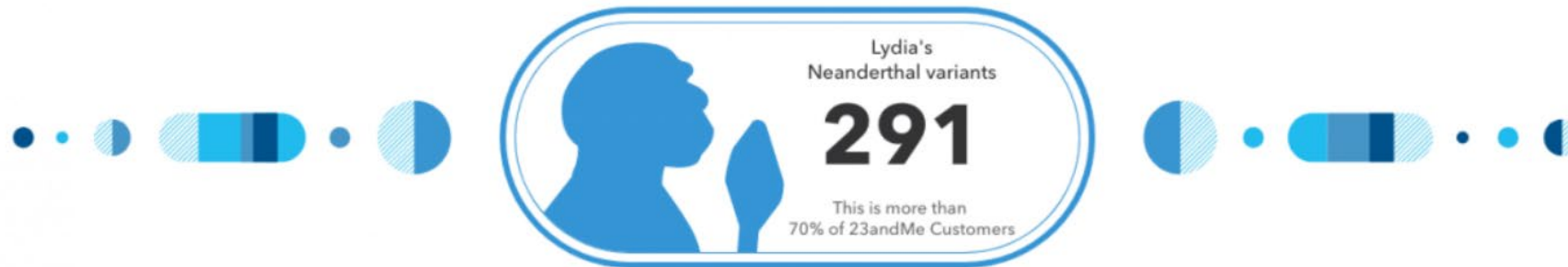
Recreational Genomics????



Neanderthal Ancestry

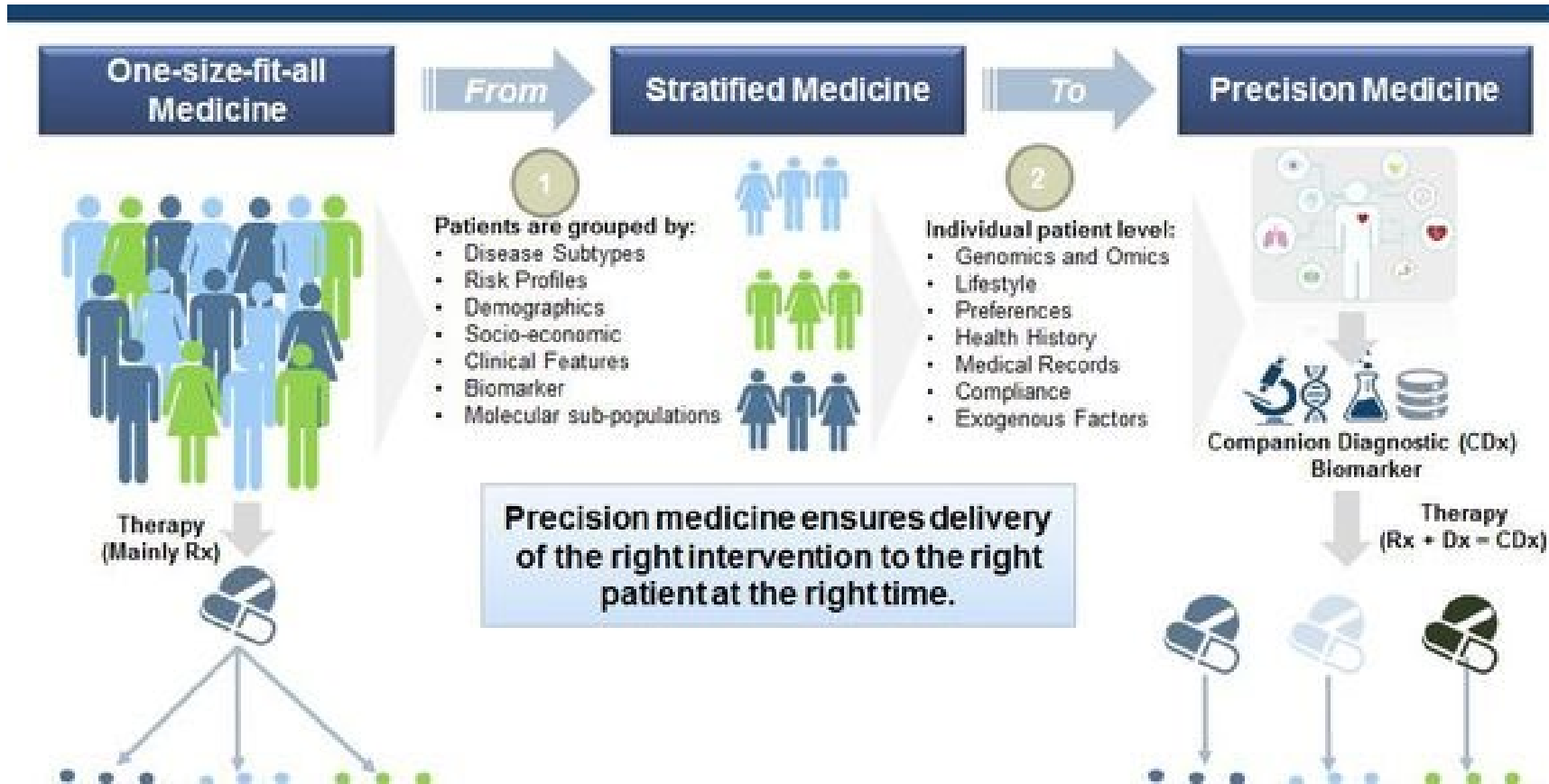
Neanderthals were ancient humans who interbred with modern humans before becoming extinct 40,000 years ago. This report tells you how much of your ancestry can be traced back to Neanderthals.

You have 291 Neanderthal variants.



You have more Neanderthal variants than 70% of 23andMe customers. However, your Neanderthal ancestry accounts for less than 4% of your overall DNA.

Evolution of Precision Medicine





Your GENOME & YOU



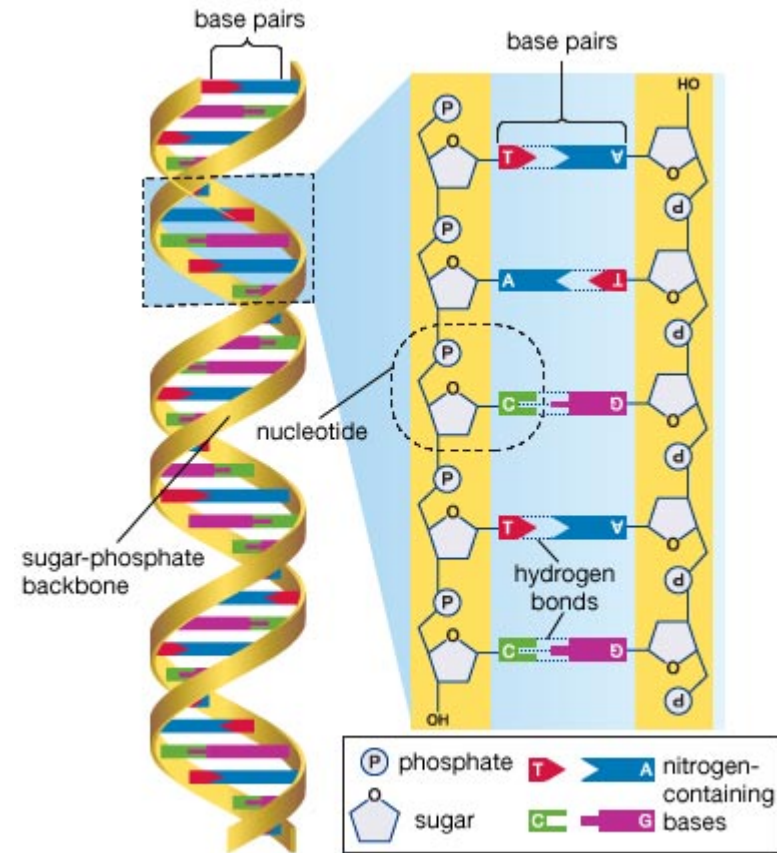
Knowing about your genome helps you understand your health and supports your health decisions.

