Bioethics, implementation, and law

Learning objectives

- Understand principles of bioethics and engaging stakeholders in study design and implementation.
- Frame genetic epidemiology within legal framework.
- Translate odds ratios and allele frequencies into genetic test screening metrics.

2000: Railroad worker develops carpal tunnel

Gary, 46, has maintained railroad track since he was 20 years old. He ties new track with bolts by squeezing the trigger of an impact wrench with high vibrations. He develops carpal tunnel (inflammation in the wrists that pinches the nerves) that causes pain and numbness.

He takes time off work, gets surgery, and return to work.

He bills the railroad for his surgery.

Railroad asks to perform tests

A few weeks later, he gets a letter telling him that he has to go see a doctor for “x-rays and other medical” tests. His wife sleuths around and figures out that these will be genetic tests.

She tells the railroad that her husband will not take the tests.

Railroad headquarters tells her they will investigate her husband with disciplinary action if he does not come in for the medical visit.

125 cases of carpal tunnel go unreported

The railroad is required to report carpal tunnel to authorities, but none of these cases are reported.

Rule: Only need to file **work-related** carpal tunnel syndrome injuries (caused from work activities).

What is happening here?

Genetics to show carpal tunnel is not work-related

By showing these workers had a genetic predisposition to carpal tunnel, the railroad could claim that these **cases were not work-related,** thus not having to report the cases or pay for the surgeries.

Looking for a gene deletion or nonsynonymous variant in the gene *PMP22*, which encodes peripheral myelin protein 22. PMP22 connects nervous system to muscles.

In 2001, worker sues Burlington Northern Railroad for genetic discrimination

ARCHIVE

Railroad Will Pay $2.2 Million to Settle Worker DNA Testing Case

The Brave New World envisioned by Aldous Huxley got a setback this week when the Burlington Northern Sante Fe Corp. settled a case charging it illegally tested workers for genetic defects.

EHS Today Staff | May 09, 2002

Genetic predisposition to carpal tunnel syndrome

Dr. Philip Change (Professor of Pediatrics and Neurology at UW) discovered the association between *PMP22* variants and risk for carpal tunnel syndrome.

Of this railroad testing case, he said: "If they had just bothered to call me, I could have saved them a lot of money and a lawsuit they richly deserve."

What is happening with the genetics?

PMP22: 4 exon gene on chromosome 17.

Gene deletion (80%) and nonsynonymous SNPs (20%) lead to low concentrations of PMP22, increasing risk for carpal tunnel. It is inherited in an autosomal dominant fashion, though many people with one copy of defective *PMP22* do not develop carpal tunnel. Example of **Gene x Environment interaction!**

What is happening with the genetics?

This genetic form of carpal tunnel is found in 2-5 out of 100,000 people.

Carpal tunnel is found in 2 of every 100 people (2000 of 100,000), costing $2 billion a year to treat, and accounting for 3% of workers comp.

What can we tell already about genetic causes of carpal tunnel??

What is happening with the genetics?

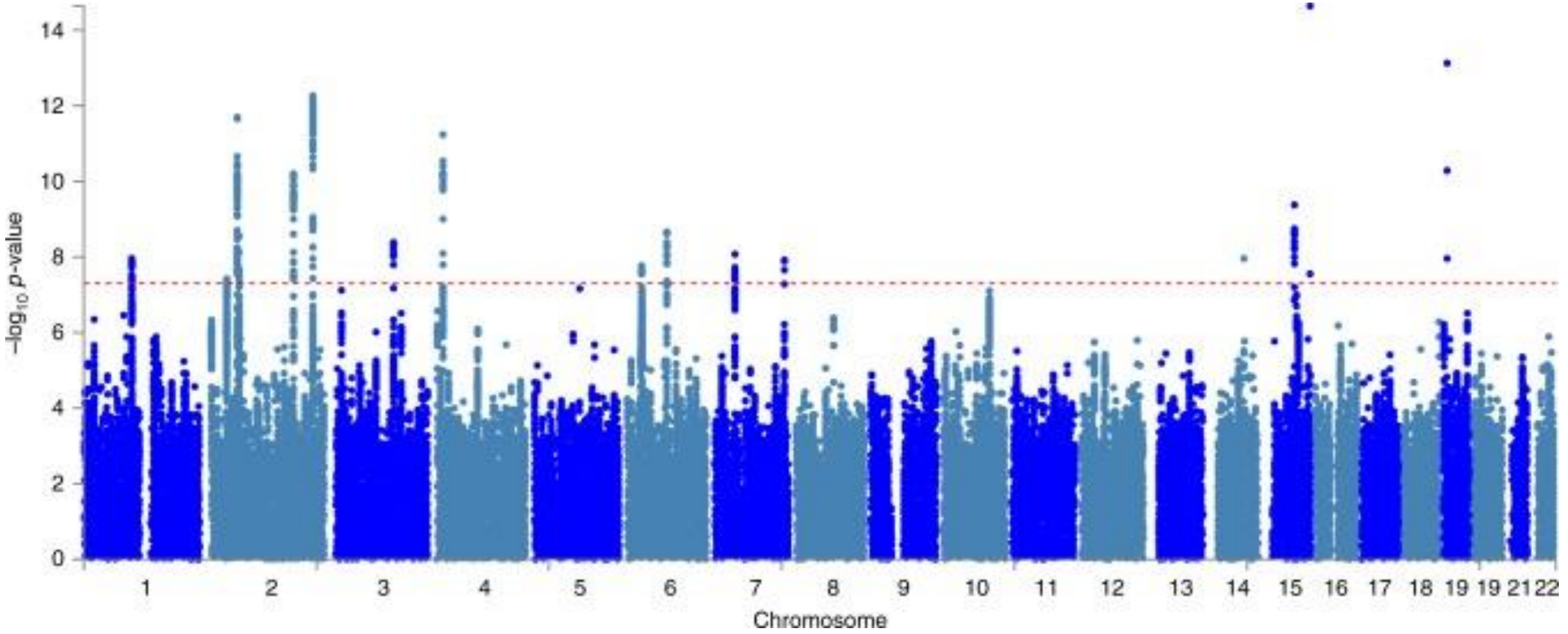
Frequency of bad variants (either deletion or nonsynonymous variant) is 0.00016 in a Northern European population.

