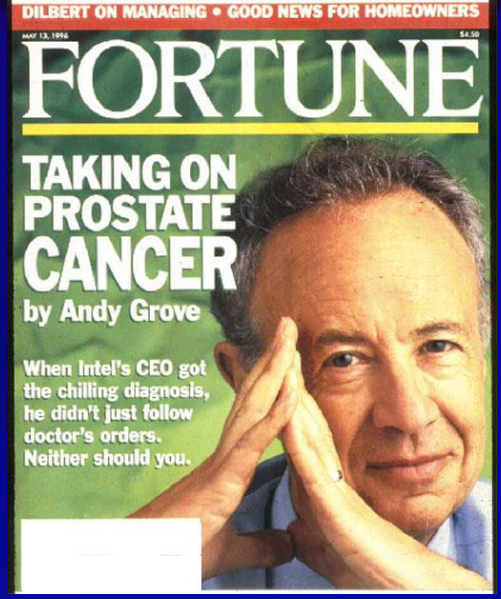
National Alliance of State Prostate Cancer
Coalitions Webinar Series

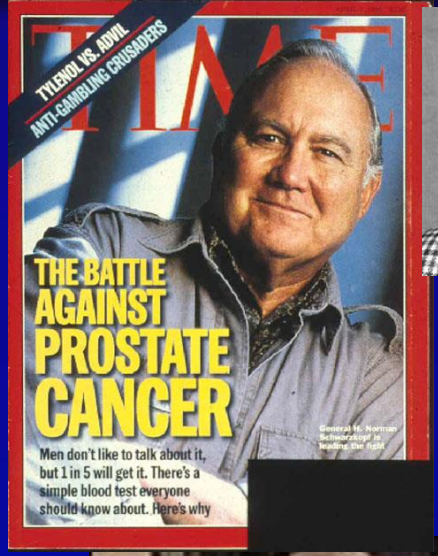
"Genetic Testing and Genetic Counseling in Prostate Cancer"

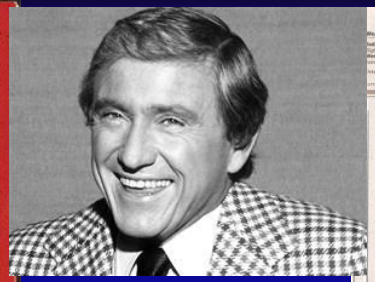
Leonard G. Gomella, MD
Chairman
Department of Urology
Sidney Kimmel Cancer Center
Philadelphia, PA

Jefferson
HEALTH IS ALL WE DO

BEST HOSPITALS
U.S.News
NATIONAL
UROLOGY
2017-18


DILBERT ON MANAGING • GOOD NEWS FOR HOMEOWNERS
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.


TIME
TYLENOL VS. ADVIL
ANTI-GAMBLING CRUSADERS
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

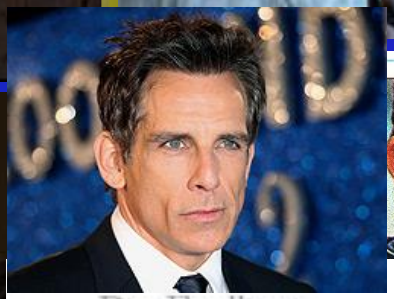


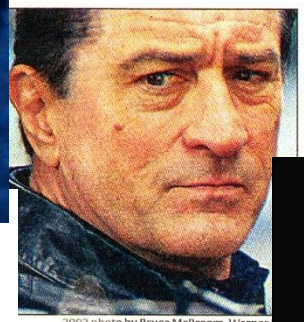

The Washington Post
FINAL
Powell Has Surgery for Prostate Cancer
Doctors Predict Complete Recovery
By Glenn Kessler
Washington Post Staff Writer


Health and behavior
Tutu tries to melt silence on pro
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

Freezing out a ki
Uretha
Tumor
Freezing creates an ice ball at the tumor site


Palmer to need radiation
ASSOCIATED PRESS




2002 photo by Bruce McBroom, Warner

Prostate cancer's high profile
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Kellogg's
FROSTED FLAKES
OF CORN
THEY'RE GR-R-REAT!
TONY

Dan Fogelberg
The Innocent Age

got prostate cancer?
Lotsa mothers give their kids lotsa milk. Now, some of their sons have prostates the size of the Empire State Building. Studies show that dairy consumption may increase your risk of prostate cancer. Hmmm, maybe that explains why Hillary Clinton's campaign headquarters kept sending over 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
  - Laparoscopic prostatectomy
- Johnny Ramone, Jerry Orbach, Thurl Ravenscroft, Merv Griffin, Dan Fogelberg, Dennis Hopper
  - Died from prostate cancer

Prostate Cancer Issues and Controversies

- Prostate cancer crisis due to aging population.
  - "Death *with* rather than *of* prostate cancer"
- Cost from screening to treatment: mostly older men, government pays most.
- Prevention: no options.
- Imperfect and controversial screening.
- Local disease: too may options, side effect issues.
- Advanced disease: *suddenly* too many options.
- Technology: Rapid and expensive.
- Genetic Testing: Rapidly evolving.

Jefferson™
HEALTH IS ALL WE DO

17 genes

that run in families have been discovered that have overlap from prostate cancer to other cancers.

If the prostate cancer is caught at an early stage, most men will not experience any symptoms.

Prostate cancer has one of the highest survival rates of any cancer.

Since 1993, deaths from prostate cancer have been cut in half.

100%

Prostate cancer is 100% treatable if detected early.

10 THINGS TO KNOW

A man of African descent is 70% more likely to develop prostate cancer.

70%

As men age, their risk of developing prostate cancer increases exponentially.

Thanks to emerging science, in the next 5 years, we may see an end to all incurable prostate cancer.

Prostate cancer is the **most common** non-skin cancer in America.

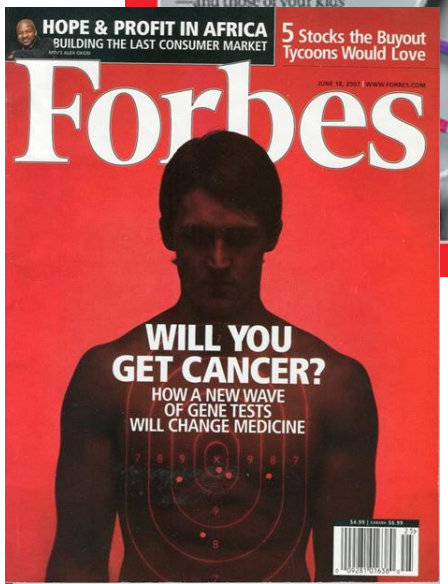
2x

Men with relatives with a history of prostate cancer are twice as likely to develop the disease.

PCF 2017

Background

- Approximately 5-10% of 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, cancer risk reduction, and other preventive measures.



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

60,000 Genetic Tests!!!

Feb 04, 2016 | Turna Ray

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????

