

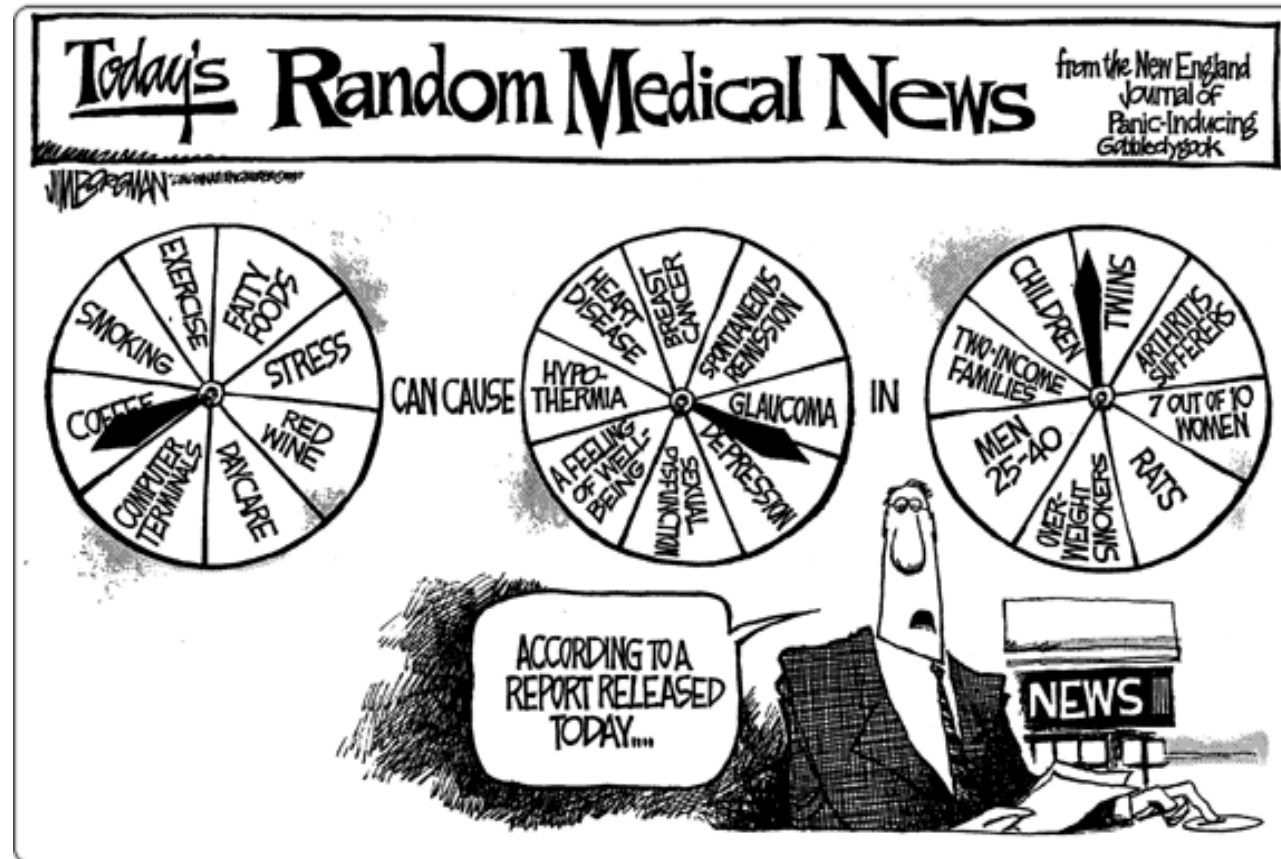
Introduction to Epidemiology and Genetic Epidemiology

ep·i·de·mi·ol·o·gy

/,epə,dēmē'äləjē/

noun

the branch of medicine that deals with the incidence, distribution, and possible control of diseases and other factors relating to health.