Genetics may be responsible for just 1-4% of carpal tunnel syndrome.

None of the 125 railroad workers had one of these forms of *PMP22* that increase risk for carpal tunnel.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6399342/

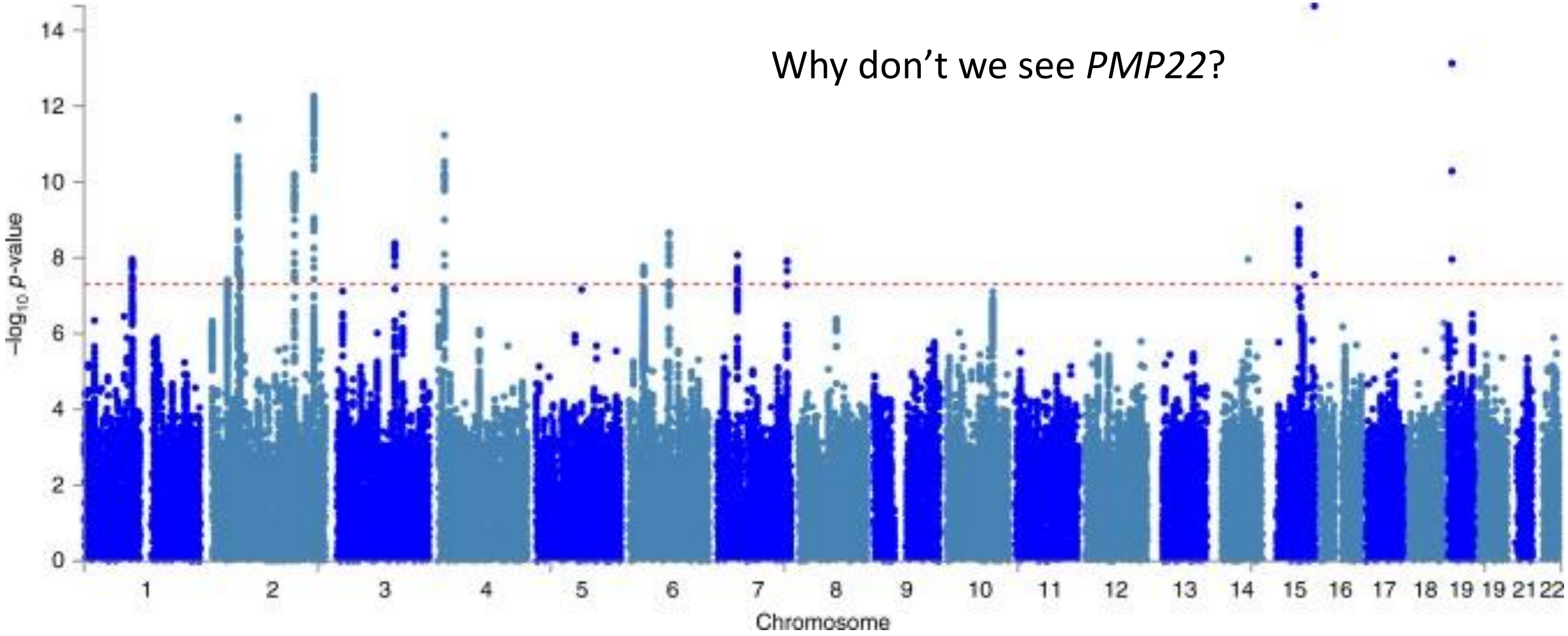
GWAS of carpal tunnel (*PMP22* on chr17)



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6399342/

GWAS of carpal tunnel (*PMP22* on chr17)

Why don't we see *PMP22*?



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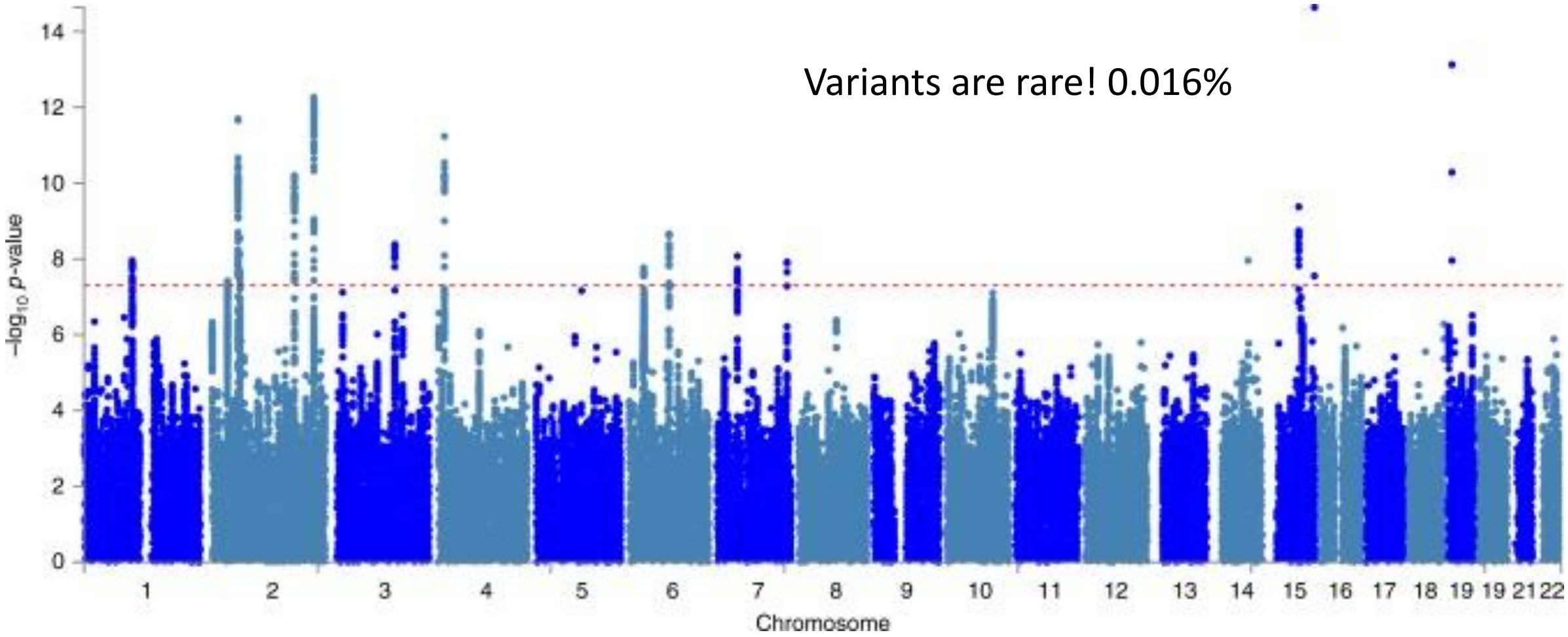
GWAS of carpal tunnel (*PMP22* on chr17)