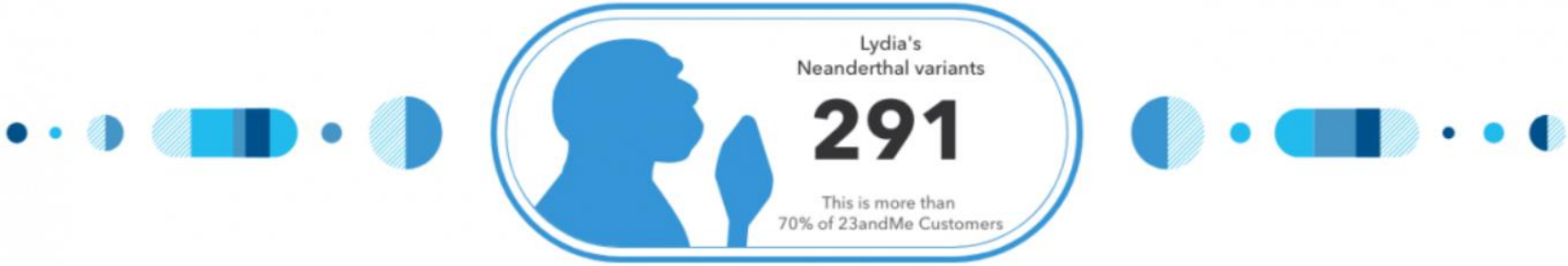
23andMe

ancestry.com

Neanderthal Ancestry

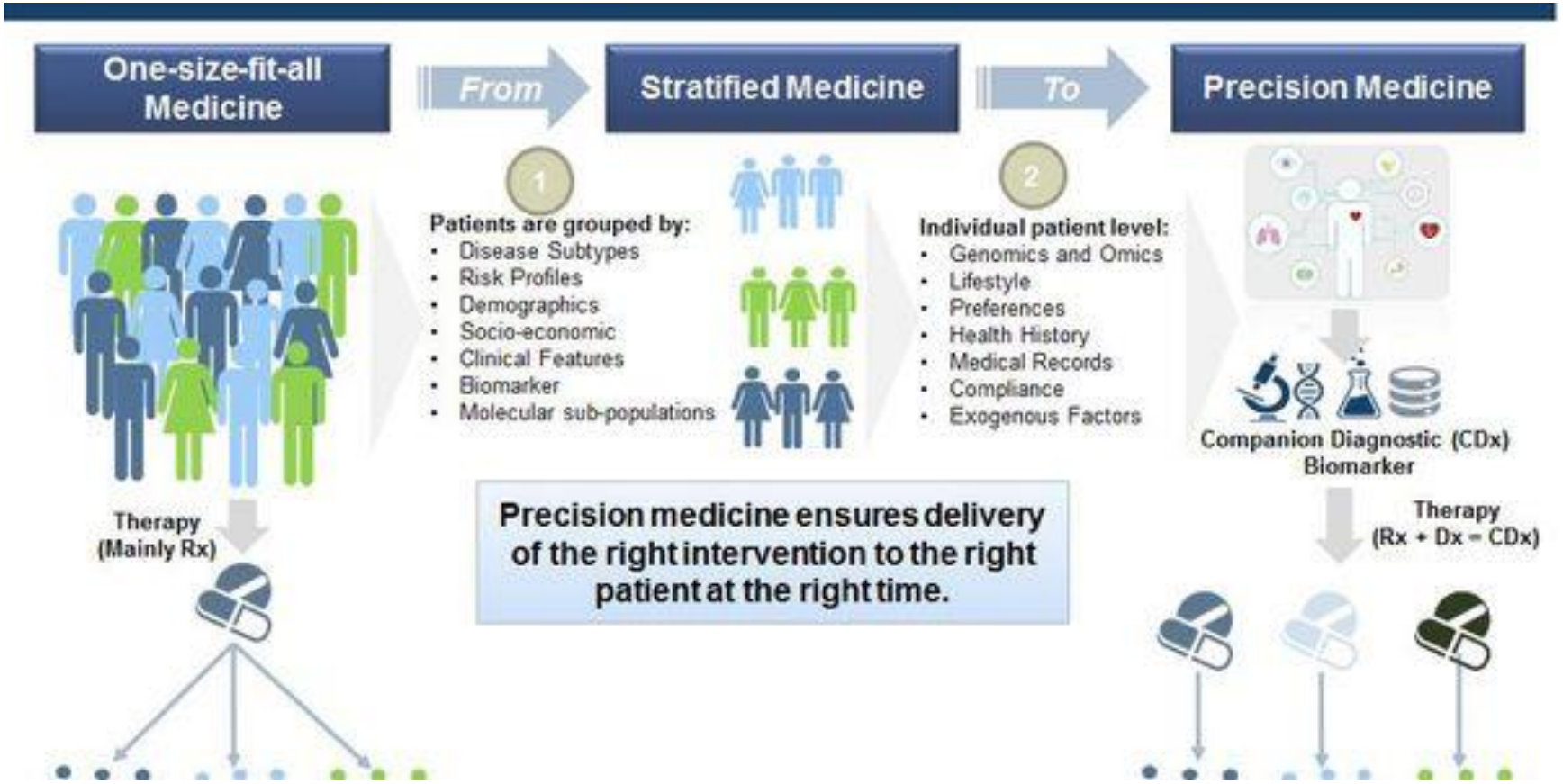
Neanderthals were ancient humans who interbred with modern humans before becoming extinct 40,000 years ago. This report tells you how much of your ancestry can be traced back to Neanderthals.

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.