GENOME is just a fancy word for all your DNA.

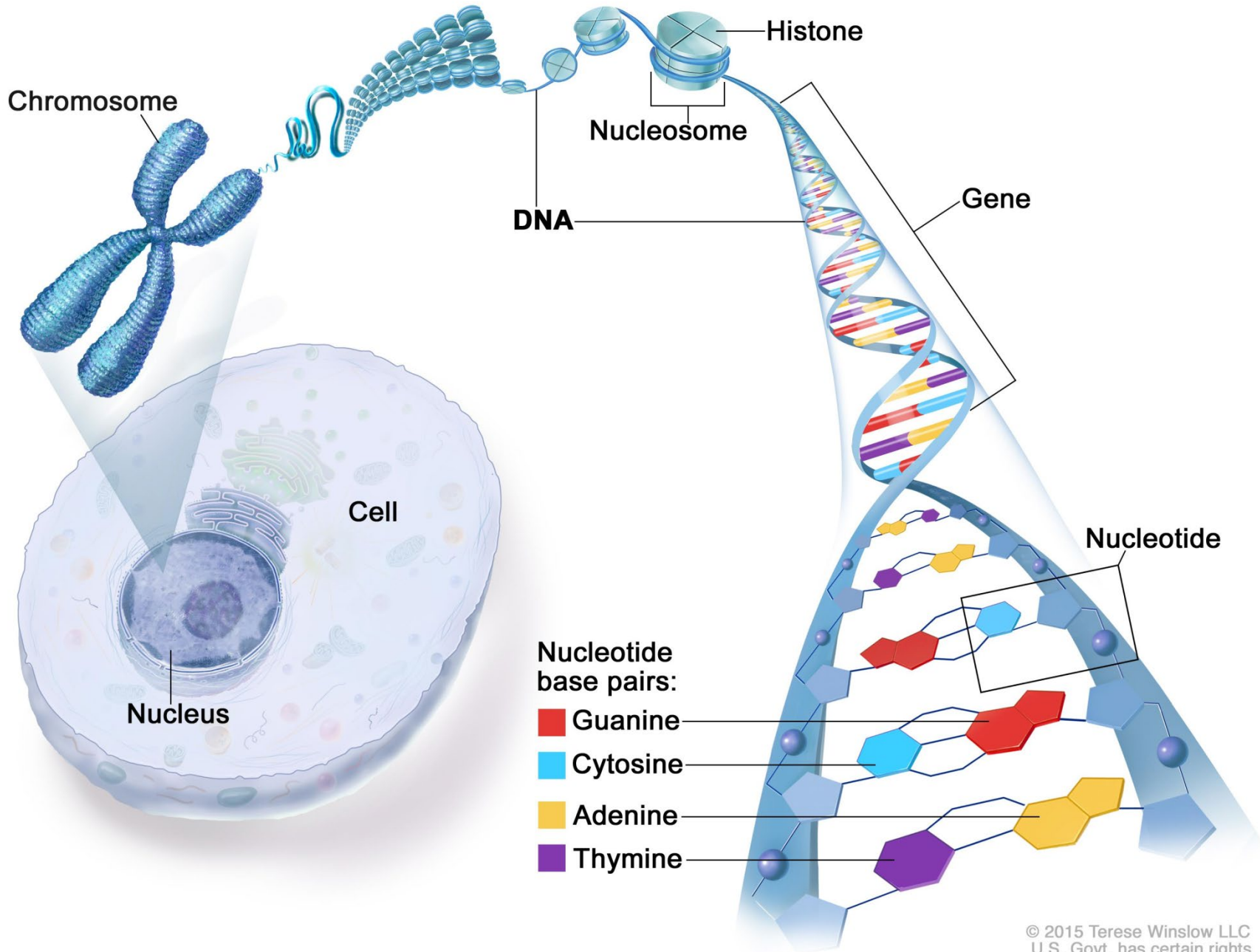


Welcome to the genome...

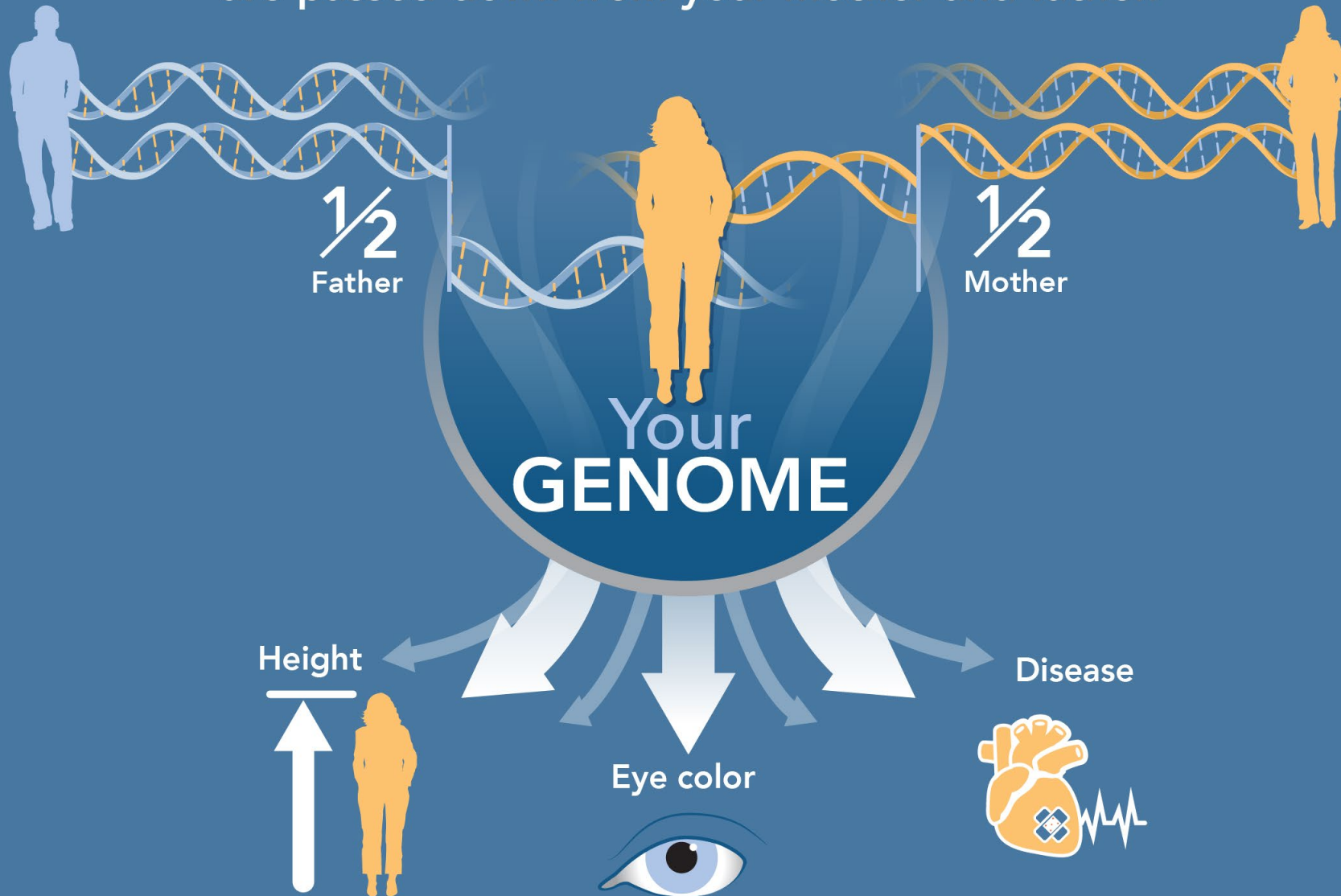
..the miraculous blueprint of your DNA, coiled tight as a spring in the nucleus of each cell of your body. If unwound, the DNA from just one cell, while only a molecule in width, would stretch six feet in length! The information stored in its double helix structure - three billion bits worth - could fill 142 Manhattan phone books.