Burlington Northern Sante Fe Railroad

Settled out of court, but railroad violated Americans with Disabilities Act and forced people to get a genetic test against their will. **Genetic Discrimination.**

Genetic Information Nondiscrimination Act (GINA)

Federal law signed in 2008.

Protects against genetic discrimination in employment and health insurance. Covers genetic information of the individual and their family.

Insurance companies cannot use genetic information (collected purposely or accidentally) to set eligibility, coverage, underwriting, or premium-setting decisions.

Employer may not use genetic information in making decisions regarding hiring, promotion, terms or conditions, privileges of employment, compensation, or termination.

GINA limits

Does not apply to:

- Business with fewer than 15 employees.
- Indian Health Services, US armed forces.
- Life insurance, long term care insurance, disability insurance.
- “employee wellness programs”

https://www.congress.gov/bill/110th-congress/house-bill/00493

http://www.geneticfairness.org/act.html

The New York Times

Myriad Genetics Ending Patent Dispute on Breast Cancer Risk Testing

By Andrew Pollack

Jan. 27, 2015

Myriad Genetics has essentially given up trying to stop other companies from offering tests for increased risk of breast cancer, ending a dispute that was the subject of a landmark Supreme Court ruling that human genes cannot be patented.

The company has settled or is in the process of settling patent-infringement lawsuits it filed against other companies that now offer such testing, a Myriad spokesman said on Tuesday.

Myriad's lucrative monopoly on testing for mutations in two genes linked to an increased risk of breast and ovarian cancer ended in 2013, when the Supreme Court ruled that human genes were not eligible for patents because they were products of nature.

Patenting human genes = testing monopoly

In the 90's, Myriad Genetics received a patent on the human genes BRCA1 and BRCA2 because they isolated cDNA (synthetic DNA containing only exons). By 'owning' the BRCA sequences, no other companies could use them.

in 1998, UPenn's Genetic Diagnostic Laboratory received a cease and desist letter due to patent infringement from Myriad, asking clinical pathologists to stop testing patient samples for BRCA.

They charge ~$4000/test to sequence BRCA1 and 2 (at the time in 2010, that was the same cost as whole genome sequencing)

The New York Times

Justices, 9-0, Bar Patenting Human Genes

The news media waited for rulings outside the Supreme Court building on Thursday morning. Jonathan Ernst/Reuters

Supreme court opens the playing field in 2013

"A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated", invalidates Myriad's patents on the BRCA1 and BRCA2 genes.

Other companies start testing… for $250 (though many of these are genotyping). **Why does this matter?**

Official law and legal precedent are often reactionary

How can we as researchers and implementers get ahead of the laws and lawsuits and help genetic epidemiology be used for good?

Laws vs Ethics

Principles of Bioethics

- Beneficence: maximize benefit.
- Non-maleficence: minimize harm.
- Justice: fairness, equity (populations studied, harms and benefits distributed fairly).
- Autonomy: respect individuals to make own decisions (informed consent).

Beauchamp and Childress 2001

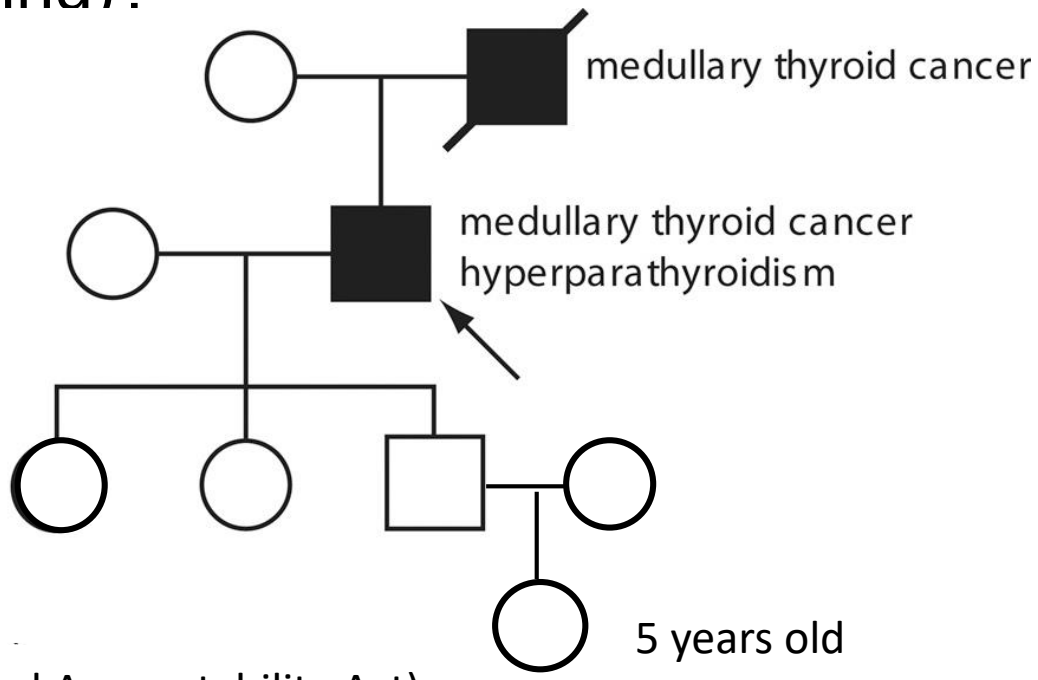
Stakeholder analysis

- Process of assessing a system and potential changes to it as they relate to all affected and interested parties.
  - What are important outcomes for communities and participants?
  - What genetic information would be valuable?