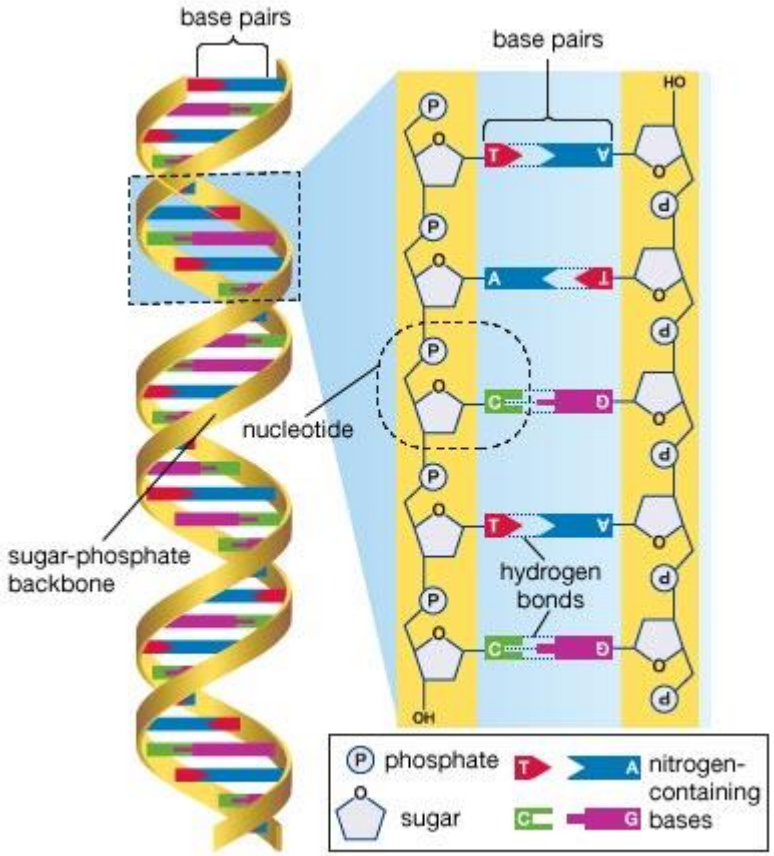
Evolution of Precision Medicine



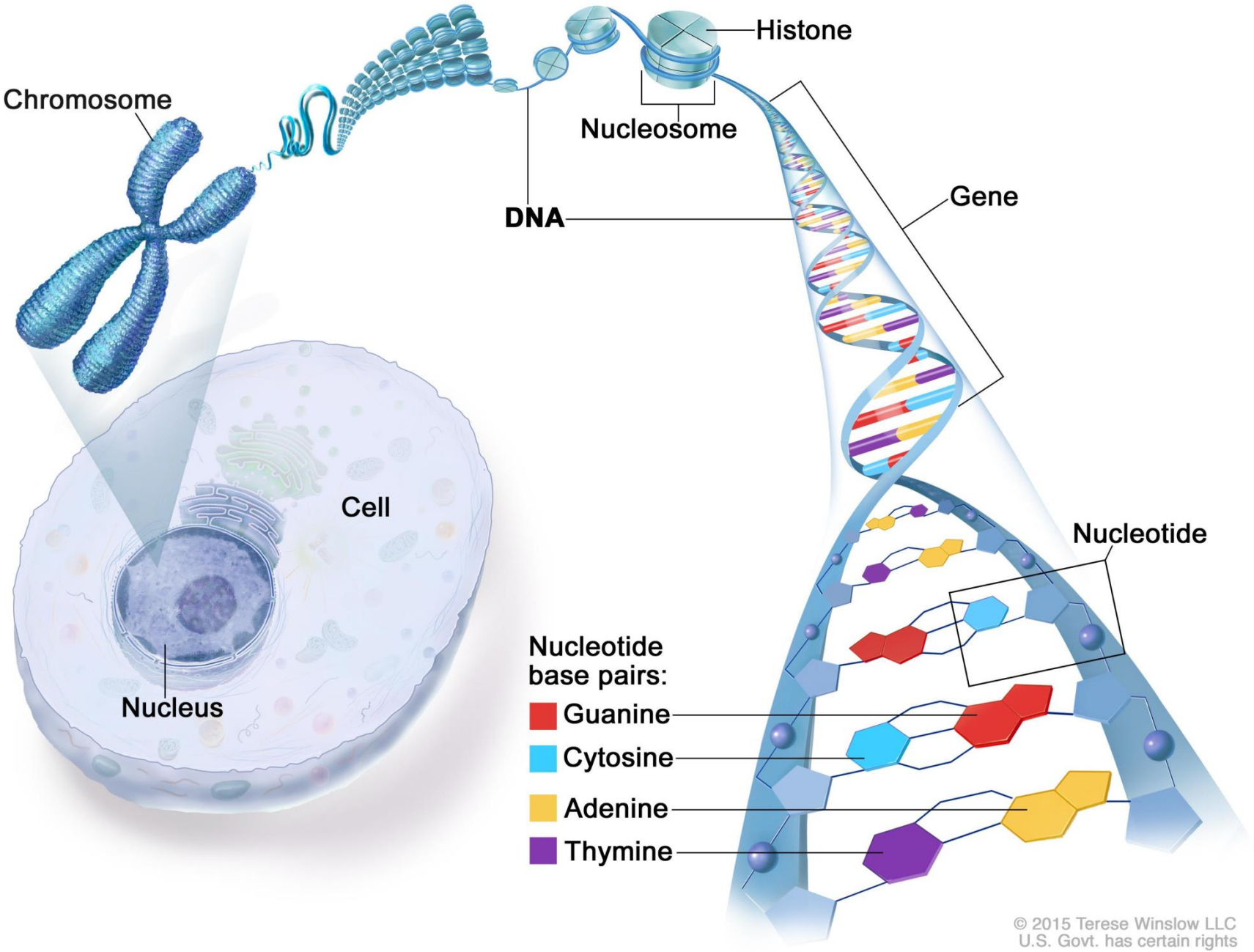

Your
GENOME
& YOU
Knowing about your genome helps you understand your health and supports your health decisions.
GENOME is just a fancy word for all your DNA.

Welcome to the genome…

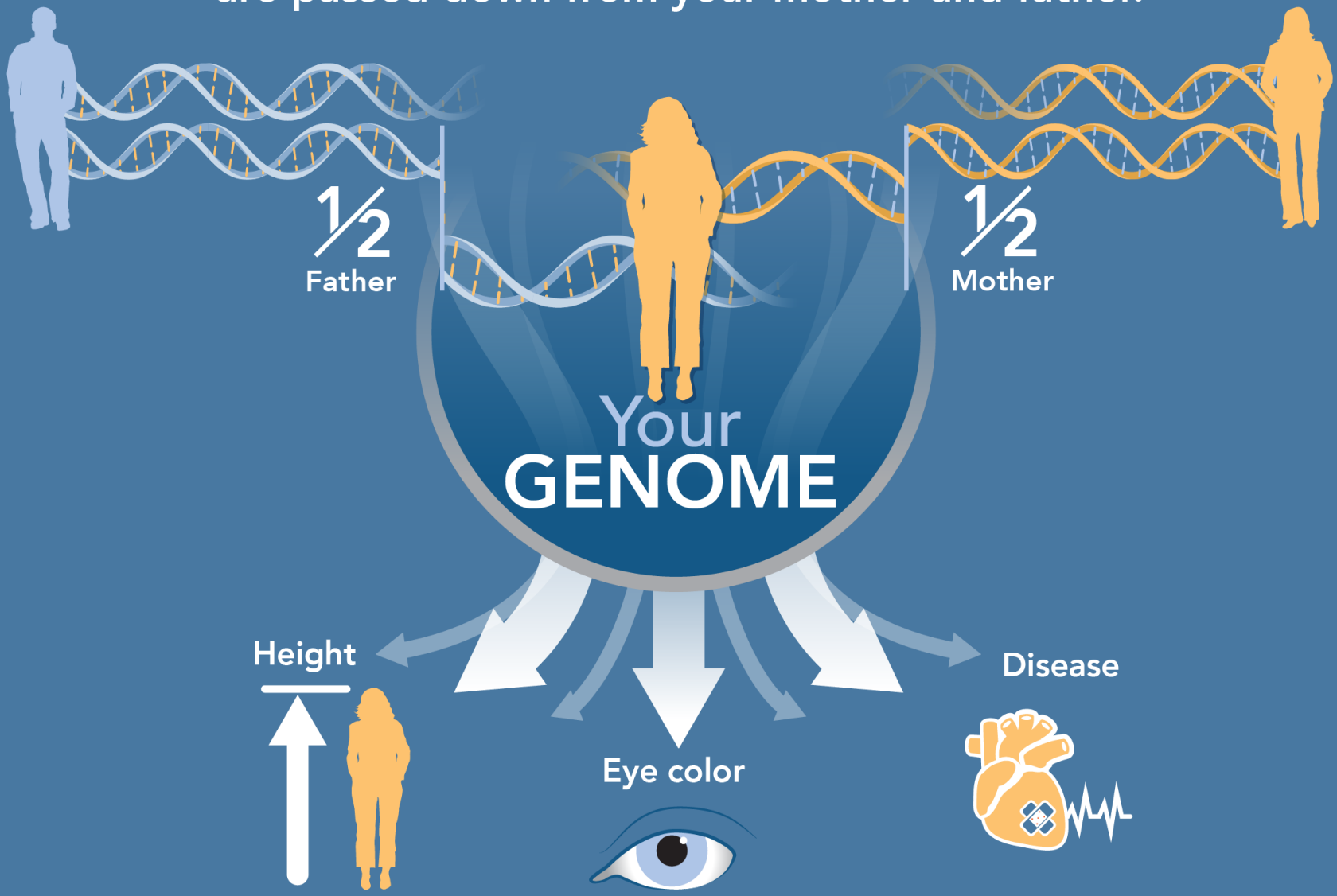
..the miraculous blueprint of your DNA, coiled tight as a spring in the nucleus of each cell of your body. If unwound, the DNA from just one cell, while only a molecule in width, would stretch six feet in length! The information stored in its double helix structure - three billion bits worth - could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



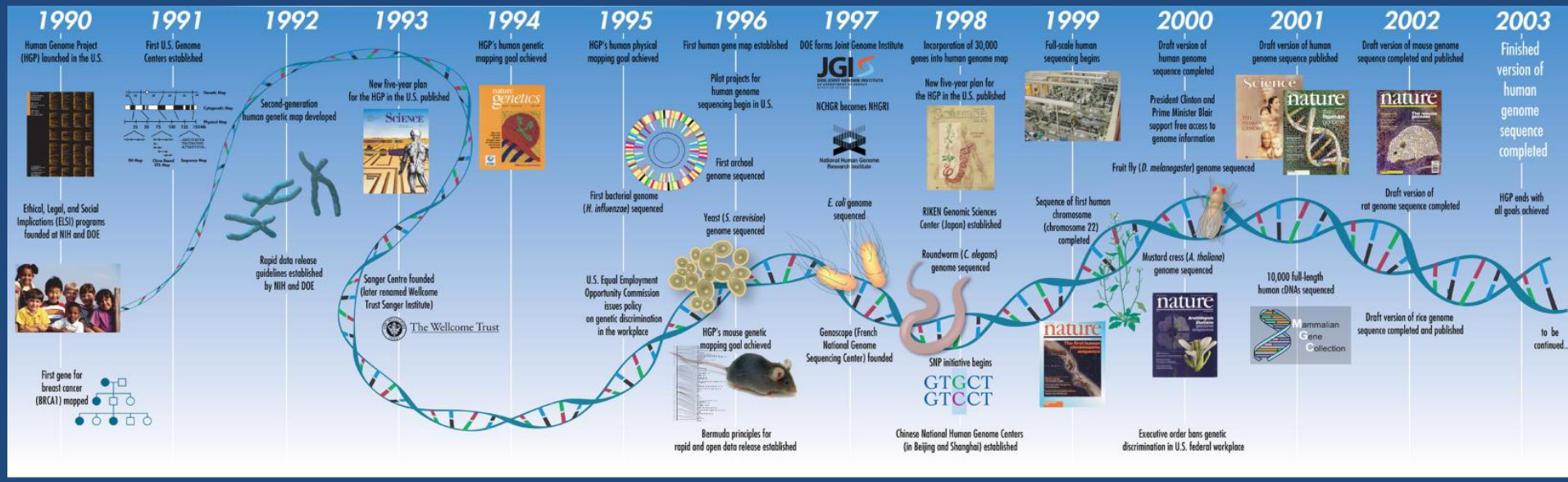
These instructions make you unique.