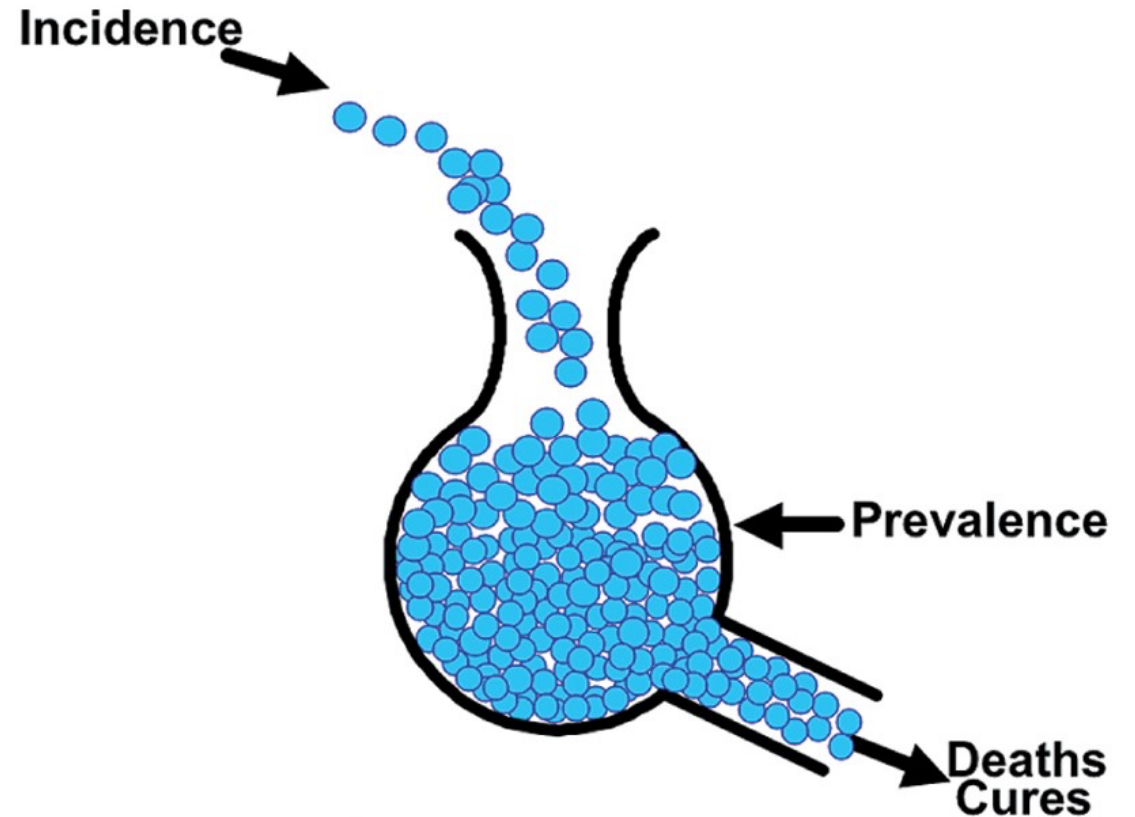
Key concepts in Epidemiology

- Incidence

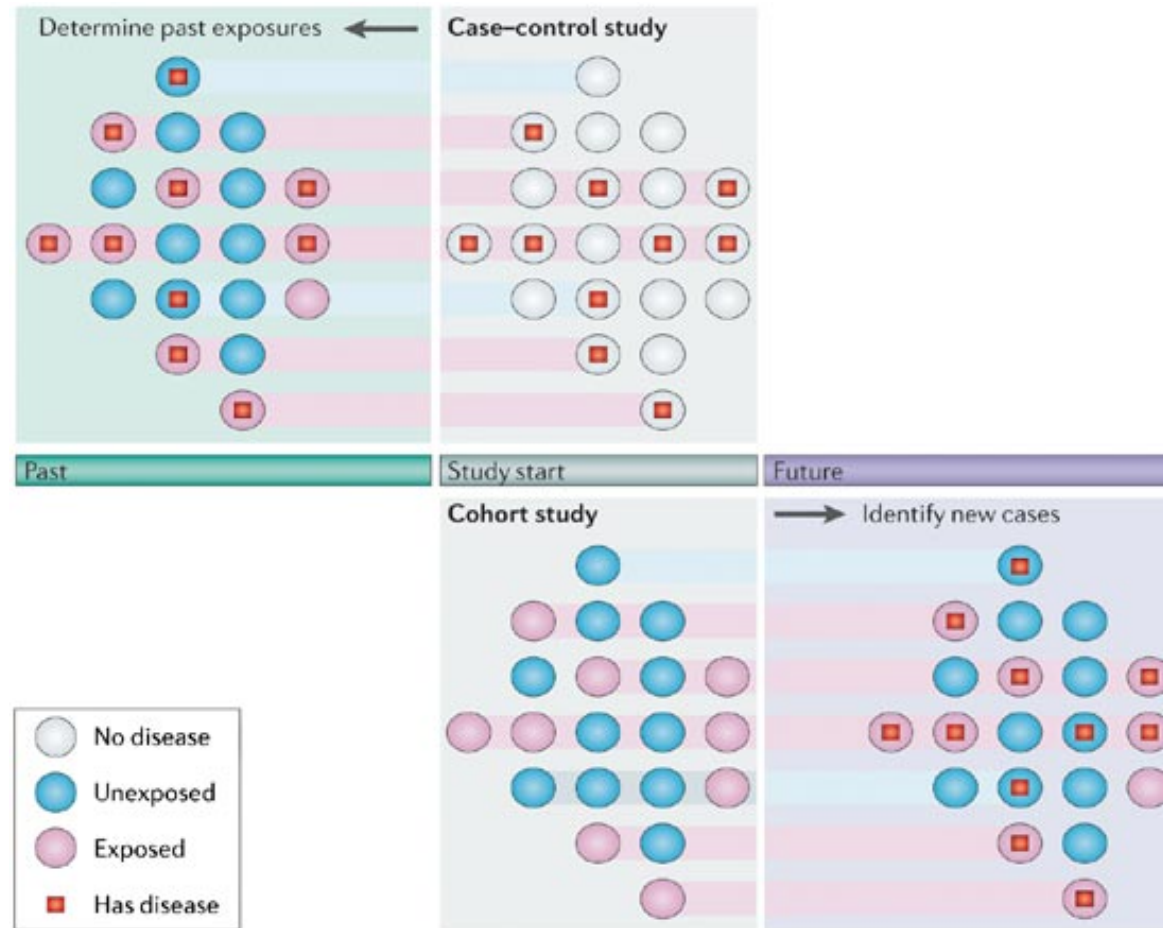
- Number of new cases in a population during a fixed time period
 - The reported number of new prostate cancer cases in United States during 2015 was 183,529.

- Prevalence

- Number of existing cases in a population at a given time
 - In 2015, there were an estimated 3,120,176 men living with prostate cancer in the United States.



Cohort vs. case-control studies



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Nature Reviews | Genetics

Estimated incidence rates in cohorts

Disease incidence per 100,000 per year (%)	Disease examples	Number of incident cases in 5 years for different cohort sizes		
		200,000	500,000	1,000,000
10 (0.01)	Parkinson disease, schizophrenia	91	228	457
50 (0.05)	Colorectal cancer, renal failure	456	1,141	2,282
100 (0.10)	Breast cancer, hip fracture	912	2,279	4,559
200 (0.20)	Diabetes, stroke, heart failure	1,820	4,550	9,100
500 (0.50)	Myocardial infarction, all cancers	4,524	11,309	22,618
3,000 (3.00)	Cataracts, hypertension	25,858	64,644	129,289

Estimated numbers of incident cases available after 5 years of follow-up across the entire age range in the US population are shown, assuming an attrition rate of 3% per year. Data are taken from the Incidence and Prevalence Database.

Manolio. *Nature Reviews Genetics* 2006

Compared to cohorts, case-control studies are cheap, fast and powerful.

However, case-control studies suffer from several drawbacks:

the need to identify appropriate controls

they are more sensitive to recall bias

it is difficult to assess rare exposures due to small sample sizes

Main Measures of Association in Epidemiology

- Relative Risk

measure of the relative probability of developing disease given exposure status

- Odds Ratio

measure of the relative odds of exposure given disease status (can approximate the Relative Risk when disease is rare)

The 2x2 Table For Count Data

		Disease status		
		Cases	Controls	Total
Exposure	Exposed	a	b	a+b
	Not Exposed	c	d	c+d
Total		a+c	b+d	a+b+c+d

Relative Risk (RR) For Count Data

- Relative probability of developing disease given exposure status
- Used in cohorts
- Also known as risk ratio
- If no association $RR=1$

	Cases	Controls	Total
Exposed	a	b	a+b
Not Exposed	c	d	c+d
	a+c	b+d	a+b+c+d

$$RR = \frac{a/(a+b)}{c/(c+d)} = \frac{\text{(Incidence of Disease in Exposed)}}{\text{(Incidence of Disease in Unexposed)}}$$

Odds Ratio (OR) For Count Data

- Relative odds of exposure given disease status
- Used primarily in case-control studies
- Good *estimate* of RR
- If no association $OR=1$

	Cases	Controls	Total
Exposed	a	b	a+b
Not Exposed	c	d	c+d
	a+c	b+d	a+b+c+d

$$OR = \frac{a/c}{b/d} = \frac{a*d}{b*c} = \frac{\text{(Odds of Exposure among Cases)}}{\text{(Odds of Exposure among Controls)}}$$

Confidence Intervals and p-values

- Relative risks and odds ratios give information on the magnitude of association
- Important to consider precision and statistical significance, along with estimate of magnitude of association.
- Statistical software will in addition to relative risks and odds ratios provide estimate of confidence intervals and p-values

Association and Causality

- An exposure and outcome are associated if there is a differential distribution:
 - Incidence of outcome differs for exposed and unexposed group (cohorts); or
 - Prevalence of exposure differs between cases and controls (case-control study)
- An exposure is causal for the outcome if the presence (or absence) of the exposure directly or indirectly influences whether the outcome occurs.