Case study – Family risk

50yr old man is diagnosed with advanced thyroid cancer. Genetic testing finds a known variant in *RET,* which causes thyroid cancer and is highly penetrant. There is no treatment, but early detection and surgery improves outcomes. He doesn't want to tell his estranged family about his cancer or genetic test result. Should doctors tell his family anyways (cascade screening)?

- Autonomy:
- Beneficence:
- Non-maleficence:
- Justice:



(Duty to warn with HIPAA- Health Information Portability and Accountability Act)

Principles of Bioethics

- Beneficence: maximize benefit.
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- Autonomy: respect individuals to make own decisions (informed consent).

Beauchamp and Childress 2001

Bioethics and Cascade screening

Principles	Points to consider
Beneficence	
Non-maleficence	
Justice	
Autonomy	

Bioethics and Cascade screening

Principles	Points to consider
Beneficence	• Telling would alert children to their potential risk, allowing increased surveillance and early detection for better survival if they test positive for the same variant.
Non-maleficence	• Telling could threaten family relationships. • Not telling would withhold valuable information from people who are at increased risk for life-threatening illness. • Telling could disrespect patient.
Justice	• Children may not have means (insurance coverage) to pay for genetic test or treatment.
Autonomy	• Patient did not want to tell children. • Children may not want to know that they are at increased risk. • Grandchild is not considered old enough to make her own decision as to whether to know risk.

Genetic epidemiology in public health

Population impact of genetic variation

- What do we do once we have a reliable genetic association result?
- Combining allele frequencies, odds ratios, and baseline risk to understand value of genetic testing for improving care and preventing bad outcomes.

Odds: How having a variant increases/decreases risk of an outcome

- Importance of the reference allele.
- Odds ratio is a comparison of odds -- there is often still a risk among people who don’t have the variant

Overall importance of the variant

Depends on:

- Proportion of people with a genetic variant.
- Change in odds of an outcome because of that variant.
- Frequency of the outcome among people without that variant.

What information can help us decide whether/how to implement genetic testing?

Implementing testing in clinical care

Test parameter	Definition
Sensitivity	Among people with an outcome, the proportion who have a positive test result
Specificity	Among people who do not have the condition, the proportion who have a negative test result
Positive predictive value	Among people with a positive test result, the proportion who have the condition
Negative predictive value	Among people with a negative test result, the proportion who do not have the condition

Burke 2014

The metrics we want: Why do we want these?

Sensitivity: Among all the people who will get a disease, how many could we prevent using a genetic test?

Specificity: If we identify someone as not being at risk because of not having a genetic variant, how often would we be wrong?

Positive predictive value: If we tell someone they have genetic risk, how comfortable do we feel them assuming they will get a disease and should take (sometimes drastic) steps to prevent it?

Negative predictive value: If someone does not have a genetic variant, are we certain they will not get the disease? Can we safely exclude these people from normal preventative measures?

Measures of screening test performance

Condition truly present

Screening test result*	+	-	
+	a	b	a+b
-	c	d	c+d
	a+c	b+d	a+b+c+d

*Affected by error, genotype prevalence, and penetrance

Sensitivity = a/(a+c)

Specificity = d/(b+d)

Positive predictive value = a/(a+b)

Negative predictive value = d(c+d)

Calculate screening test performance

- Variants in *RET* are found in 98% of people with thyroid cancer (positive test result).
- Because of the high penetrance, specificity is 99% (99% of people who do not have the MEN2 have a negative result).
- These numbers seem pretty good!
- MEN2 thyroid cancer is rare ~1/30,000 of the general population.

- Calculate positive and negative predictive values in a random sample of 30,000 people.

Measures of screening test performance

Condition truly present

Screening test result*	+	-	
+	a	b	a+b
-	c	d	c+d
	a+c	b+d	30,000

*Affected by error, genotype prevalence, and penetrance

Sensitivity = a/(a+c)

Specificity = d/(b+d)

Positive predictive value = a/(a+b)

Negative predictive value = d(c+d)

Calculate screening test performance

Condition truly present

Screening test result	+	-	
+	a 0.98	b	
-	c	d 29,699	
	1	b+d 29,999	30,000

From the text,
we can fill in these boxes

98% of people with MEN2 with test positive
0.98*1 = 0.98

Specificity = 99%
d/(29,999) = 0.99
d= 29,699.01

Sensitivity = a/(a+c)
Specificity = d/(b+d)
Positive predictive value = a/(a+b)
Negative predictive value = d(c+d)

Calculate screening test performance

Condition truly present

Screening test result	+	-	
+	0.98	300	300.98
-	0.02	29,699	29699.02
	1	29,999	30,000

Then we can use row/column sums to fill in the rest

Sensitivity = a/(a+c)
Specificity = d/(b+d) = 99%
Positive predictive value = a/(a+b)
Negative predictive value = d(c+d)

Calculate screening test performance

Condition truly present

Screening test result	+	-	
+	0.98	**300**	300.98
-	0.02	29,699	29699.02
	1	29,999	30,000

Then we can use row/column sums to fill in the rest

Sensitivity = a/(a+c)
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Negative predictive value = d(c+d)