DNA Structure



Your GENOME contains all the instructions for you to grow throughout your lifetime. These instructions are passed down from your mother and father.



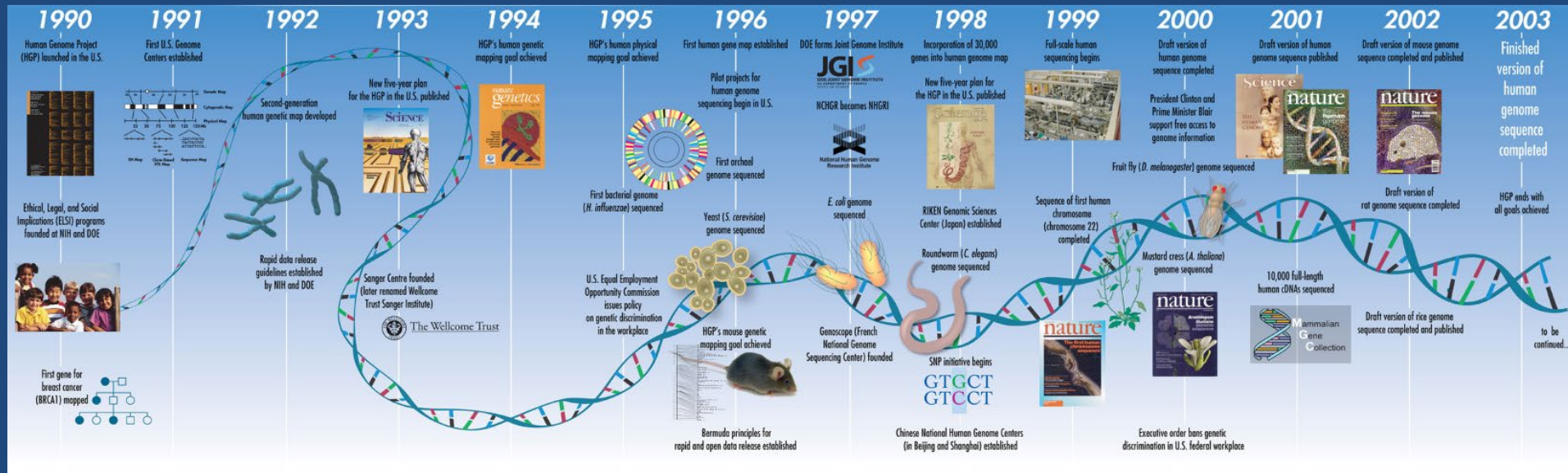
These instructions make you unique.

You can play an active role in keeping your genome healthy.
You can eat healthy foods. You can exercise.
You can avoid things that might cause diseases.



We are learning new things about the human genome every day.

Human Genome Project 1990-2003



3.2 billion base pairs

https://www.mun.ca/biology/scarr/Human_Genome_Project_timeline.html

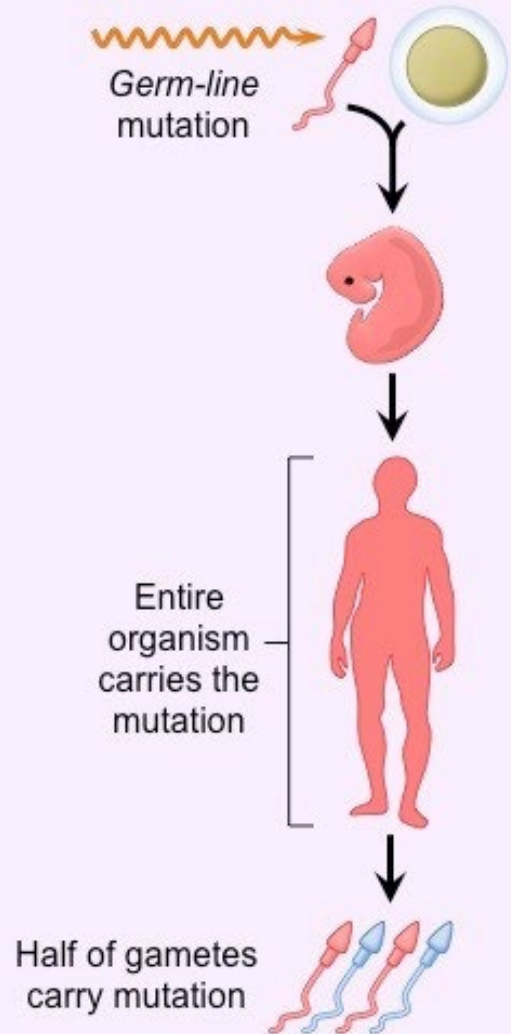
Genetics vs Genomics

- Genetics:
 - **TRADITIONAL:** the study of specific, individual genes and their inheritance
 - Eg, sickle cell anemia and cystic fibrosis, a single gene
 - **MODERN:** multiple genes inheritance pattern
- Genomics:
 - **MORE COMPLEX;** refers to an organism's entire genetic makeup (genome) or an extensive number of genes
 - MODERN GENETIC TESTING RELIES ON GENOMICS

Genomic Testing Basics

- DNA made up of base pairs (e.g., AT TC CG GA)
- Base pairs: Bacterium 600,000; Humans >3 billion
- Except for RBC all cells have entire set of genes
- Humans 23 chromosome pairs w/50-250 10^6 base pairs
- Genes, the sequence that makes proteins
 - only 2% of genome
 - Most of DNA “non-coding” (structural, housekeeping)
 - Human have 30-40,000 genes