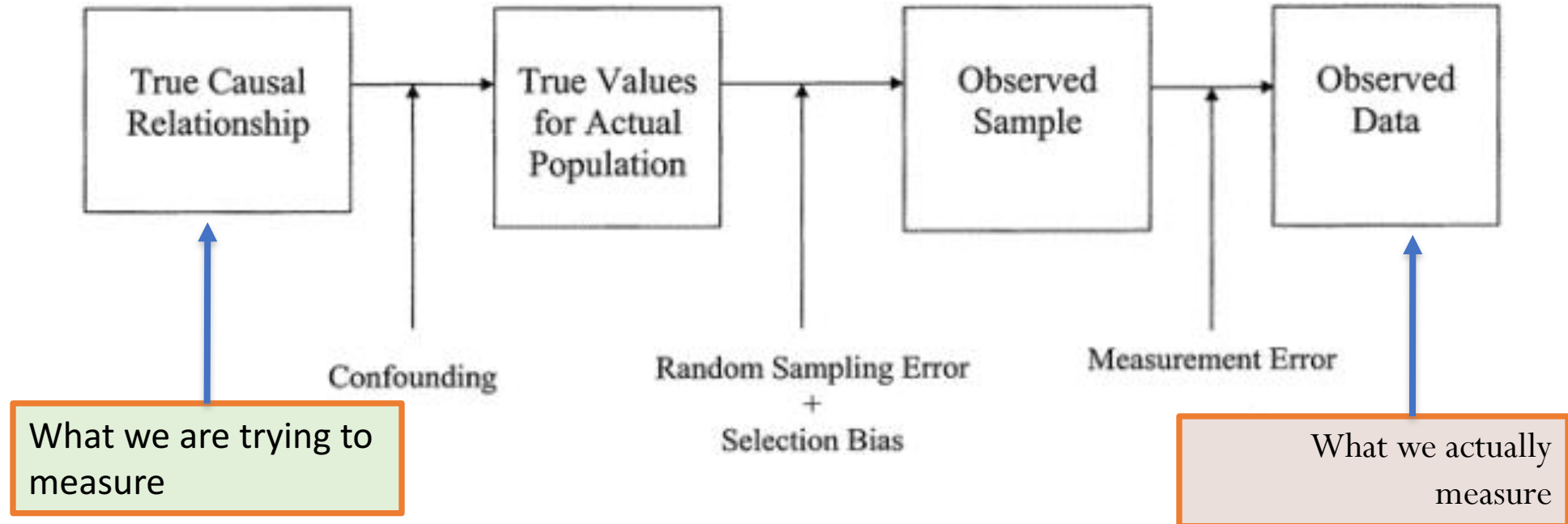
THE FAMILY CIRCUS



8-5
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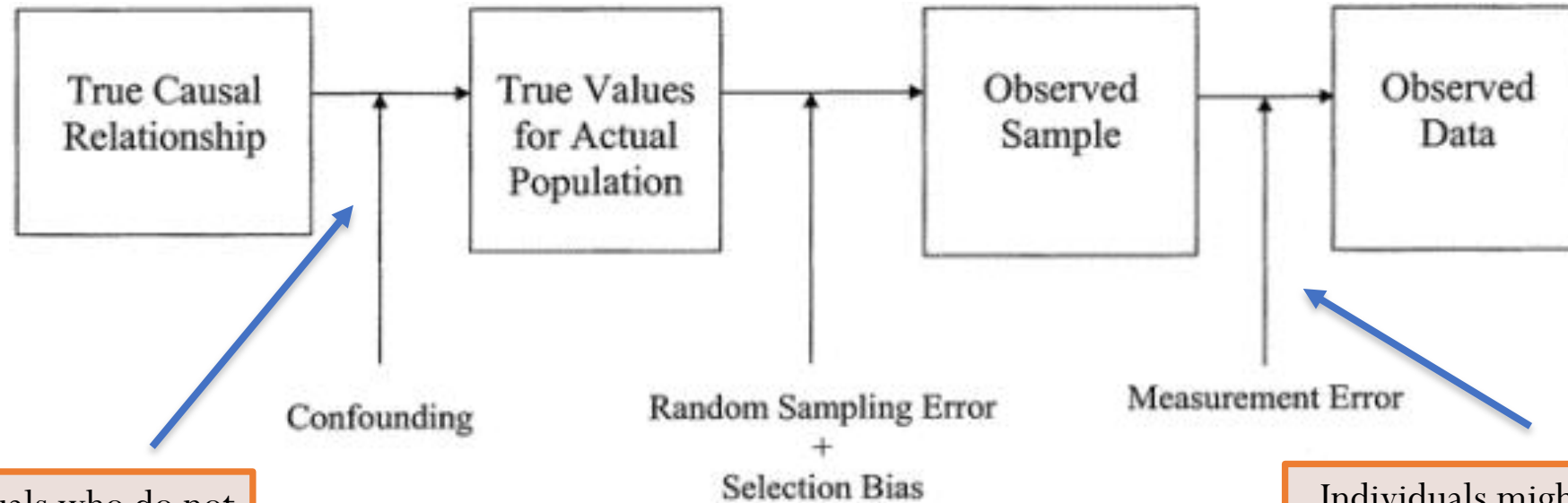
"I wish they didn't turn on that seatbelt sign so much! Every time they do, it gets bumpy."

Sources of Bias in Epidemiology



Bias = Systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure's true effect on the risk of disease

Exercise and cardiovascular disease



Individuals who do not exercise tend to smoke more, have a more unhealthy diet and are more likely to have diabetes.

Your cases and controls might come from different underlying populations (e.g. men vs. women, old vs. young).

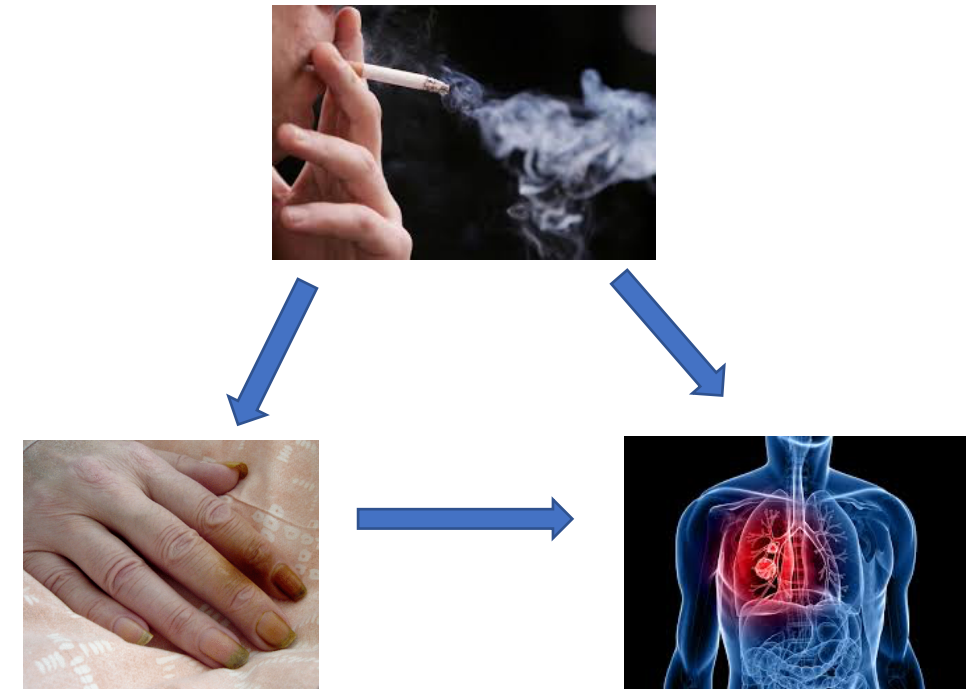
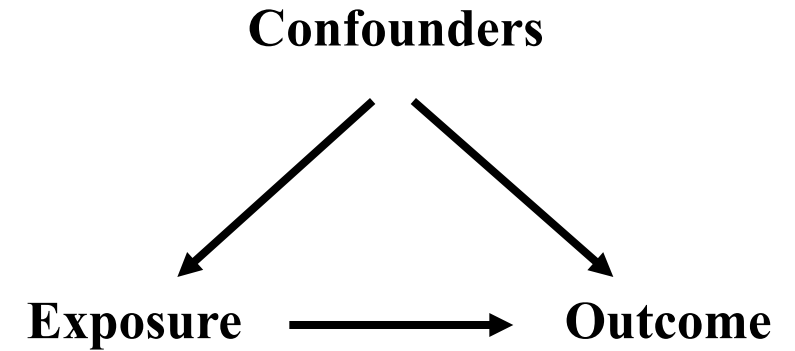
Individuals might misremember or give false information about their exercise routine.