Calculate screening test performance

Condition truly present

Screening test result	+	-	
+	0.98	300	300.98
-	0.02	29,699	29699.02
	1	29,999	30,000

And to calculate the screening test performance measures

Sensitivity = a/(a+c) = 0.98/(0.98+0.02) = 98% (people who will have disease who test positive)

Specificity = d/(b+d) = 99% (people who will not have disease who test negative)

Positive predictive value = a/(a+b) = 0.98/(0.98+300) = 0.3% (people who test positive who will have the disease)

Negative predictive value = d(c+d) = 29,699/(29,699+0.02) = 99.9% (people who will not have disease who test negative)

	General population
Risk for cancer in tested individual	1/30,000
Test sensitivity	98%
Test specificity	99.9%
Positive predictive value	0.3%
Negative predictive value	99.9%

Burke 2014

	General population	History of affected 1st- degree relative with identified mutation
Risk for cancer in tested individual	1/30,000	1/2
Test sensitivity	98%	99.9%
Test specificity	99.9%	99.9%
Positive predictive value	0.3%	99.9%
Negative predictive value	99.9%	99.9%

Burke 2014

What are good testing metrics?

- Depends!

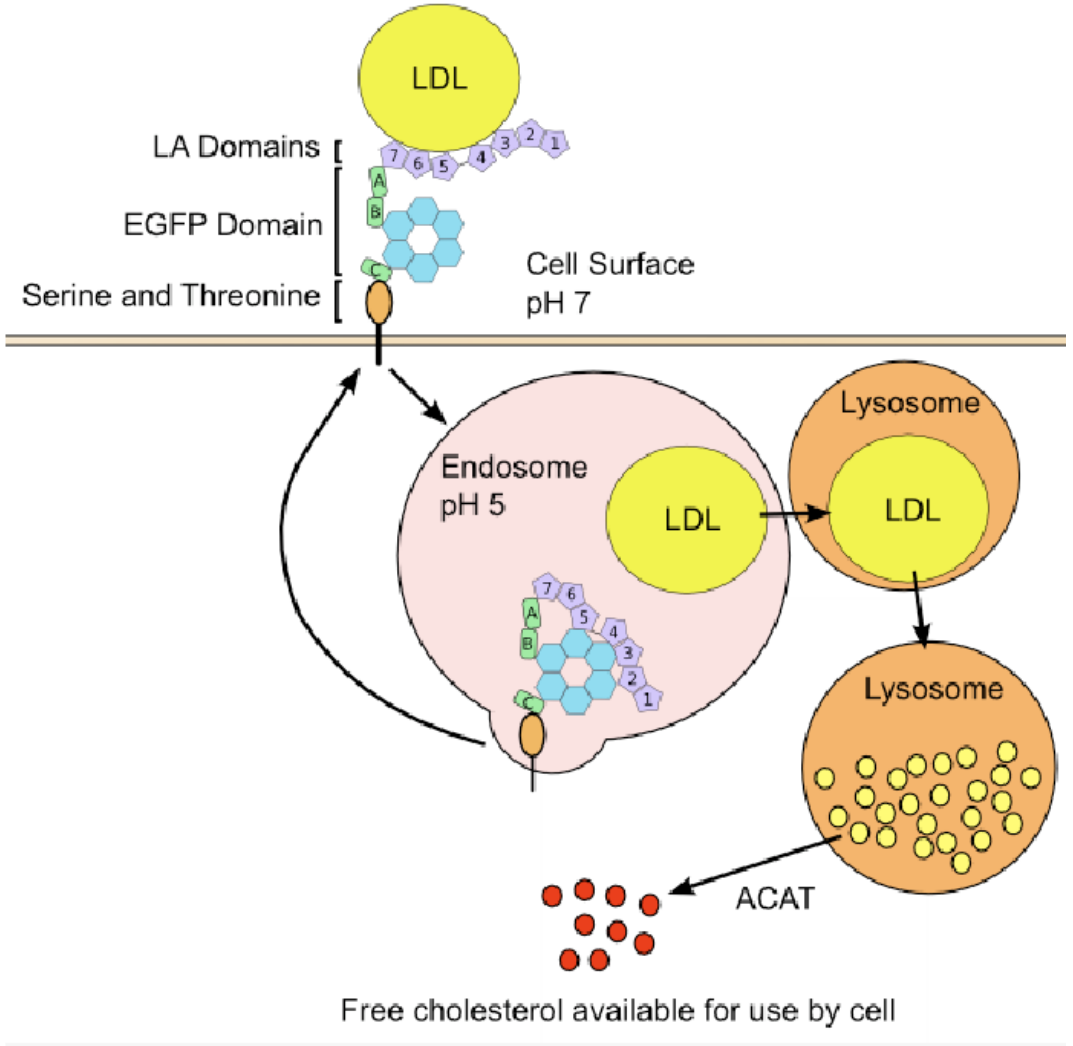
Familial Hypercholesterolemia (FH)

Severely **elevated LDL cholesterol levels causing atherosclerotic plaque** in the coronary arteries and proximal aorta.

Occurs **earlier and quicker** than in the general population, increasing risk for cardiovascular disease and heart attack.

The *LDLR* gene encodes a receptor that removes LDL

from the bloodstream.



Treatment for FH

Early identification through genetic testing or cholesterol testing.

Treatment with statins.

Encouraged to change lifestyle: better diet, more physical activity, no smoking.

½ of untreated men will have a heart attack by age 50;

⅓ of untreated women will have a heart attack by age 60.

⅔ of people with FH have at least one modifiable risk factor.

In a sample of 100,000 random people

1/10 have a heart attack

1/300 have a *LDLR* variant

Odd ratio for heart attack is 20x with *LDLR* variant compared to no variant

Confusion matrix: How well can a LDLR test find the right people for heart disease treatment?

		Has heart attack		
		+ yes	- never	Total
LDLR variant	+ (at least one)			
	- (no variants)			
	Total			100,000

Confusion matrix: How well can a LDLR test find the right people for heart disease treatment?