GERM-LINE MUTATIONS



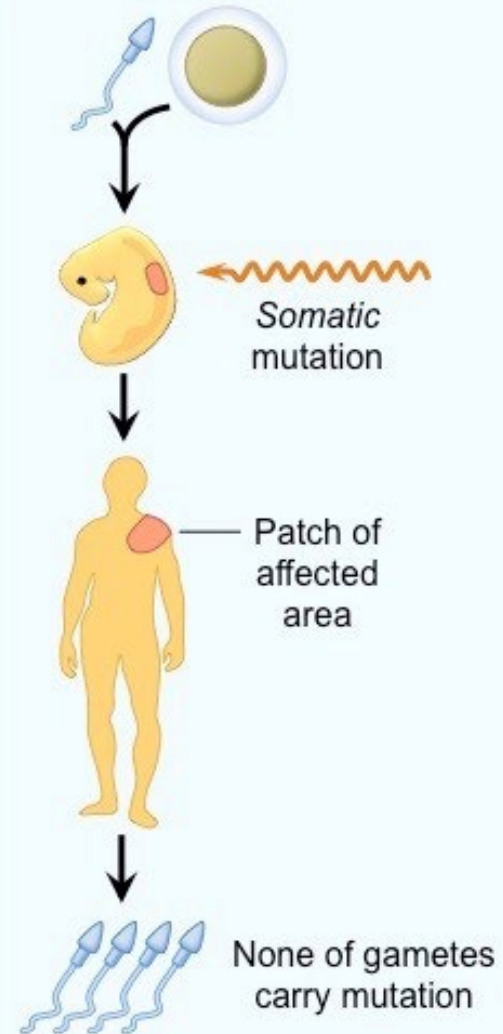
Parental Gametes

Embryo

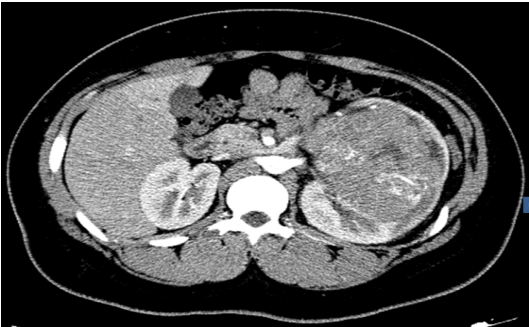
Organism

Gametes of Offspring

SOMATIC MUTATIONS



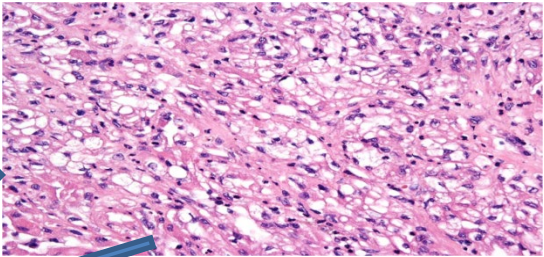
EVOLUTION OF TUMOR EVALUATION



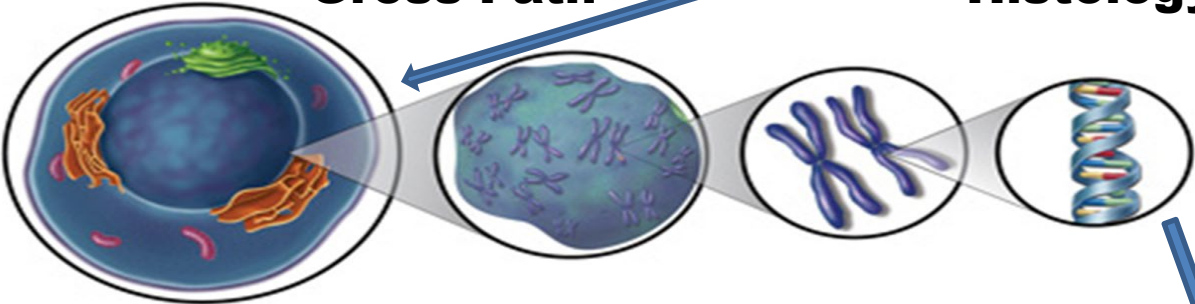
Imaging



Gross Path



Histology Path



Cell Nucleus Chromosomes DNA

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```

Base Pairs

Our understanding of genomics relies on computational biology support

```
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CTCCAGAACATTTAATATCCCAAAAAGGCTTTTTCATATAATGTGGTAAATTCATCTG
```

BRCA2 gene section

-27 exons total

-coding region

10,433 base pairs

-12 pages long

-image is a very

small portion of

exon 11

Genomic Tissue Testing

- Relies on tumor tissue in pathology lab



ARCHIVED
FFPE TISSUE

Genetic Testing

- Buccal saliva swab most common



- “Recreational” testing unlikely to deep sequence
- Medical labs: beware low cost

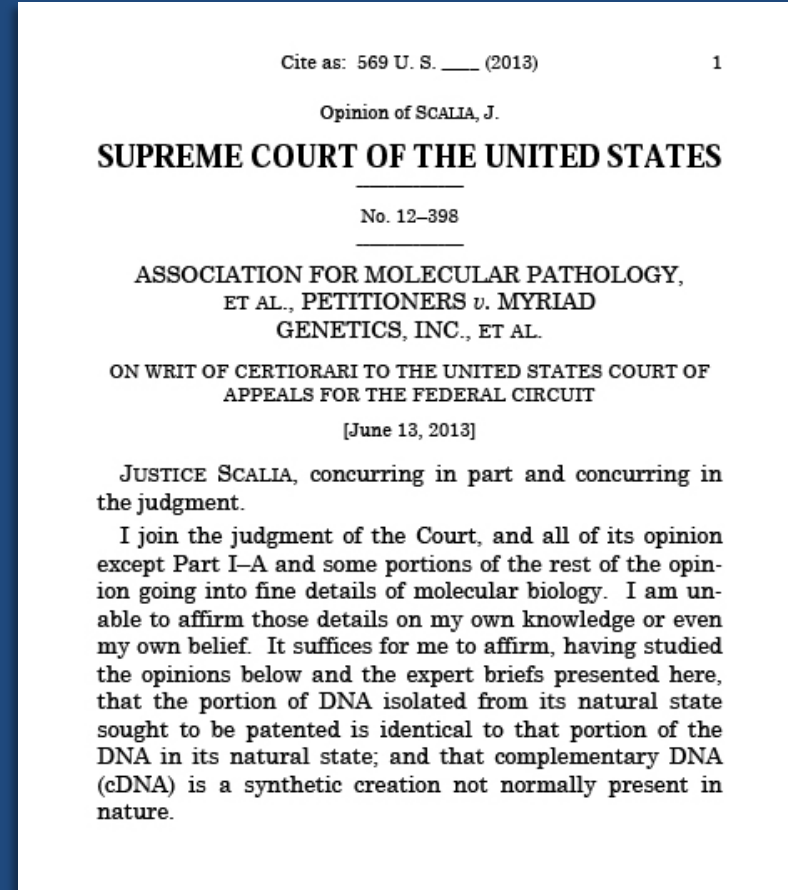
- Deep sequencing (hours to days):
 - Sequencing a region many times
 - Minimizes errors
 - More sequencing = more expensive = more accurate