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



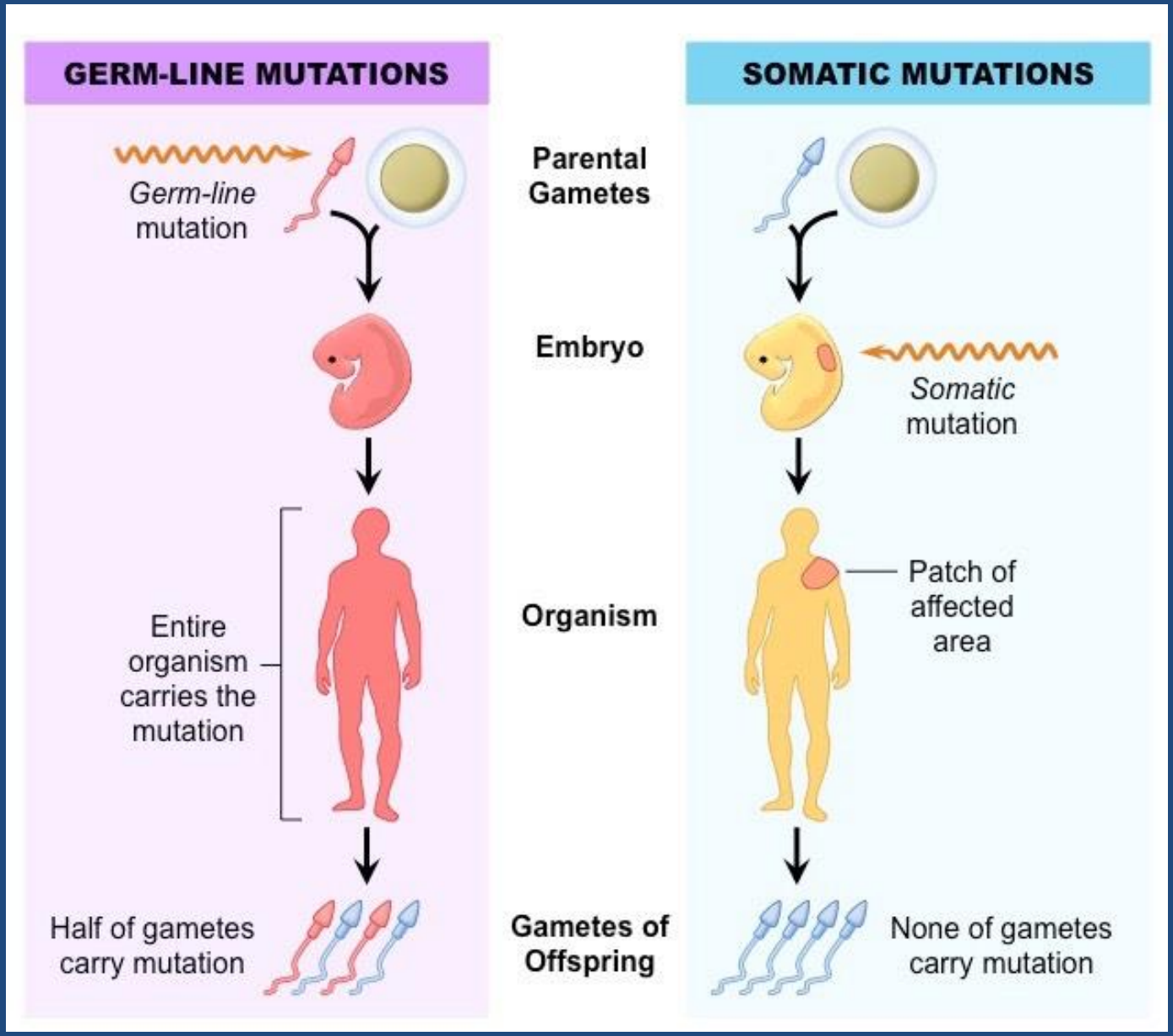
3.2 billion base pairs

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

Genetics vs Genomics

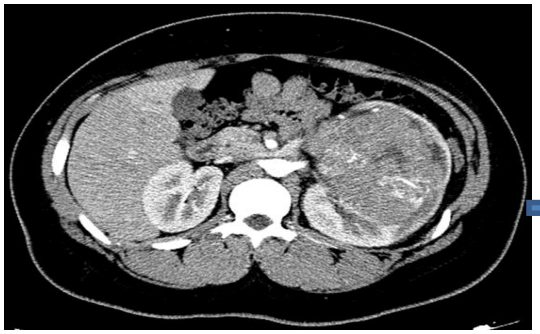
- **Genetics:**
  - **TRADITIONAL**: the study of specific, **individual genes** and their inheritance
    - Eg, sickle cell anemia and cystic fibrosis, a single gene
  - **MODERN:** multiple genes inheritance pattern

- **Genomics:**
  - **MORE COMPLEX**; refers to an organism's entire genetic makeup (genome) or an **extensive number of genes**
  - Study diseases caused by multiple genes interacting with each other and the environment (ie. cancer, diabetes)
  - MODERN GENETIC TESTING RELIES ON GENOMICS