		Has heart attack		
		+ yes	- never	Total
LDLR variant	+ (at least one)	230	103	333
	- (no variants)	9,967	89,700	99,667
	Total	10,197	89,803	100,000

Confusion matrix: How well can a LDLR test find the right people for heart disease treatment?

		Has heart attack		
		+ yes	- never	Total
***LDLR* variant**	+ (at least one)	**230**	**103**	**333**
	- (no variants)	**9,967**	**89,700**	**99,667**
	Total	**10,197**	**89,803**	**100,000**

Positive predictive value:
230/333 = 0.69

69% of people with a *LDLR* variant would have had a heart attack. You can prevent heart attacks that would have occurred in ⅔ of people who you identify!*
*assuming your intervention is 100% successful

Confusion matrix: How well can a LDLR test find the right people for heart disease treatment?

		Has heart attack		
		+ yes	- never	Total
LDLR variant	+ (at least one)	230	103	333
	- (no variants)	9,967	89,700	99,667
	Total	10,197	89,803	100,000

Negative predictive value:
89,700/99,667 = 0.900

90% of people without a *LDLR* variant would not have had a heart attack. If you don't find an *LDLR* variant and so don't encourage heart-healthy lifestyles, 10% of those people will still have heart attacks.

Confusion matrix: How well can a LDLR test find the right people for heart disease treatment?

		Has heart attack		
		+ yes	- never	Total
***LDLR* variant**	+ (at least one)	**230**	**103**	**333**
	- (no variants)	**9,967**	**89,700**	**99,667**
	Total	**10,197**	**89,803**	**100,000**

Sensitivity: 230/10,197 = 0.0226

Only 2.3% of people who have a heart attack could have been identified (and the heart attack prevented) because of having an *LDLR* variant!

Confusion matrix: How well can a LDLR test find the right people for heart disease treatment?

		Has heart attack		
		+ yes	- never	Total
LDLR variant	+ (at least one)	230	103	333
	- (no variants)	9,967	89,700	99,667
	Total	10,197	89,803	100,000

99.9% of the time, people without a heart attack won't have an *LDLR* variant.

Specificity: 89,700/89,803= 0.999

Confusion matrix: How well can a LDLR test find the right people for heart disease treatment?

Sensitivity: 2.3% what proportion of people with heart disease can you catch by testing for *LDLR* variants?

Specificity: 99.9%

Positive predictive value: 69%

Negative predictive value: 90%

Confusion matrix: How well can a LDLR test find the right people for heart disease treatment?

Sensitivity: 2.3% what proportion of people with heart disease can you catch by testing for *LDLR* variants?

Specificity: 99.9%

Positive predictive value: 69%

Negative predictive value: 90%

Huge odds ratio (20x!!) but overall impact can still be quite low based on allele frequencies and baseline odds. Just the OR is not enough.

Confusion matrix: How well can a LDLR test find the right people for heart disease treatment?

Sensitivity: 2.3% proportion of people with heart attack can you catch by testing for *LDLR* variants?

Specificity: 99.9% proportion of people without heart attacks without *LDLR* variants.

Positive predictive value: 69% proportion of people with a *LDLR* variant who will have a heart attack.

Negative predictive value:

Confusion matrix: How well can a LDLR test find the right people for heart disease treatment?

Sensitivity: 2.3% proportion of people with heart attack can you catch by testing for *LDLR* variants?

Specificity: 99.9% proportion of people without heart attacks without *LDLR* variants.

Positive predictive value: 69% proportion of people with a *LDLR* variant who will have a heart attack.

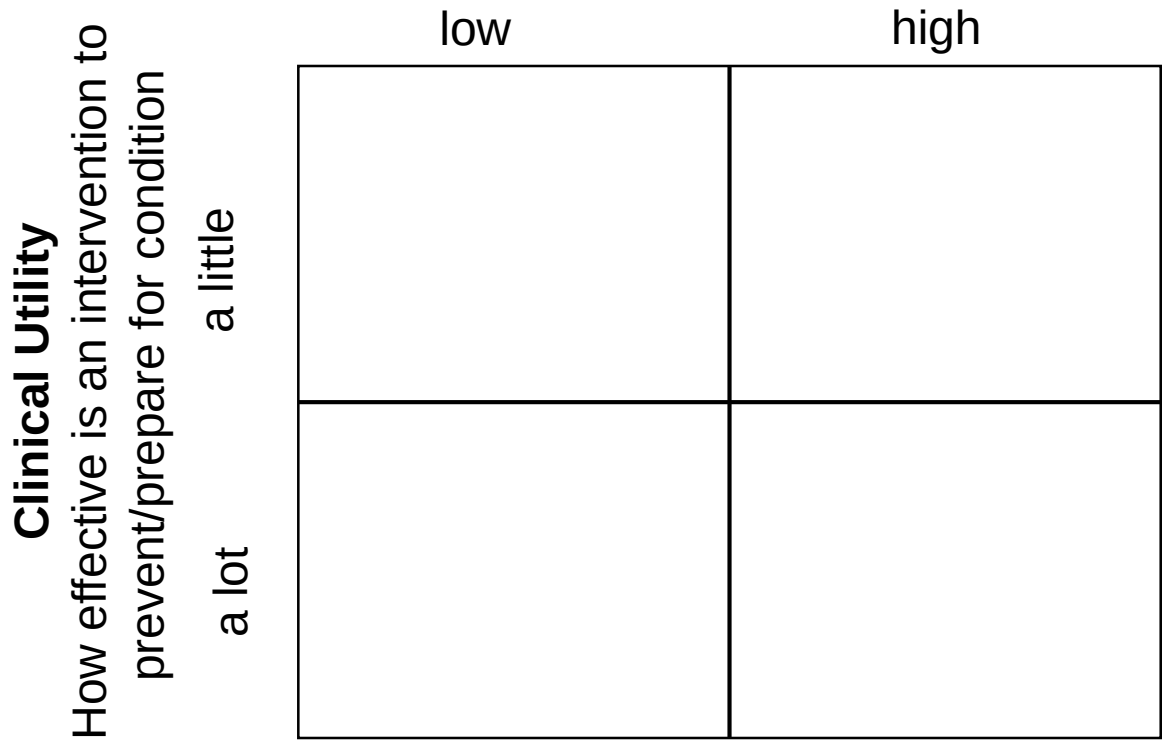
Negative predictive value: 90% proportion of people without an *LDLR* variant who won't have a heart attack.