Some common sources of bias

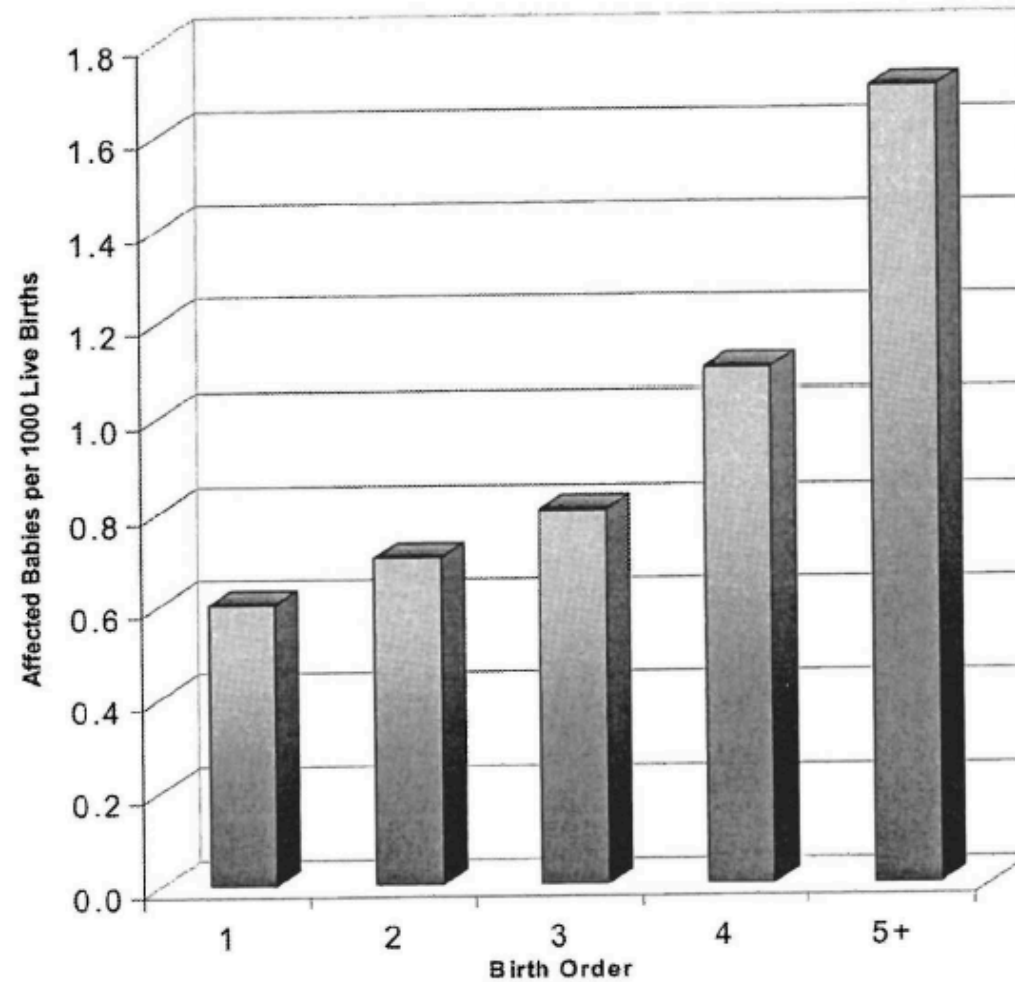
- **Selection Bias**
 - Arises when cases and controls are coming from different source populations (e.g. female cases, male controls)
- **Survival bias**
 - When cases are recruited some time after they were diagnosed. Might lead to a milder form of disease. This is especially true for aggressive/fatal disease (e.g. pancreatic cancer, heart attack)
- **Diagnostic bias**
 - If the investigator determining the outcome knows whether the person was exposed or not to the risk factor under study (e.g. if the radiologist knows that a potential pulmonary disease patient smokes, she may look more carefully at the x-ray).
- **Recall bias**
 - Accuracy and completeness of exposures, life style behaviors etc (e.g. cases might be more motivated to complete a questionnaire accurately).

Confounding

- A confounder is often defined as a factor that is:
 - ① A risk factor for disease
 - ② Associated with exposure
 - ③ Not a direct result of exposure
- Confounding can lead to false positive findings.



Confounding example: Birth order and Down syndrome



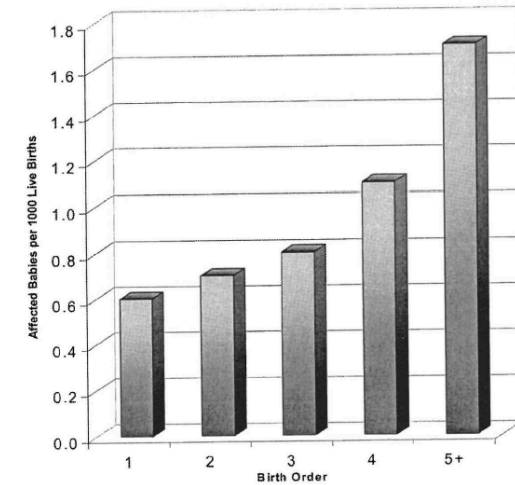
Data from Stark and Mantel (1966)

Source: Rothman 2002

Confounding example: Birth order and Down syndrome

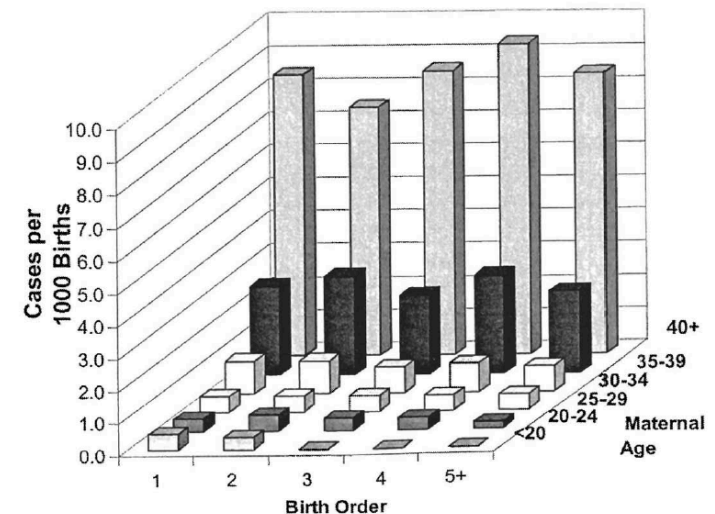
- Later order children have higher risk
 - Maternal age is associated with birth order
 - Maternal age is associated with Down Syndrome
- Stratifying on maternal age, there is no longer evidence of an association between birth order and Down syndrome

Association between birth order and Down syndrome



Data from Stark and Mantel (1966)

Source: Rothman 2002



Data from Stark and Mantel (1966)

Source: Rothman 2002

Summary

- Epidemiology is the study of the distribution and determinants of health-related outcomes in populations
- Study design is a key component of epidemiology
- Relative risks and odds ratios are used to measure association
- It is important to consider and address bias in epi studies
- Understanding confounding is important when conducting association studies

Genetic Epidemiology

***Genetic epidemiology** is the study of the role of **genetic** factors in determining health and disease in families and in populations, and the interplay of such **genetic** factors with environmental factors.*



**Ed was unlucky enough to find
the needle in the haystack!**

April 13, 2007

'Fat' gene found by scientists



Mark Henderson, Science Editor

A gene that contributes to obesity has been identified for the first time, promising to explain why some people easily put on weight while others with similar lifestyles stay slim.



Smoking addiction gene found

Scientists say a gene makes people more likely to get hooked on tobacco, causing them to smoke more, making it harder to quit, and leading more often to deadly lung cancer. **Full story**

Newsweek: Differing conclusions

Researchers make human-cow embryos

Science wishy-washy on water benefits | Vote



Newsroom

SCHOOLS FOR FACULTY AND STAFF TOPICS

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Brain-Aging Gene Discovered

Genetic variant accelerates normal brain aging in older people by up to 12 years

March 15, 2017

Posted in: [Neurology](#) / [Medicine](#)