Spring 2013: Everything Changed

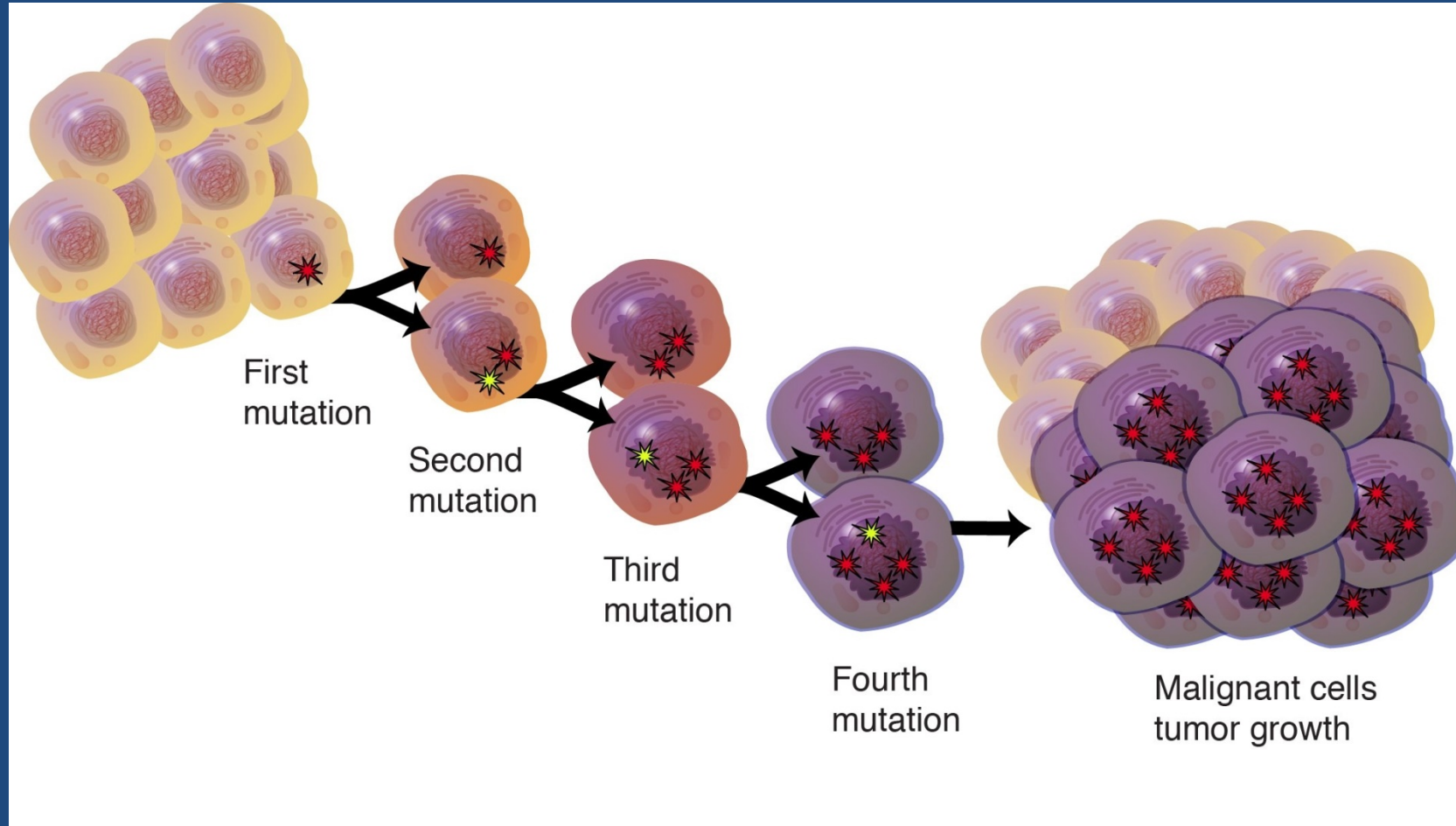


May 13, 2013



June 13, 2013

All Cancer is Genetic Not All Cancer is Hereditary



CANCER SUSCEPTIBILITY PATTERNS

Sporadic

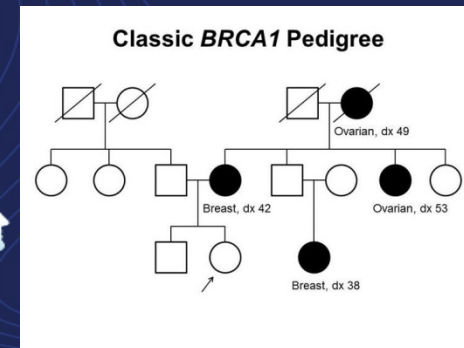
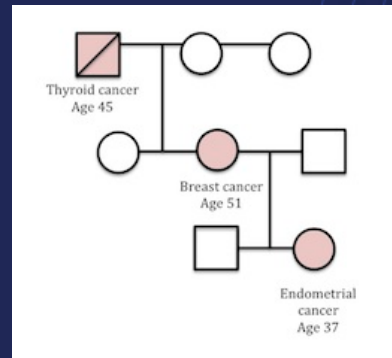
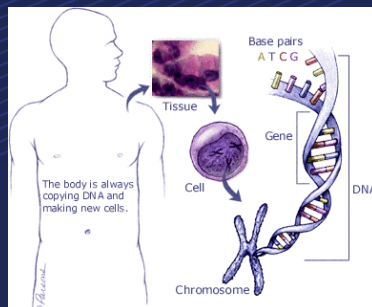
- Cancers in family likely occurred due to chance or environmental exposure

Familial

- More cancers than expected by chance in family due to mixture of environmental and genetic factors

Hereditary

- Known inherited reason for cancers in family



April 8, 2019

FDA: Unapproved Genetic Tests Claim to Predict Drug Response



Can Genetic Testing Guide Treatment Decisions for Prostate cancer?