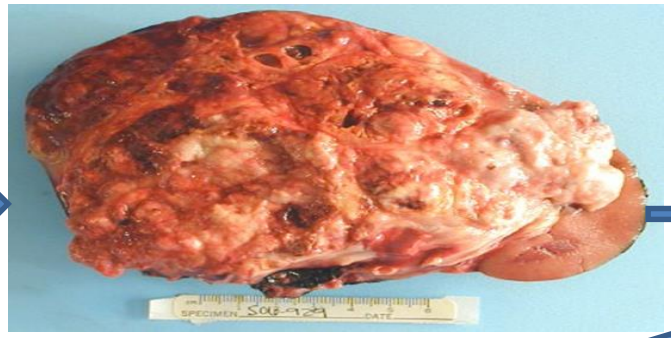


http://ib.bioninja.com.au/

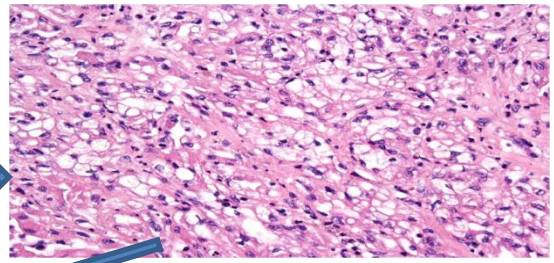
EVOLUTION OF TUMOR EVALUATION



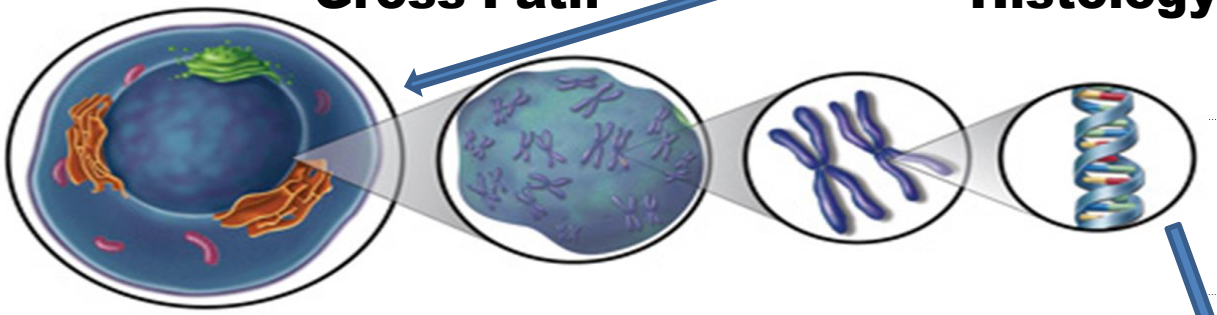
Imaging



Gross Path



Histology Path



AAGGTACAGTTGAAATTAAACGGAAGTTTGCTGGCCTGTTGAAAAATGACTGTAAC
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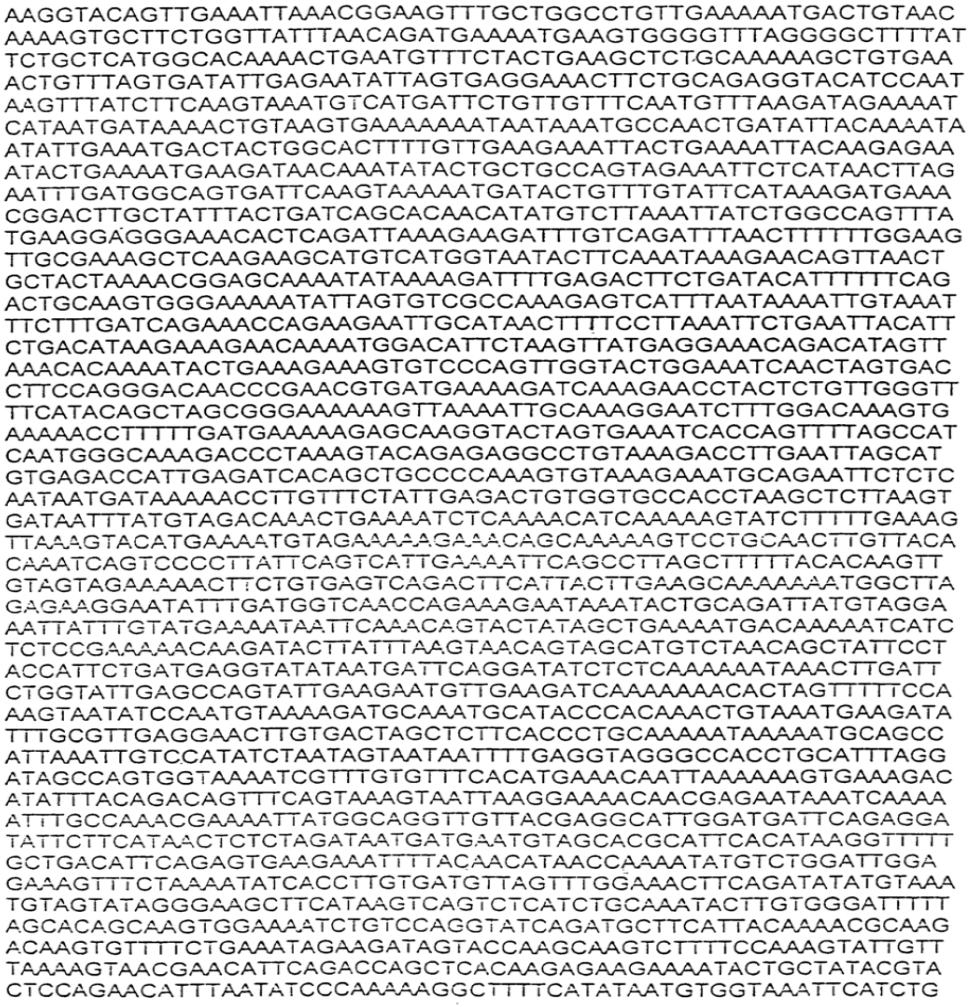
TCTGCTCATGGCACAAAACTGAATGTTTCTACTGAAGCTCTGCAAAAAGCTGTGAA
ACTGTTTAGTGATATTGAGAATATTAGTGAGGAAACTTCTGCAGAGGTACATCCAAT
AAGTTTATCTTCAAGTAAATGTCATGATTCTGTTGTTTCAATGTTTAAGATAGAAAAT
CATAATGATAAAACTGTAAGTGAAAAAAATAATAAATGCCAACTGATATTACAAAATA
ATATTGAAATGACTACTGGCACTTTTGTTGAAGAAATTACTGAAAATTACAAGAGAA
ATACTGAAAATGAAGATAACAAATATACTGCTGCCAGTAGAAATTCTCATAACTTAG
AATTTGATGGCAGTGATTCAAGTAAAAATGATACTGTTTGTATTCATAAAGATGAAA
CGGACTTGCTATTTACTGATCAGCACAACATATGTCTTAAATTATCTGGCCAGTTTA
TGAAGGAGGGAAACACTCAGATTAAAGAAGATTTGTCAGATTTAACTTTTTTGGAAG

Base Pairs

Our understanding of genomics relies on computational biology support



BRCA2 gene section

-27 exons total
-coding region 10,433 base pairs
-12 pages long
-image is a very small portion of exon 11

Patent Novel coding sequence haplotypes of the human BRCA2 gene US 20060154272 A1

Genomic Testing Basics

- Genome = organisms complete DNA set
- 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 genome 30-40,000 genes

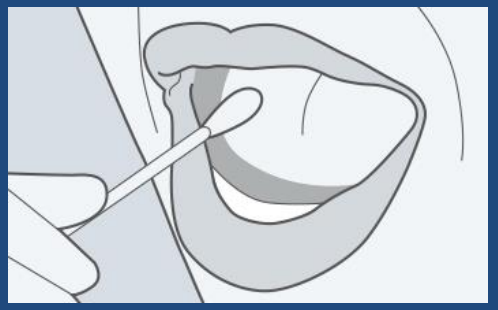
Genomic Tissue Testing

- 5 x 5µ FFPE sections (0.5-1.0mm length) + H&Es

- Most through Pathology
- Price: $3000-5000
- > 90% success (Warn patients!)

Genetic Testing

- Buccal saliva swab most common



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

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

Spring 2013: Everything Changed

May 13, 2013

SUPREME COURT OF THE UNITED STATES

No. 12–398

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL., PETITIONERS *v.* MYRIAD GENETICS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