HUTCH NEWS

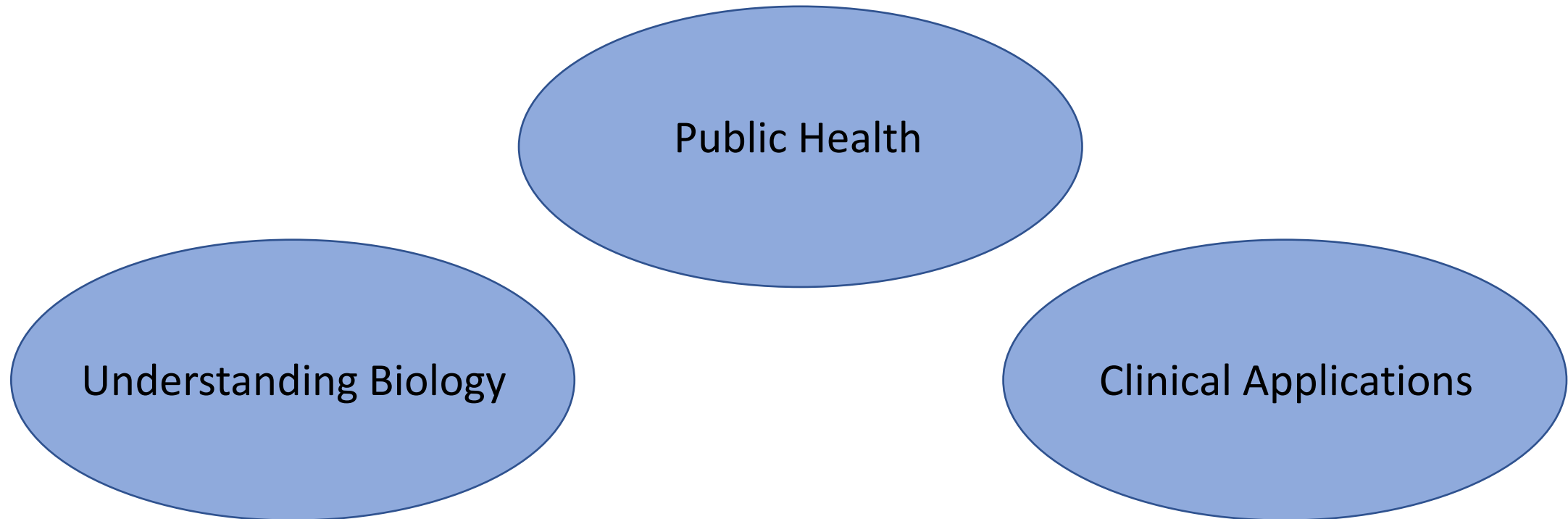
Does aspirin prevent colorectal cancer? Depends on your DNA

Fred Hutch researchers move closer to cracking the code on how genes and environmental factors influence colorectal cancer risk

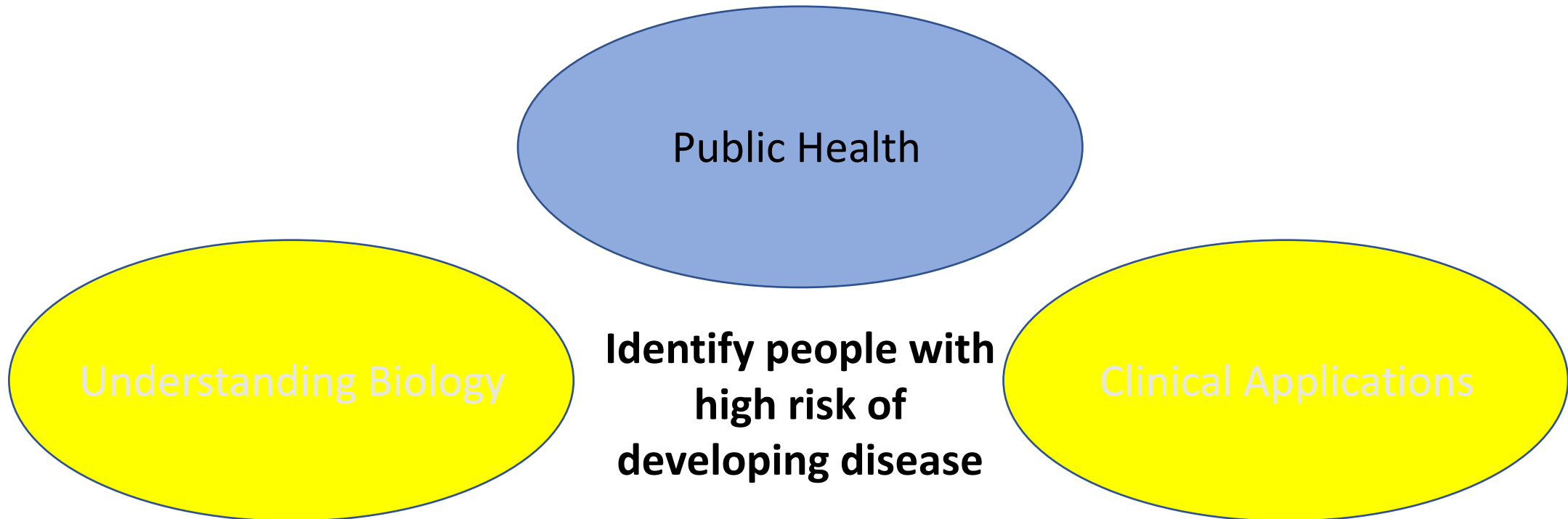
March 17, 2015 | By Diane Mapes / Fred Hutch News Service

Why do we want to study how our genome is involved in disease?

Why do we want to study how our genome is involved in disease?



Why do we want to study how our genome is involved in disease?



OP-ED CONTRIBUTOR

My Medical Choice

By ANGELINA JOLIE

Published: May 14, 2013 | 1712 Comments

LOS ANGELES

[Enlarge This Image](#)



Loren Capelli

MY MOTHER fought cancer for almost a decade and died at 56. She held out long enough to meet the first of her grandchildren and to hold them in her arms. But my other children will never have the chance to know her and experience how loving and gracious she was.

We often speak of “Mommy’s mommy,” and I find myself trying to explain the illness that took her away from us. They have asked if the same could happen to me. I have always told them not to worry, but the truth is I carry a “faulty” gene, BRCA1, which sharply increases my risk of developing breast cancer and ovarian cancer.

FACEBOOK

TWITTER

GOOGLE+

SAVE

E-MAIL

SHARE

PRINT

REPRINTS

Enough Said
Now Playing

TIME

MAY 27, 2013

THE ANGELINA EFFECT

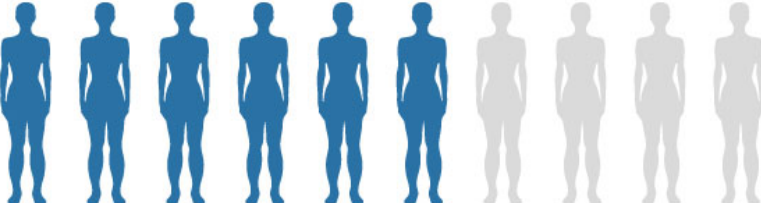
Angelina Jolie's double mastectomy puts genetic testing in the spotlight. What her choice reveals about calculating risk, cost and peace of mind

BY JEFFREY KLUGER & ALICE PARK

time.com

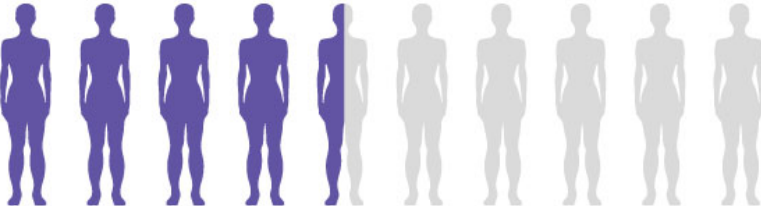
NATIONAL CANCER INSTITUTE CHANCES OF DEVELOPING BREAST CANCER BY AGE 70

Specific inherited mutations in the BRCA1 and BRCA2 genes increase the risk of breast and ovarian cancers. Testing for these mutations is usually recommended in women without breast cancer only when the person's individual or family history suggests the possible presence of a harmful mutation in BRCA1 or BRCA2. Testing is often recommended in younger women newly diagnosed with breast cancer because it can influence treatment decisions and have implications for their family members.