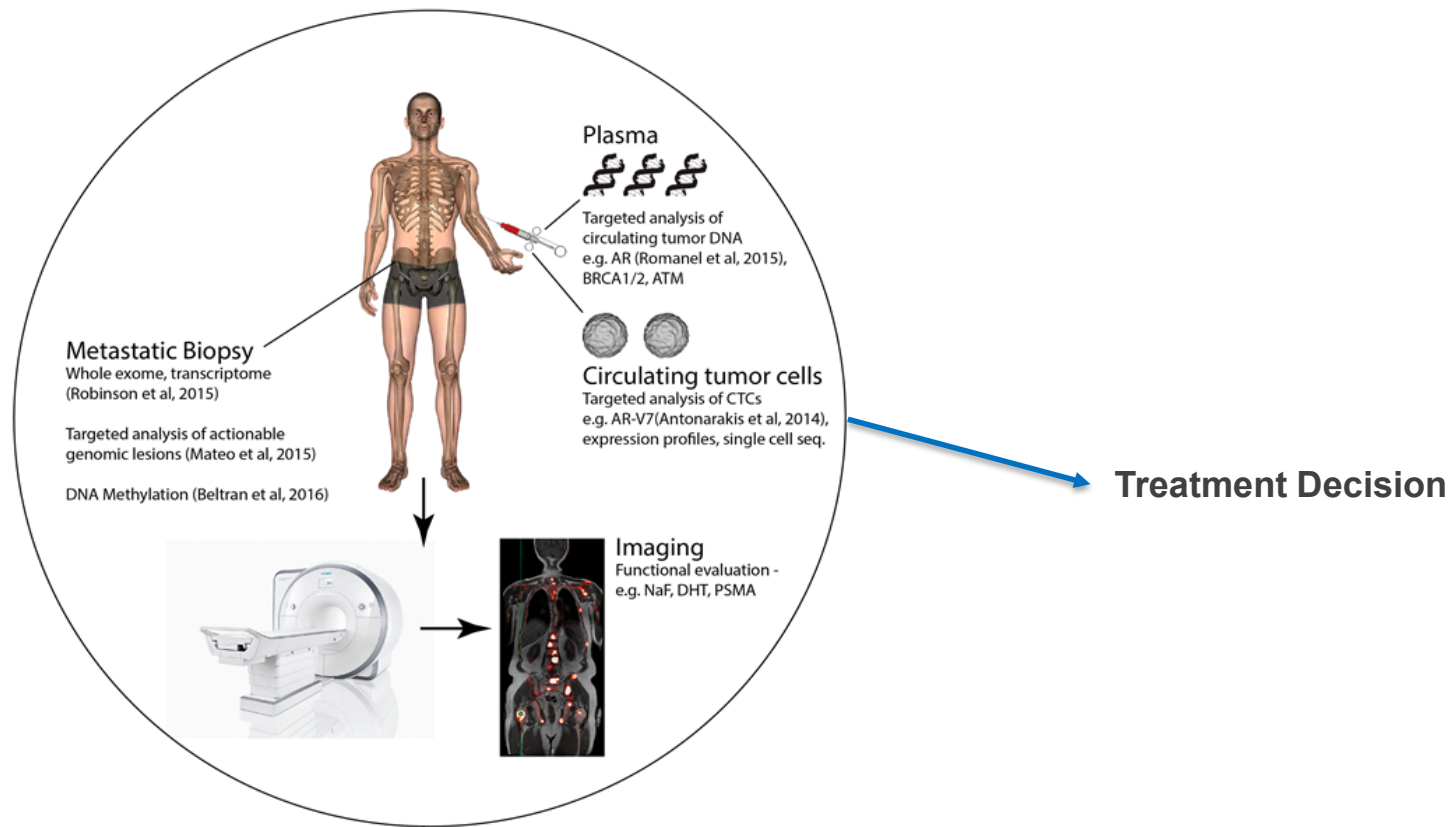


Image from Bertran, et al. 2016 ASCO Educational Book. Presented June 4, 2016.

Genetic Testing and Prostate Cancer Risk: Philadelphia Prostate Cancer International Consensus Conference 2017 and 2019



Sidney Kimmel Cancer Center, Thomas Jefferson University
and
The Foundation for Breast and Prostate Health
Philadelphia, Pennsylvania
March 3 & 4, 2017



“Implementation of Genetic Testing for Inherited Prostate Cancer”

2019 Consensus Conference

October 4,5 2019

Sidney Kimmel Cancer Center, Thomas Jefferson University



**Sidney Kimmel
Cancer Center.**
at Jefferson
NCI – designated

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Role of Genetic Testing for Inherited Prostate Cancer Risk:
Philadelphia Prostate Cancer Consensus Conference 2017

J Clin Oncol. 2018 Feb 1;36(4):414-424

Co-Chairs:
Leonard G. Gomella, MD
Veda N. Giri, MD
Karen E. Knudsen, PhD

Genomic/Genetic Testing for Inherited Prostate Cancer Risk

• Background:

- 10-15% PCa are hereditary.
- Several abnormal genes linked to an increased risk of Pca but may not always cause cancer
 - Also increased risk for other cancers
 - Actionable genes identified

• Why do Genomic Testing?

- Potential impact on therapeutic options
- Potential to screen/prevent for other at-risk cancers in the patient and family

Composition of Typical PCa Panel:

Gene	PCa Risk	
ATM	elevated	DNA-damage response
BRCA1	~ 20%	DNA damage repair
BRCA2	~ 20%	DNA damage repair
CHEK2	elevated	DNA repair through phosphorylation of BRCA2
EPCAM	up to 30%	upregulate c-myc
HOXB13	up to 60%	AR repressor
MLH1	up to 30%	DNA repair
MSH2	up to 30%	DNA Repair
MSH6	up to 30%	DNA repair
NBN	elevated	DNA repair
PMS2	up to 30%	DNA mismatch repair
TP53	unknown	Tumor suppressor
PALB2	preliminary evidence	Tumor suppressor
RAD51D	preliminary evidence	DNA repair

Based on data in Nicolosi, et al ASCO Abstract 5009 2017 Chicago;
<https://www.ncbi.nlm.nih.gov/gene/>

BRCA 1/2 Prostate Cancer Risks

- If mutated or abnormal gene
- 2-6 fold increased lifetime risk
 - (BRCA2 > BRCA1)
- 8.6-fold increased risk by age 65 (BRCA2)
- PCa Prognosis: More likely to have aggressive features: Gleason 8 or higher, node positive disease, mets, poor survival
- Other hereditary cancers: breast, ovarian, melanoma, pancreatic, Lynch Syndrome, colorectal, gastric