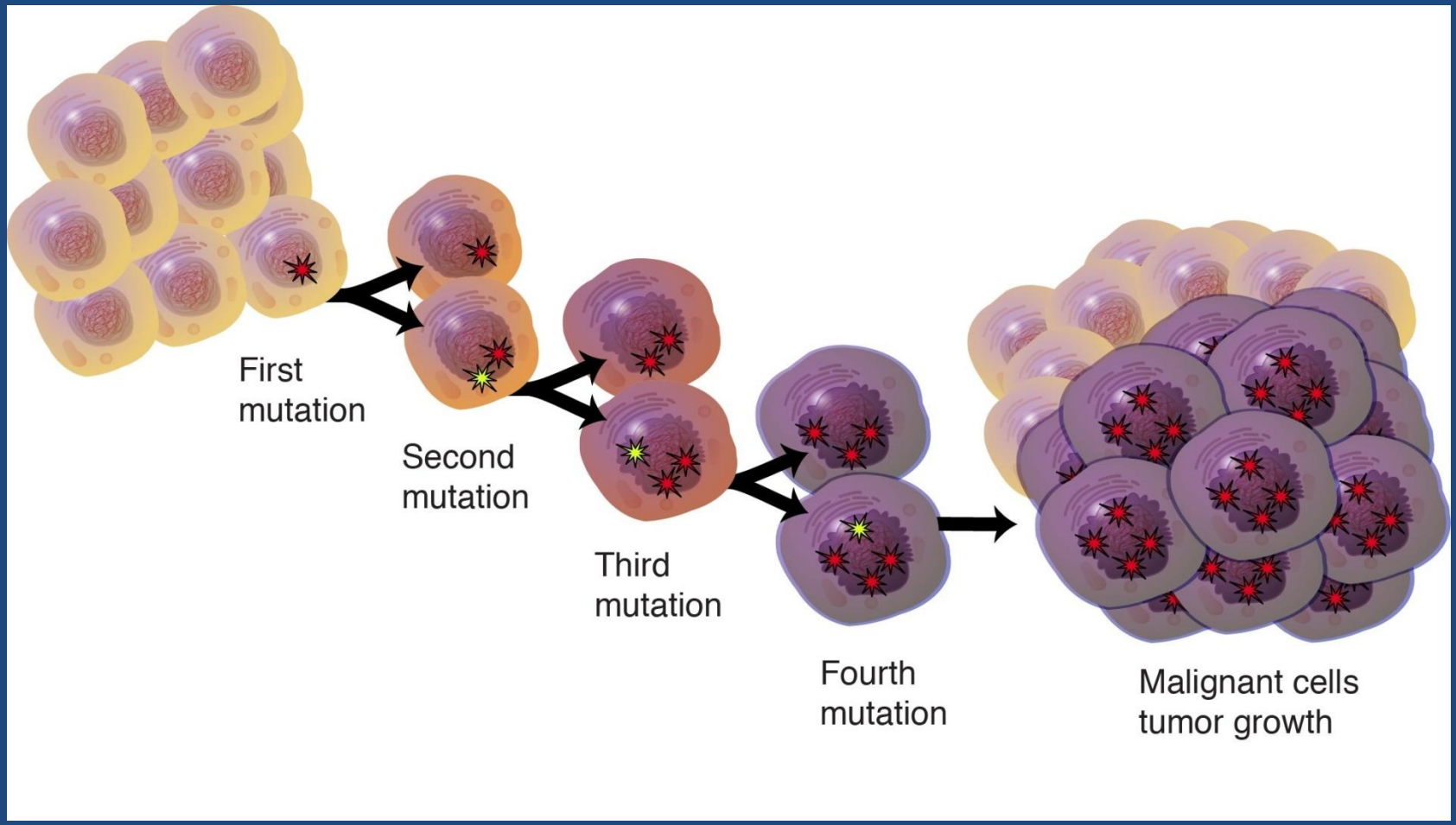
[June 13, 2013]

JUSTICE SCALIA, concurring in part and concurring in the judgment.

I join the judgment of the Court, and all of its opinion except Part I–A and some portions of the rest of the opinion going into fine details of molecular biology. I am unable to affirm those details on my own knowledge or even my own belief. It suffices for me to affirm, having studied the opinions below and the expert briefs presented here, that the portion of DNA isolated from its natural state sought to be patented is identical to that portion of the DNA in its natural state; and that complementary DNA (cDNA) is a synthetic creation not normally present in nature.

June 13, 2013

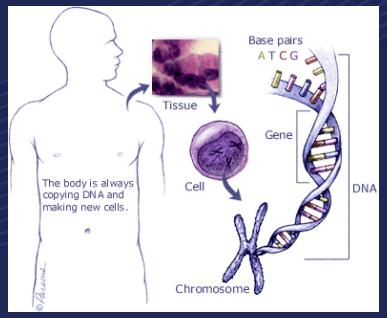
All Cancer is Genetic
Not All Cancer is Hereditary



CANCER SUSCEPTIBILITY PATTERNS

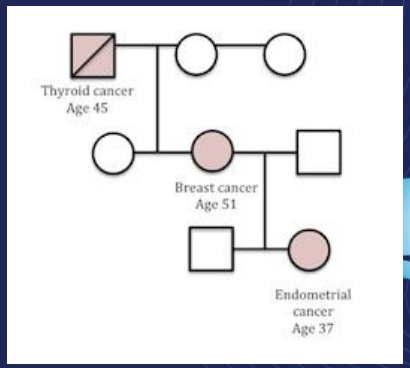
Sporadic

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



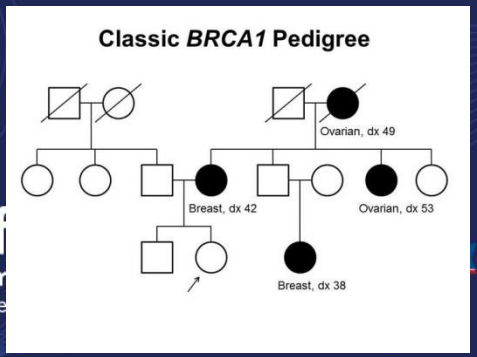
Familial

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



Hereditary

- Known inherited reason for cancers in family



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

Sidney Kimmel Cancer Center at Jefferson
NCI – designated

Sidney Kimmel Cancer Center, Thomas Jefferson University

and

The Foundation for Breast and Prostate Health

Philadelphia, Pennsylvania

March 3 & 4, 2017

FOUNDATION FOR Breast & Prostate Health

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

www.phillyprostate.com

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

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

Veda N. Giri, Karen E. Knudsen, William K. Kelly, Wassim Abida, Gerald L. Andriole, Chris H. Bangma, Justin E. Bekelman, Mitchell C. Benson, Amie Blanco, Arthur Burnett, William J. Catalona, Kathleen A. Cooney, Matthew Cooperberg, David E. Crawford, Robert B. Den, Adam P. Dicker, Scott Eggener, Neil Fleshner, Matthew L. Freedman, Freddie C. Hamdy, Jean Hoffman-Censits, Mark D. Hurwitz, Colette Hyatt, William B. Isaacs, Christopher J. Kane, Philip Kantoff, R. Jeffrey Karnes, Lawrence I. Karsh, Eric A. Klein, Daniel W. Lin, Kevin R. Loughlin, Grace Lu-Yao, S. Bruce Malkowicz, Mark J. Mann, James R. Mark, Peter A. McCue, Martin M. Miner, Todd Morgan, Judd W. Moul, Ronald E. Myers, Sarah M. Nielsen, Elias Obeid, Christian P. Pavlovich, Stephen C. Peiper, David F. Penson, Daniel Petrylak, Curtis A. Pettaway, Robert Pilarski, Peter A. Pinto, Wendy Poage, Ganesh V. Raj, Timothy R. Rebbeck, Mark E. Robson, Matt T. Rosenberg, Howard Sandler, Oliver Sartor, Edward Schaeffer, Gordon F. Schwartz, Mark S. Shahin, Neal D. Shore, Brian Shuch, Howard R. Soule, Scott A. Tomlins, Edouard J. Trabulsi, Robert Uzzo, Donald J. Vander Griend, Patrick C. Walsh, Carol J. Weil, Richard Wender, and Leonard G. Gomella

<u>Representation:</u> Urology (National and International), Medical Oncology, Radiation Oncology, Clinical Cancer Genetics, Genetic Counseling, Health Policy, Bioethics, Population Science, Molecular Epidemiology, Pathology, Breast/GI/Gyn Oncology, Genetic Basic Science Research, Patient Advocates, Patient Stakeholders, NCCN, NCI, ACS

Giri, et al J Clin Oncol. 2018 Feb 1;36(4):414-424. doi: 10.1200/JCO.2017.74.1173. Epub 2017 Dec 13.

Philadelphia 2017 Consensus-Driven Framework for Multigene Testing for Inherited Prostate Cancer

Which men should consider genetic counseling and genetic testing for prostate cancer?

- Shared decision-making encouraged
- FH of HBOC, HPC, or Lynch syndrome
- FH of 2 close relatives with these cancer syndromes
- Tumor sequencing with mutations in inherited cancer genes
- All men with mCRPC

Which genes should be tested?