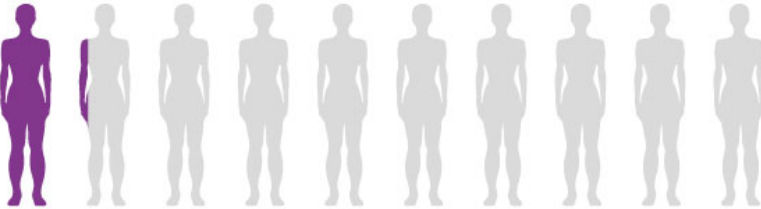
MUTATED BRCA1

55-65%



MUTATED BRCA2

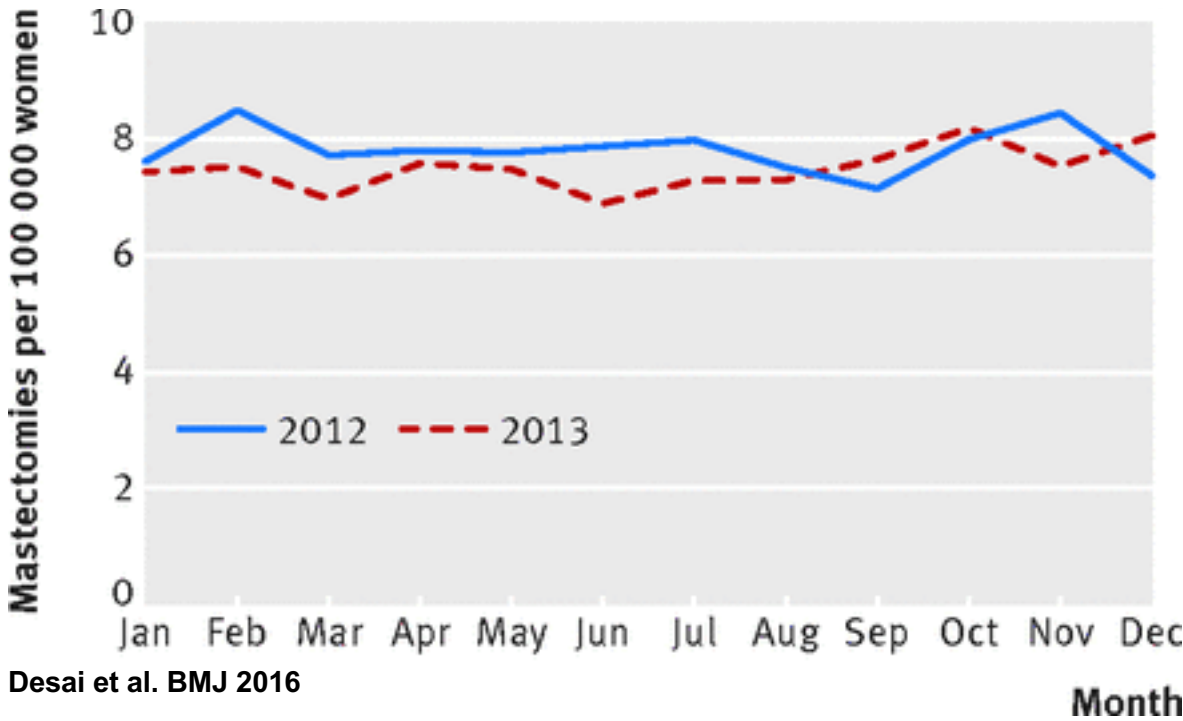
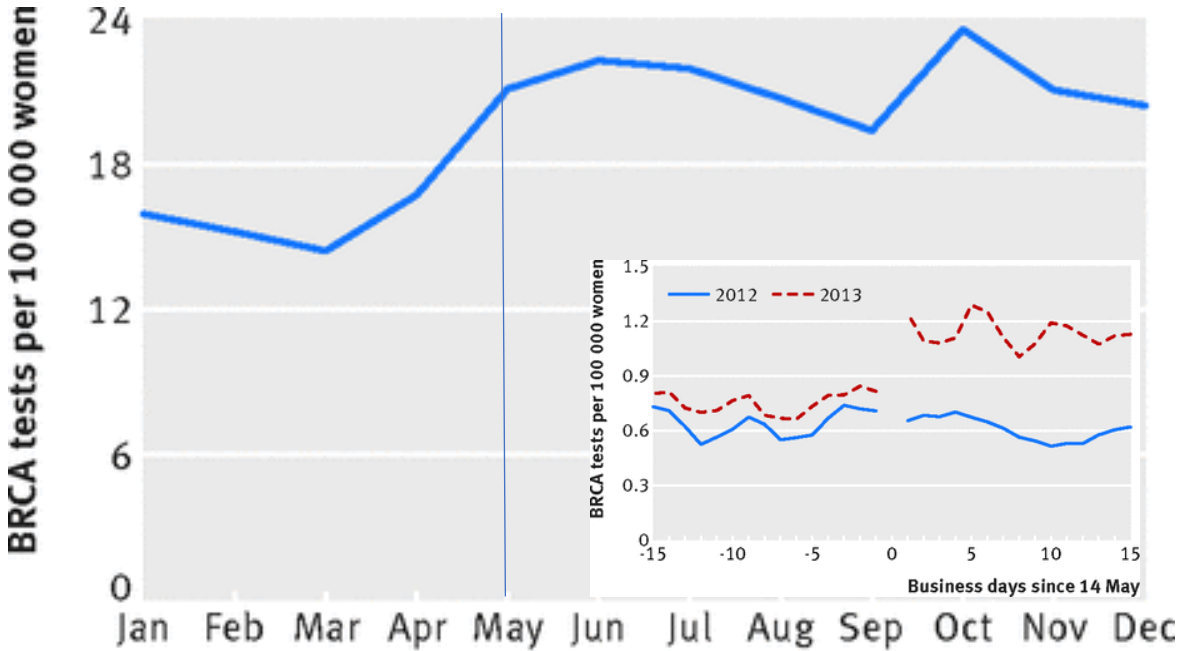
45%



NORMAL BRCA

12%

www.cancer.gov/brca-fact-sheet



Desai et al. BMJ 2016

Month



Health Risks (122) ?

↑ ELEVATED RISKS	YOUR RISK	AVERAGE RISK
Coronary Heart Disease	33.1%	24.4%
Psoriasis	15.0%	10.1%
Restless Legs Syndrome	5.2%	4.2%
Exfoliation Glaucoma	2.9%	1.0%
Lupus (Systemic Lupus Erythematosus) ♀	1.1%	0.2%

[See all 122 risk reports...](#)

Traits (62) ?

REPORT	RESULT
Alcohol Flush Reaction	Does Not Flush
Bitter Taste Perception	Can Taste
Blond Hair	28% Chance
Earwax Type	Wet
Eye Color	Likely Blue

[See all 62 traits...](#)

Inherited Conditions (53) ?

REPORT	RESULT
Hemochromatosis (HFE-related)	Variant Present
ARSACS	Variant Absent
Agnesis of the Corpus Callosum with Peripheral Neuropathy (ACCPN)	Variant Absent
Alpha-1 Antitrypsin Deficiency	Variant Absent
Autosomal Recessive Polycystic Kidney Disease	Variant Absent

[See all 53 carrier status...](#)

Drug Response (25) ?

REPORT	RESULT
Clopidogrel (Plavix®) Efficacy (CYP2C19-related) update	Reduced
Abacavir Hypersensitivity	Typical
Acetaldehyde Toxicity	Typical
Fluorouracil Toxicity	Typical
Hepatitis C Treatment Response	Typical

[See all 25 drug response...](#)

- [Parkinson's disease](#), a nervous system disorder impacting movement;
- [Late-onset Alzheimer's disease](#), a progressive brain disorder that destroys memory and thinking skills;
- [Celiac disease](#), a disorder resulting in the inability to digest gluten;
- [Alpha-1 antitrypsin deficiency](#), a disorder that raises the risk of lung and liver disease;
- [Early-onset primary dystonia](#), a movement disorder involving involuntary muscle contractions and other uncontrolled movements;
- [Factor XI deficiency](#), a blood clotting disorder;
- [Gaucher disease type 1](#), an organ and tissue disorder;
- [Glucose-6-Phosphate Dehydrogenase deficiency](#), also known as G6PD, a red blood cell condition;
- [Hereditary hemochromatosis](#), an iron overload disorder; and
- [Hereditary thrombophilia](#), a blood clot disorder.