Affected Father



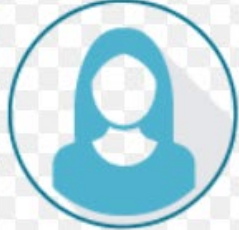
Unaffected Mother



Affected Son



Unaffected Daughter



Unaffected Son

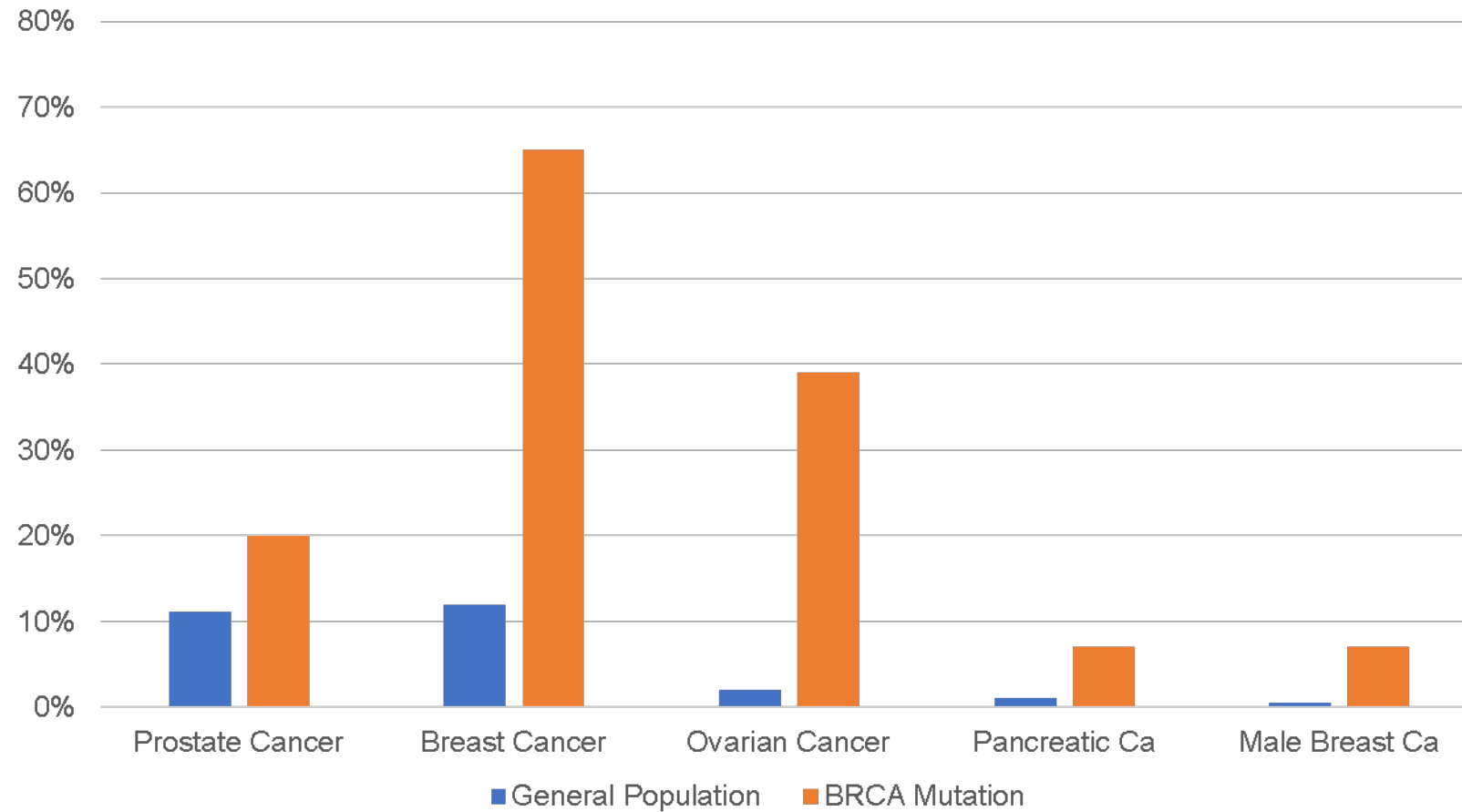


Affected Daughter



If one of your parents has a BRCA mutation, you have a **50%** chance of inheriting the mutated gene.

BRCA1/2 Cancer Risk



Hereditary Prostate Cancer

Hereditary-Associated Cancers:

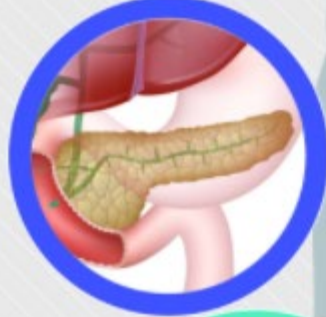
MALE BREAST
CANCER RISK
UP TO 6.8%



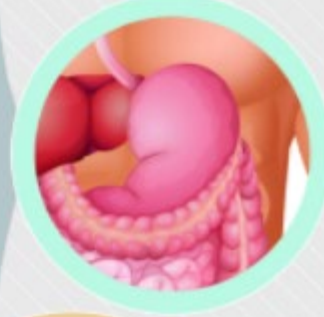
MELANOMA RISK
UP TO 3.6%



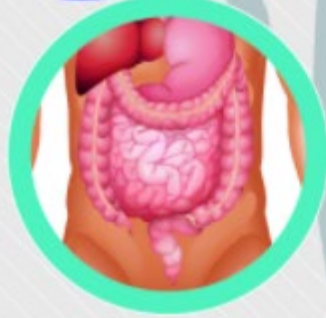
PANCREATIC
CANCER RISK
UP TO 36%



STOMACH
CANCER RISK
UP TO 80%



COLON CANCER RISK
UP TO 99%

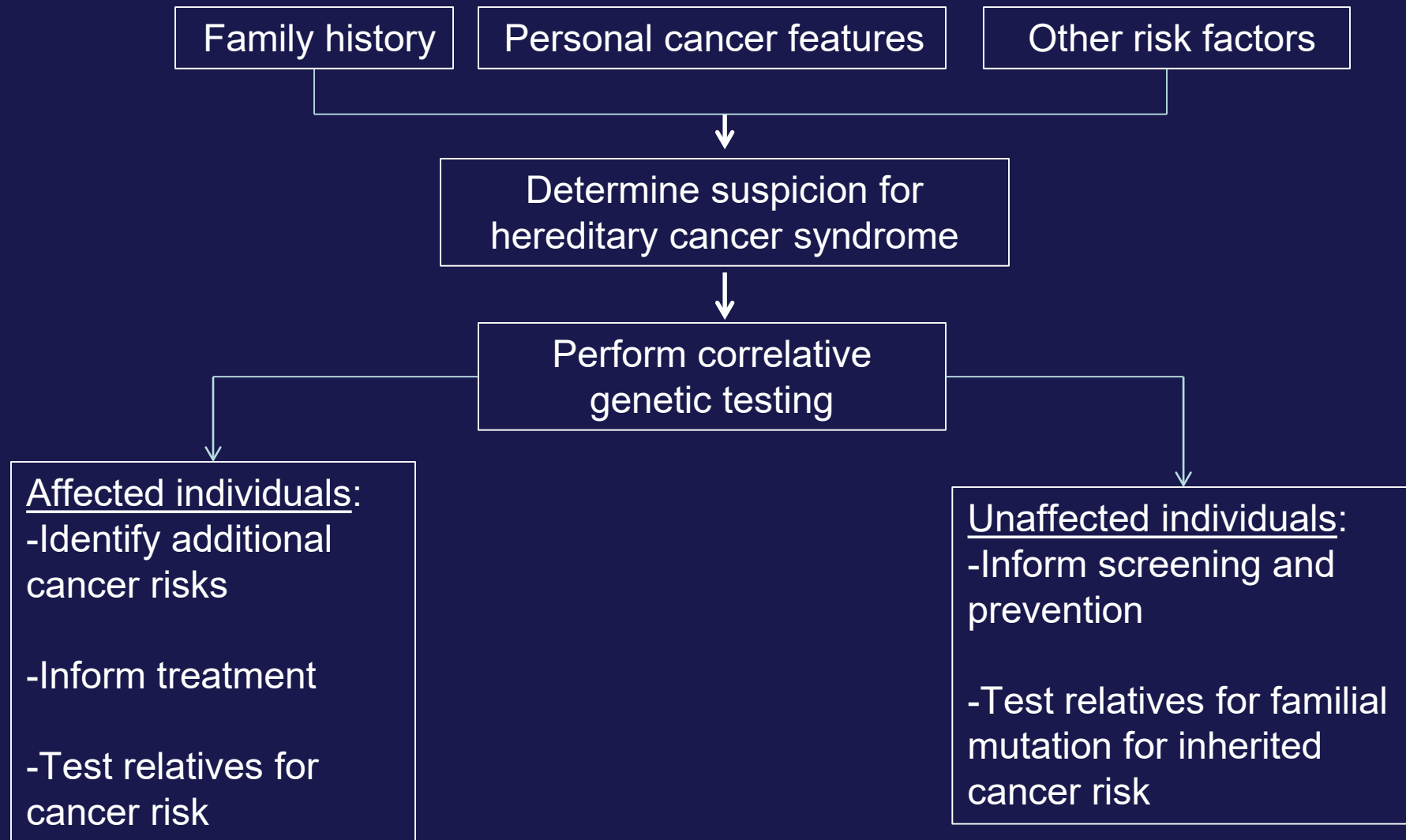


RENAL CANCER RISK
UP TO 34%



URINARY TRACT
CANCER RISK
UP TO 34%

Model for Genetic Testing for Inherited Cancer Risk



Why see a genetic counselor in a cancer setting?