Family History:
- *BRCA1/2* (HBOC)
- *HOXB13* (HPC)
- DNA MMR genes (LS)

Tumor Sequencing:
- *BRCA1/2*
- DNA MMR genes
- *HOXB13*
- *ATM*

mCRPC:
- *BRCA1/2*
- *ATM*

Which genes should be factored into management considerations regarding:

Prostate cancer Screening:	Early-stage Disease	Advanced Disease	mCRPC
• *BRCA2*	• *BRCA2*	• *BRCA2*	• *BRCA1*
• *HOXB13*		• *ATM*	• *BRCA2*
			• *ATM*

Key

- High consensus agreement
- Moderate consensus agreement

Considerations:
- Need greater insights into genetic predisposition to lethal PCA.
- mCRPC could be given stronger consideration for testing to inform cancer risks for men and their families.
- Need more data in African American males.
- Cost-effectiveness and QOL research needed.
- Need more data in screening/early-stage disease.
- Clinical trials enrollment is important.

Courtesy of Gomella, Giri and Knudsen

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

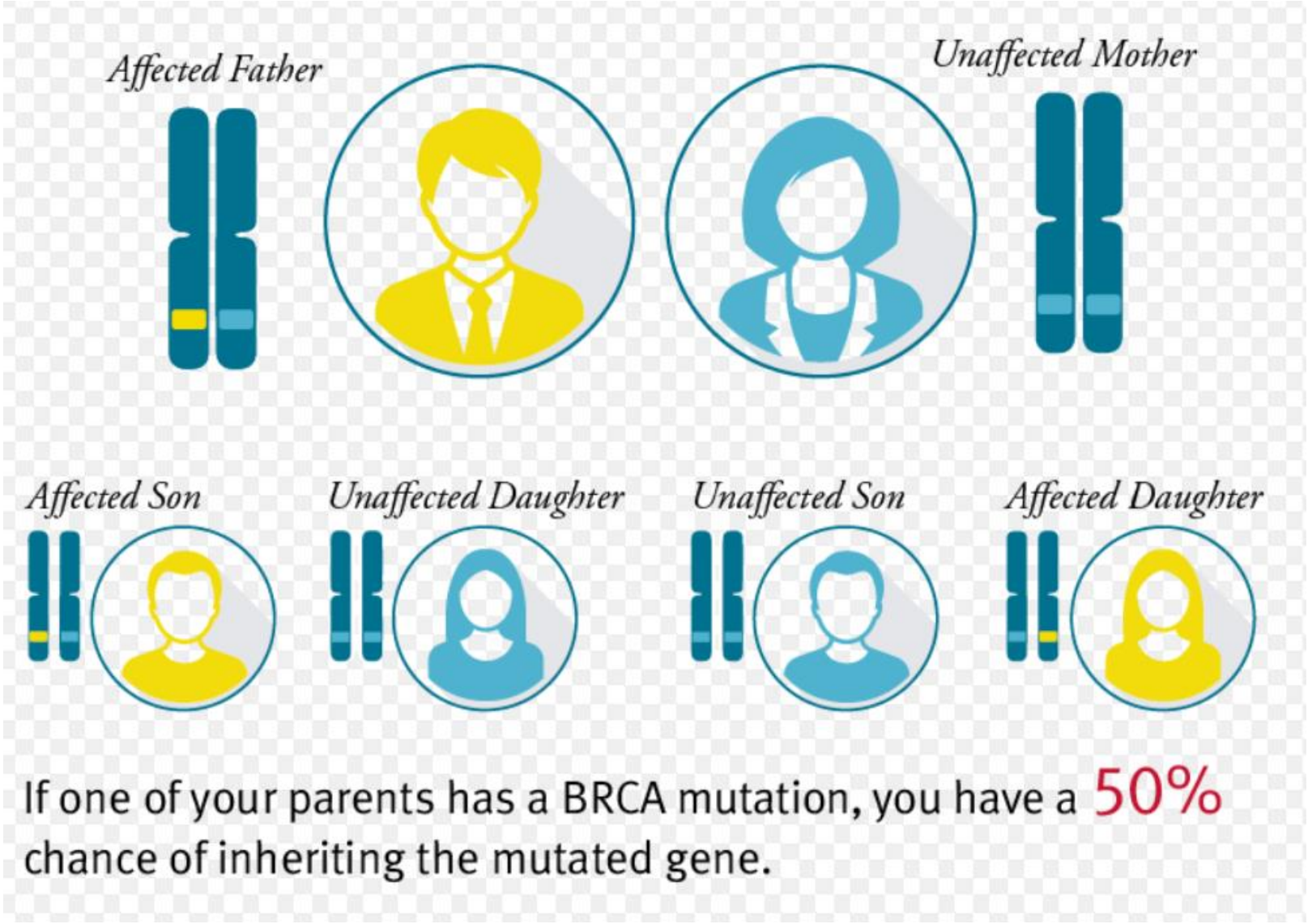
Based on data in Nicolosi, et al ASCO Abstract 5009 2017 Chicago; https://www.ncbi.nlm.nih.gov/gene/

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

BRCA 1/2 Prostate Cancer Risks

- 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.

BRCA and Cancer

Although the risk of cancer is greater for women than men with BRCA 1/2 gene mutations, both sexes face elevated lifetime chances of several types of cancer. *Risk of cancer as a percentage, by gender.*

Cancer type	U.S. white	BRCA1 mutation carriers	BRCA2 mutation carriers
MEN			
Breast	0.1%	1-5%	7%
Prostate	16	*	25
Melanoma	2	N.S.	5
Pancreas	1	Up to 3	3-5
WOMEN			
Breast	13%	60-80%	50-70%
Ovary	1-2	20-45	10-20
Melanoma	2	N.S.	Up to 5
Pancreas	1	Up to 3	3-5

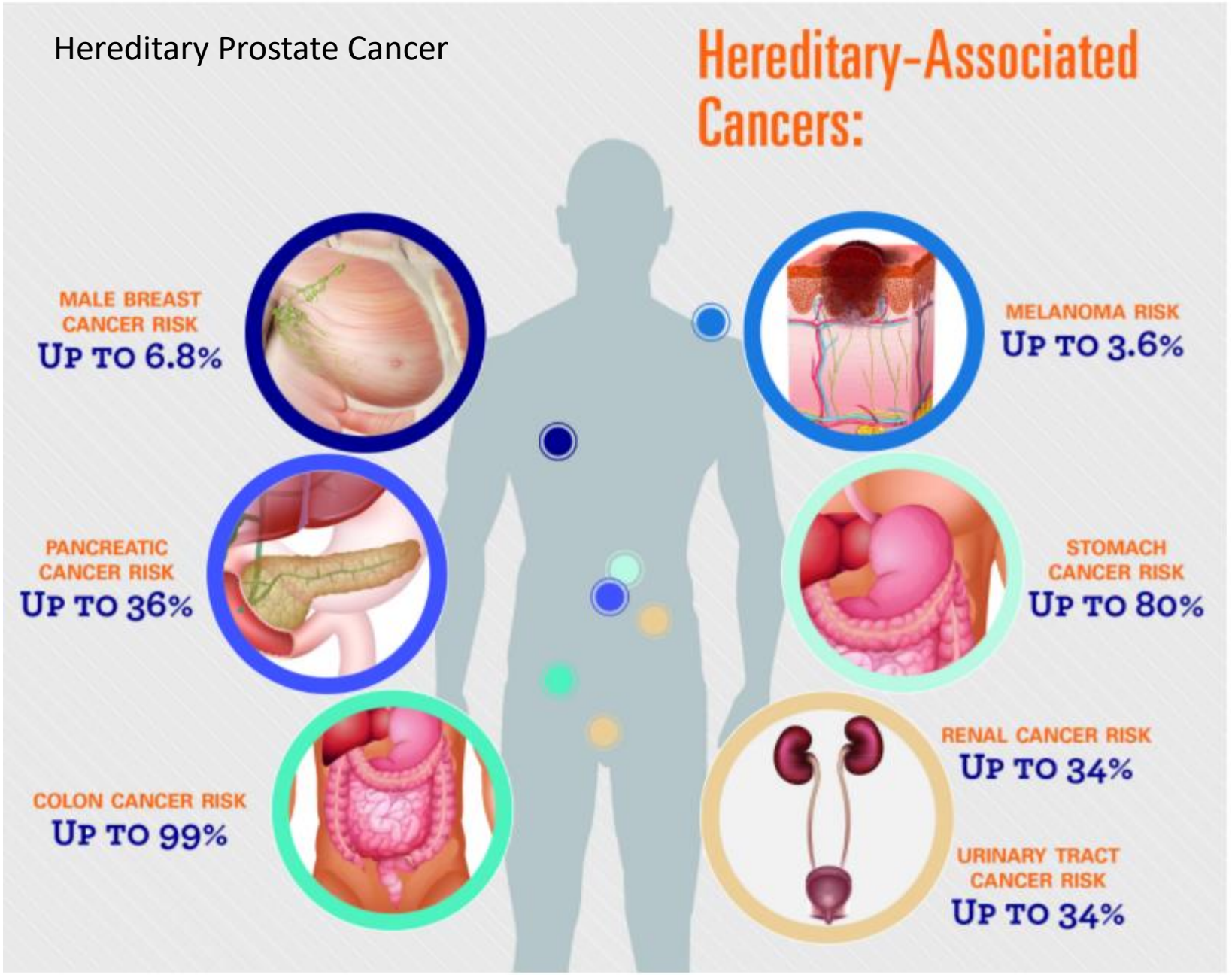
N.S. = Not significant; *Some evidence of an increased risk for men younger than 65