23andMe Granted First FDA Authorization for Direct-to-Consumer Genetic Test on Cancer Risk

March 6, 2018

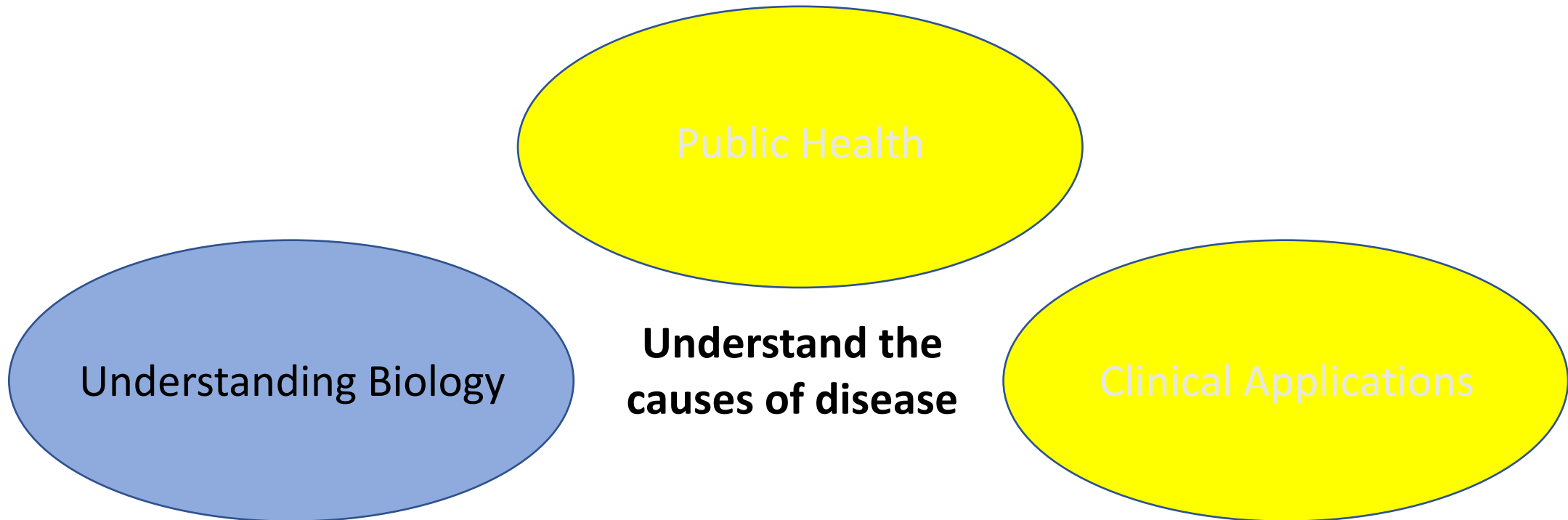
Authorization allows 23andMe to report on BRCA1- and BRCA2-related genetic risk for breast, ovarian and prostate cancer

Mountain View, California – March 6, 2018 – 23andMe, Inc., the leading personal genetics company, today received the first-ever FDA authorization for a direct-to-consumer genetic test for cancer risk. The authorization allows 23andMe to provide customers, without a prescription, information on three genetic variants found on the BRCA1 and BRCA2 genes known to be associated with higher risk for breast, ovarian and prostate cancer.

“Being the first and only direct-to-consumer genetics company to receive FDA authorization to test for cancer risk without a prescription is a major milestone for 23andMe and for the consumer,” said Anne Wojcicki, 23andMe CEO and co-founder. “We believe it’s important for consumers to have direct and affordable access to this potentially life-saving information. We will continue pioneering a path for greater access to health information, and promoting a more consumer-driven, preventative approach to health care.”

23andMe will report on three variants in the BRCA1 and BRCA2 genes associated with a significantly higher risk of breast and ovarian cancer in women, and breast cancer in men. The variants may also be associated with an increased risk for certain other cancers. These variants are

Why do we want to study how our genome is involved in disease?



“Association does not imply causation”



HDL (“Good”) Cholesterol and Myocardial Infarction (MI)

- **↑** HDL -> **↓** MI risk

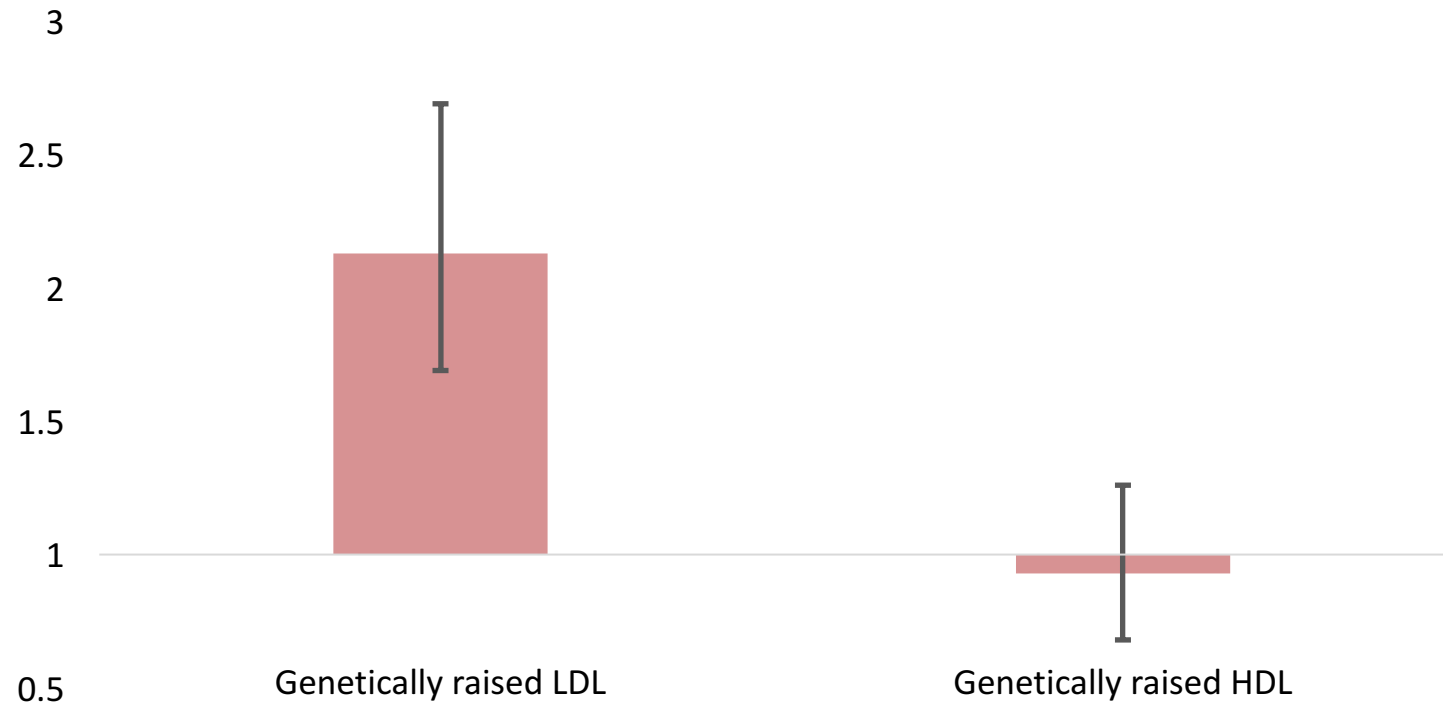


Increasing HDL concentrations
might help decrease
cardiovascular disease risk.