“What does my cancer diagnosis mean for my family?”

“What are my chances of getting cancer and what types of screening should I do?”

“Many of my family members have had cancer and I am worried about getting cancer myself.”



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Kimmel Cancer
NCI-designated



Genitourinary Cancer Genetics Clinic

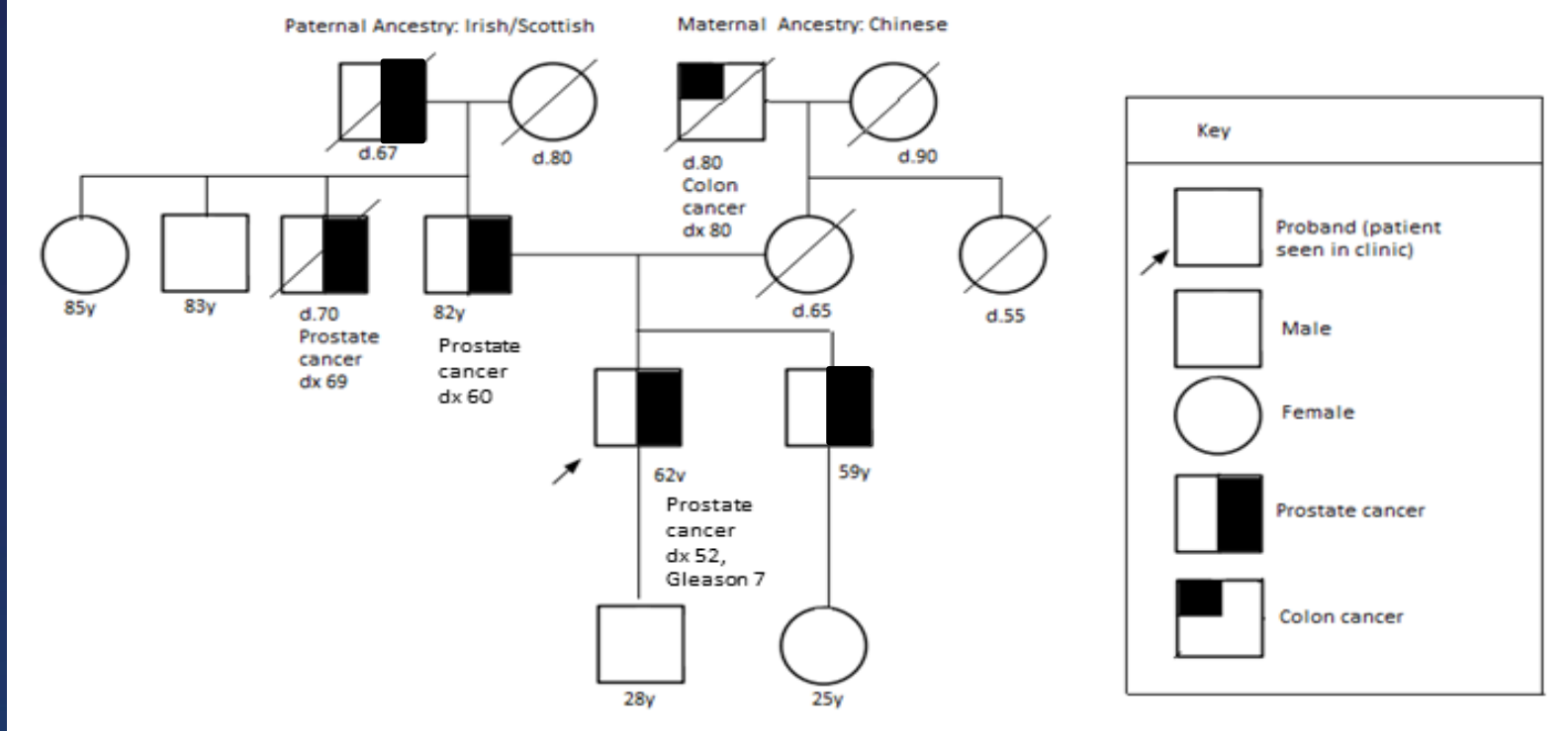
- The clinic is conducted in parallel with the GU Multidisciplinary clinic so that men presenting for prostate cancer management visits can have the opportunity to undergo genetic evaluation as well.
- First genetics clinic in the Philadelphia region focused on GU cancers
- Focus on genetic cancer risk assessment for prostate cancer, kidney cancer, and upper tract urothelial cancer
- Clinical staff include genetic counselor, Dr. Giri, and a research coordinator to enroll patients to research studies.



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Kimmel Cancer
NCI-designated



Hereditary Prostate Cancer



Who in family should be offered “cascade testing”?

Genetic Testing and Counseling for Prostate Cancer

American College of Medical Genetics and Genomics (ACMG)/National Society of Genetic Counselors (NSGC) practice guidelines

- All cases of metastatic prostate cancer
- ≥ 2 cases of prostate cancer diagnosed at age ≤ 55 in close relatives
- ≥ 3 FDRs with prostate cancer
- Aggressive (Gleason score >7) and ≥ 2 cases of breast, ovarian, and/or pancreatic cancer in close relatives

Conclusions

- Evolving recommendations for prostate ca genetic testing
- Most critical genes today:
 - BRCA 1/2, HOXB13, ATM, CHEK2
- In the future genetic testing may guide prostate cancer
 - screening, treatment with new drugs (PARP inhibitors)
- Consider referral for genetic testing AND counselling if high risk or strong family history
- Expanding role for these genetic counseling professionals in prostate cancer care
- Many new prostate cancer genetic panels are being made available commercially

Genetic tests: Experts urge caution over home testing

🕒 17 October 2019

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People should not make health decisions based on genetic tests they do at home, experts have warned.

The University of Southampton team, **writing in the British Medical Journal**, warn results can be unreliable.

The geneticists said the tests could be wrongly reassuring - or lead to unnecessary worry.

23andMe, one of the companies offering tests, said there were "many cases" where results had prompted further checks and preventative treatment.

The research does not cover genetic screening offered by the NHS to people with a family history of a disease, or other risk factors.



Two Sisters Bought DNA Kits. The Results Blew Apart Their Family.

In an age of ubiquitous direct-to-consumer genetic testing, family secrets are almost impossible to keep.

By Amy Dockser Marcus

Feb. 1, 2019 11:18 a.m. ET

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