SOURCE: Penn Medicine's Basser Research Center for BRCA

MIKE PLACENTRA / Staff Artist

http://pinkhope.org.au/what-it-means-for-men-who-carry-a-brca-gene-fault/

Hereditary Prostate Cancer



www.MyriadPro.com/References

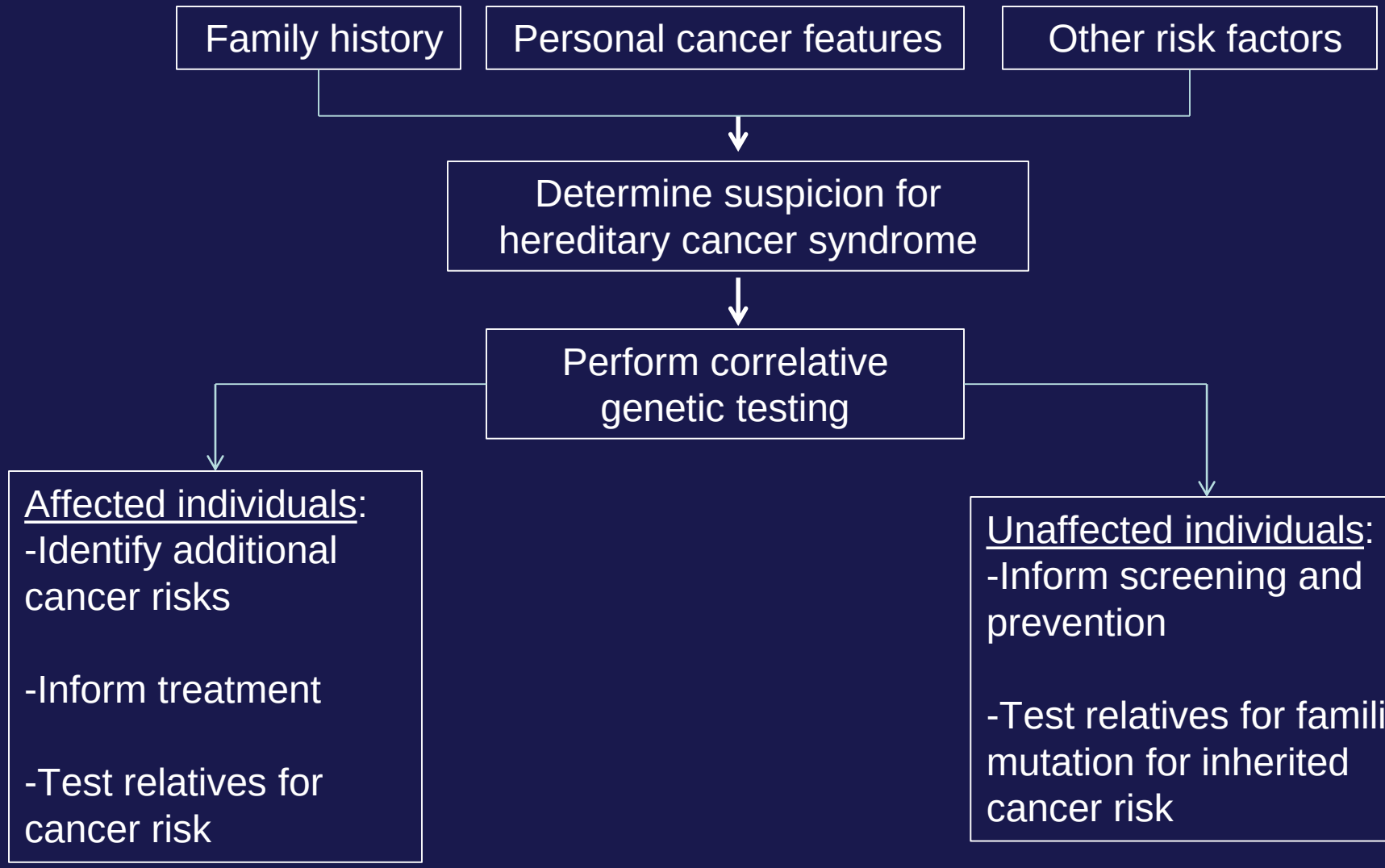
Criteria for Referral to Genetic Counseling for Prostate Cancer

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

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

American College of Medical Genetics and Genomics (ACMG)/National Society of Genetic Counselors (NSGC) practice guidelines.: https://www.acmg.net/docs/ACMG_Practice_Guideline_Referral_Indications_for_cancer_predisposition.pdf

Model for Genetic Testing for Inherited Cancer Risk



What is a Genetic Counselor?

- Health care professional trained in clinical genetics, assessment of personal risk for cancer, and options for managing the risk.
- Appointment typically lasts 1-2 hours and sometimes a second visit is necessary.
- During the appointment:
  - Information will be collected about family health history, personal health history) and pathology reports
  - Review what is seen in family and will discuss options for available genetic testing
  - Support your choices in the context of your personal values, beliefs, and goals
  - Help arrange for genetic counseling and genetic testing of other family members, as needed

National Society of Genetic Counselors, 2006

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NATIONAL
UROLOGY
2017-18

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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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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2013-14

“Red Flags” for Hereditary Cancer Predisposition

- Cancer at earlier than typical ages
  - Often younger than 50
- Cancer in paired organs
- Multifocal disease
- Rare tumors
  - Pheochromocytomas, oncocytomas, medullary thyroid cancer
- Multiple close relatives on the same side of the family with the same or related forms of cancer
  - Breast and ovarian cancer

Referral for Hereditary Prostate Cancer

- Prostate cancer diagnosis at 65 or younger
- Gleason score $\geq$ 7 and family history of cancers related to Hereditary Breast and Ovarian Cancer Syndrome (breast, ovary, pancreas, prostate)
- Family history of cancers relevant to Hereditary Breast and Ovarian Cancer Syndrome, Hereditary Prostate Cancer or Lynch Syndrome

Conclusions

- Evolving recommendations for prostate cancer genetic testing
- Most critical genes today:
  - BRCA 1/2, HOXB13, ATM, CHEK2
- In the future genetic testing my guide prostate cancer screening
- Strongly 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, need validation

23andMe

ancestry.com