People who carry gene variants that increase HDL do not have a lower risk of MI

Since HDL is correlated with exercise, weight loss, diet (nuts, fish) it is likely that these lower your risk for MI rather than HDL itself



RESEARCH

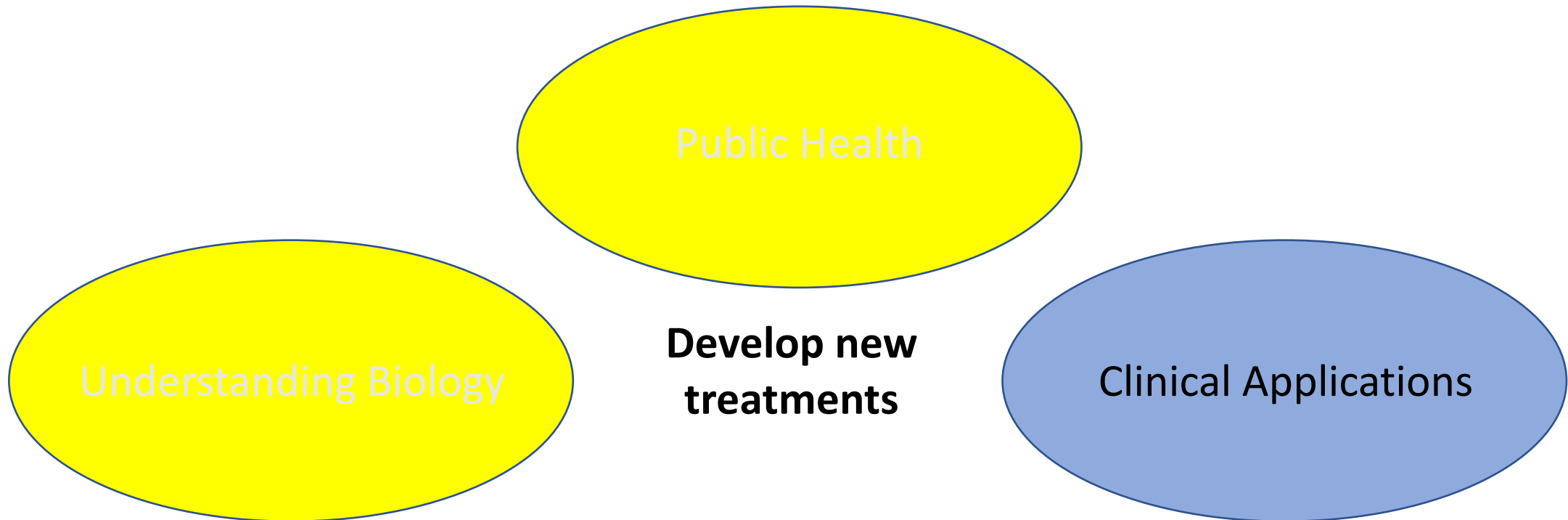
RESEARCH ARTICLES

HEART DISEASE

**Rare variant in scavenger receptor BI
raises HDL cholesterol and increases
risk of coronary heart disease**

Zanoni et al, Science 2016

Why do we want to study how our genome is involved in disease?



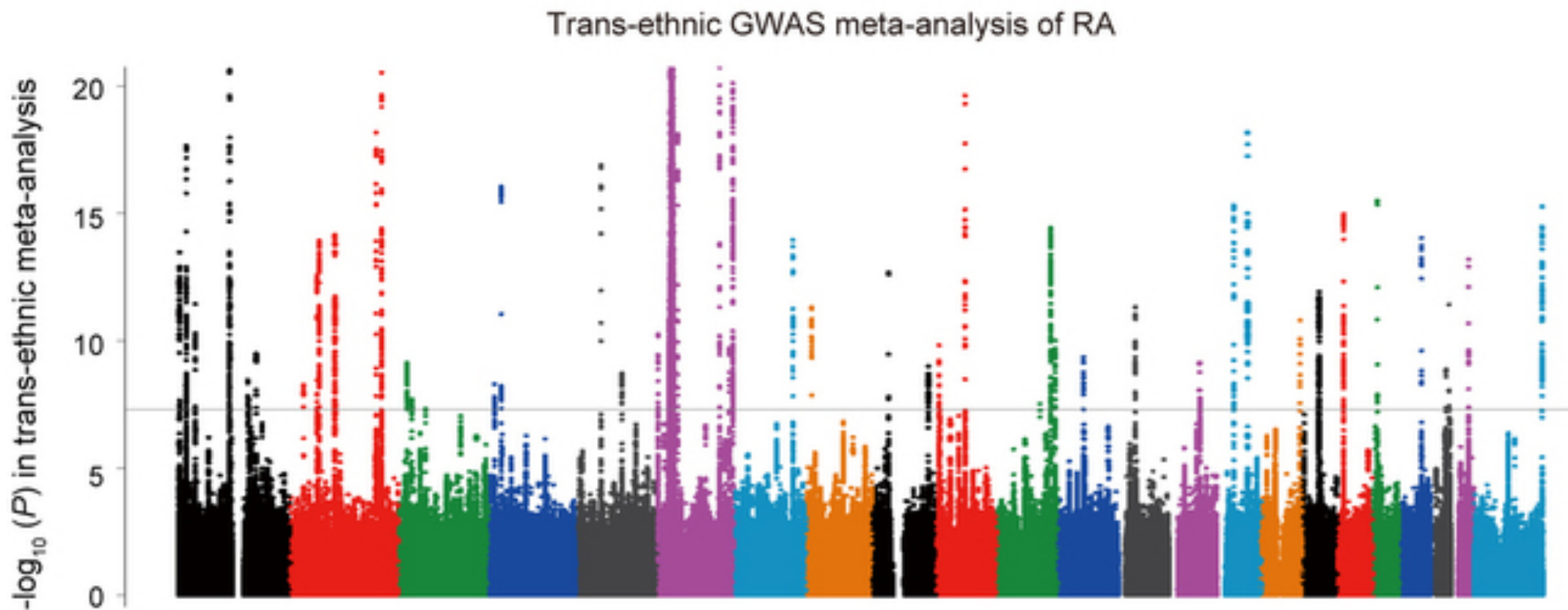
Rheumatoid Arthritis – an inflammatory, crippling, incurable disease

- In 2005, an estimated 1.5 million (0.6%) of US adults age ≥ 18 had RA.



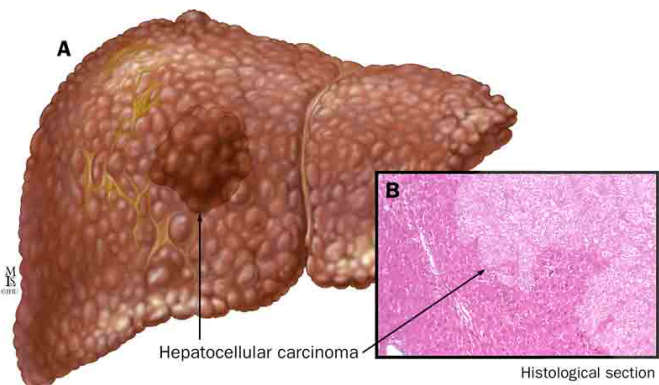
A study of 10 million genetic variants in 29,880 RA cases and 73,758 controls

b



Identified genes are targets of approved therapies for RA, and further suggest that drugs approved for other diseases may be repurposed for the treatment of RA

flavopiridol



CAPRIDINE-β
(c-1748)

Novel Chemotherapies for Prostate Cancer Patients Throughout Multiple Stages and Clinical States of Treatment

AV Therapeutics, Inc.
Advanced Cancer Chemotherapies

The advertisement features a photograph of a doctor in a white coat with his hand on the shoulder of an elderly, smiling patient. The text is positioned to the right of the image.

Cancers/psoriasis

Breast cancer

NDC 0069-0189-21

IbranceTM
(palbociclib)
capsules

The Pfizer logo is a green oval with the word 'Pfizer' in white. Below it, the product name 'Ibrance' is in large bold black letters, followed by '(palbociclib)' and 'capsules' in smaller bold black letters.

125 mg

For Oncology Use Only
21 Capsules **Rx only**

Lymphoma/Leukemia/Liver cancer

Okada, Nature, 2014