*importance of communicating risk

Even if we have good screening metrics, do we want to employ them?

Implementation of genetic testing

Analytical and clinical Validity
How accurately test result predicts developing condition
(subject to quality of test and penetrance)



Implementation of genetic testing

Analytical and clinical Validity
How accurately test result predicts developing condition
(subject to quality of test and penetrance)

Clinical Utility
How effective is an intervention to prevent/prepare for condition

	low	high
a little	No benefit	Depends on Person (Huntingtons Disease)
a lot	Depends on intervention	Recommend Testing

Considerations of genetic tests and interventions

- Severity of preventative actions (Mastectomy? Improved diet?)
- Costs of more widespread screening
- Window of error (do you have early warning signs that are good enough?)
- Age of onset

Assessing clinical utility.

Population impact depends on…

- Frequency of the variant (and knowing those frequencies)
- Penetrance (how often when someone has the variant do they develop the outcome)
- Expressivity (if the outcome develops, how “big” is it)

Freakonomics Radio:

impact and utility of polygenic risk score for lipids

23:00-23:40; 27:30-28:20

http://freakonomics.com/podcast/23andme/

So, we genetic epidemiologists are discovering genetic variants associated with outcomes. Some of these outcomes are more/less desirable.

CRISPR:

How humans can edit DNA and drive our own evolution.

Clustered Regularly Interspaced Short Palindromic Repeat

Is it that easy?

By editing the germline of humans, we can permanently alter the nature of the human species.

Scientists have agreed to use CRISPR only for infants and later (no edits of embryos or fetuses)

Editing an embryo

Changes every cell in the body, including those that would pass the changes to future generations.

Germline editing is banned in many European countries, and in the United States. (the ban was just renewed a few weeks ago by the US Congress)

Current: Preimplantation Genetic Diagnosis (PGD)

Embryos are checked for variants and embryos without those variants are chosen for implantation to become fetuses.

Despite “screening”, the DNA and variants are limited by what is already available in the parental genetic material.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5544380/

Scientific consensus on merit to edit an embryo:

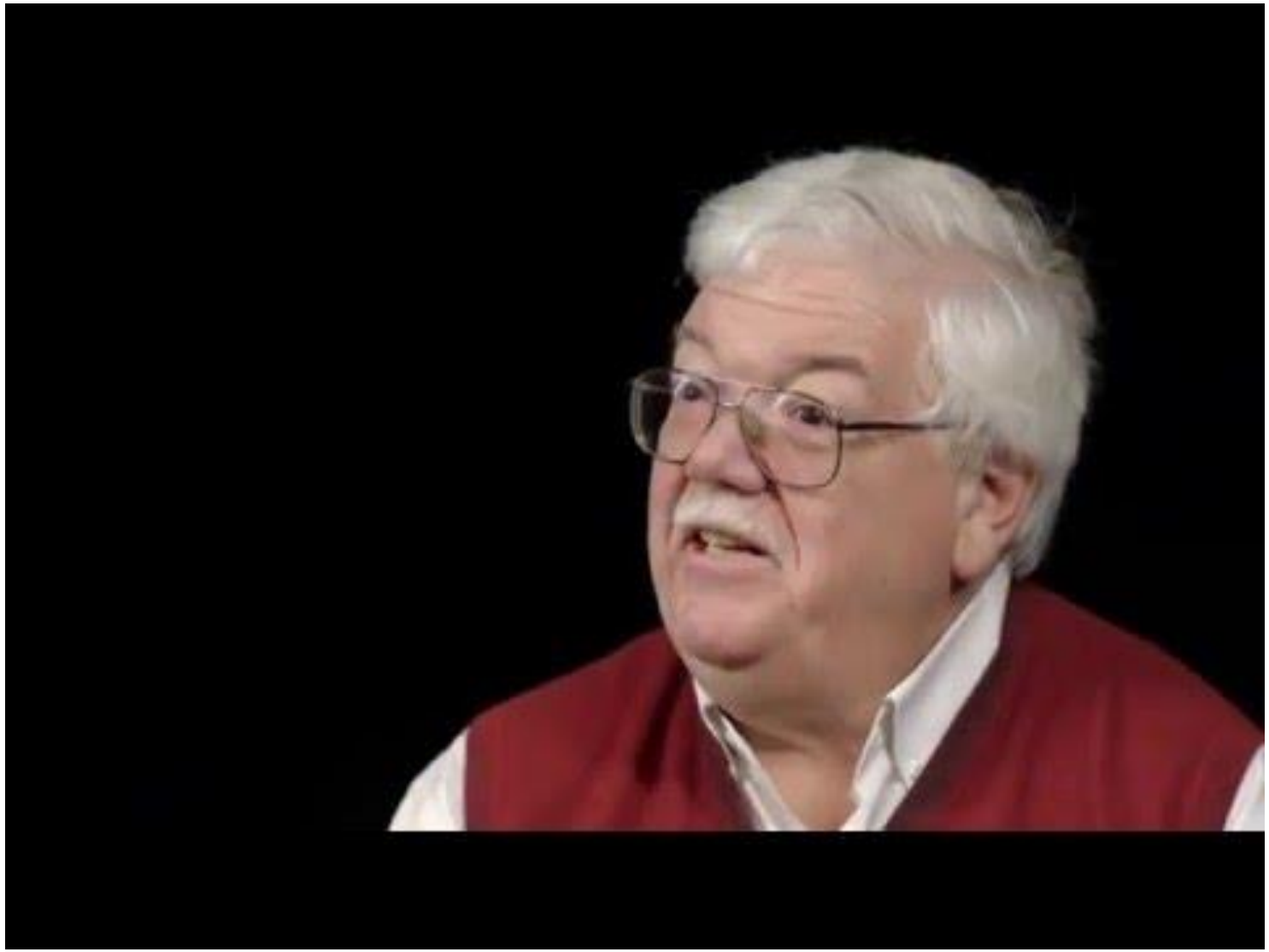
(a) a compelling medical rationale,

(b) an evidence base that supports its clinical use,

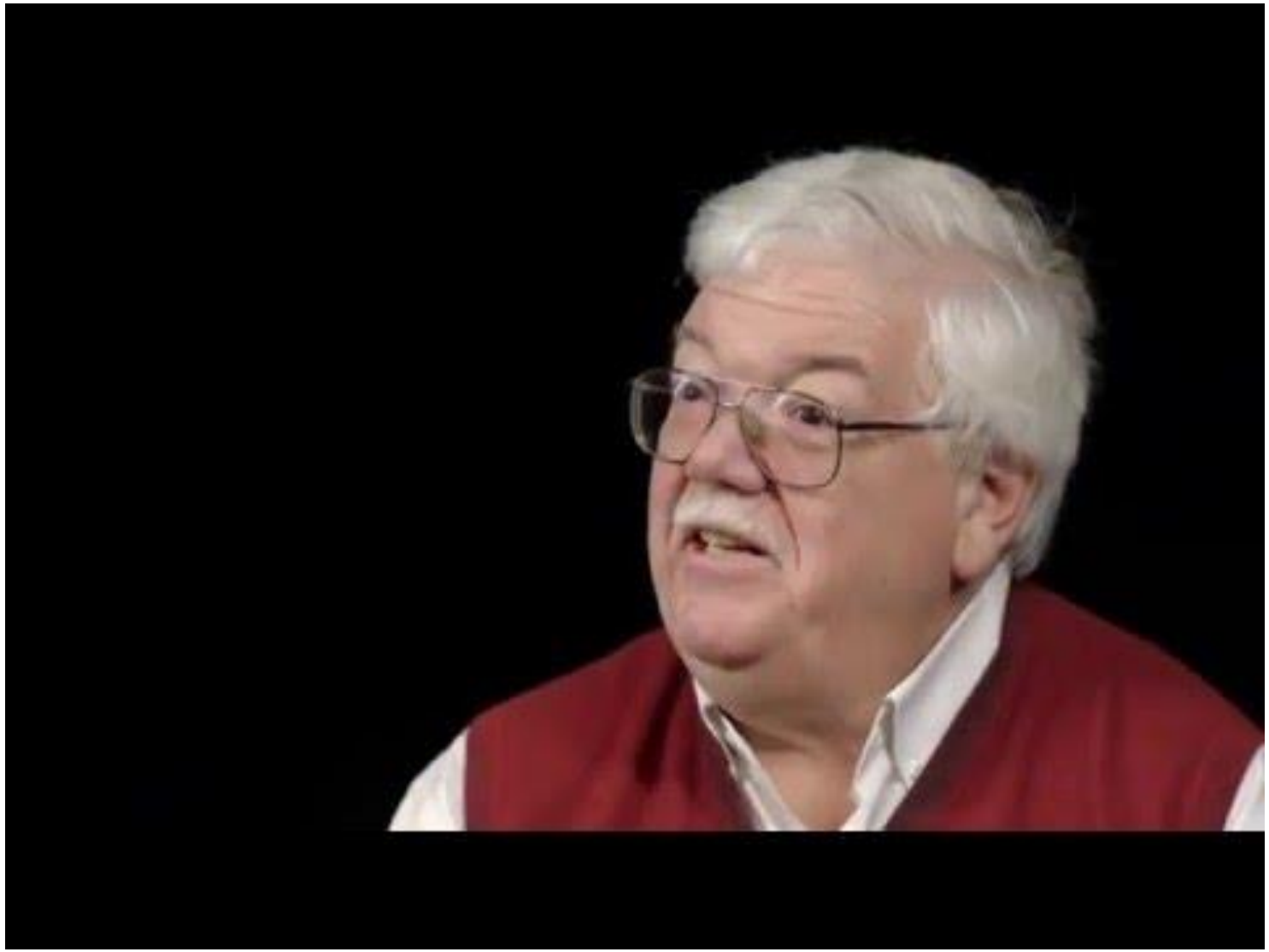
(c) an ethical justification,

(d) a transparent public process to solicit and incorporate stakeholder input.

The future of humans with Hank Greely (1)



The future of humans with Hank Greely (2)



December 2018: A video is released

Jiankui He, Stanford and Rice trained scientist, Professor at Southern University of Science and Technology in China

Reaction was immediate and severe

An analogy here would be if you and I as physicians developed a cold fusion reactor ... without ever having done nuclear reactor design, flipped the switch [without] any safety inspection or even checking if it produced power, then posted [a] vid on Instagram

-Sandip Patel, University of California San Diego

This amounts to unethical and reckless experimentation on human beings, and a grave abuse of human rights.

- **Marcy Darnovsky, Center for Genetics and Society,**

Why were scientists upset?

1) Scientists (including He) had agreed not to edit human germline.
2) The off-target consequences are unknown.
3) These were infants without consent.
4) No peer-reviewed scientific article has been published on methods.
5) The edits to the gene *CCR5* are not medically necessary.

CCR5 as an unworthy target for gene editing

The edits crippled normal versions of the *CCR5* gene. These edits prevent future infection with HIV by preventing HIV from entering lymphocytes (the babies' father was HIV+)

HIV is easily prevented with condoms, medications, needle-exchange programs. HIV is treated and controlled with effective medications.

CCR5 editing is not medically necessary.
(But who should decide really?)

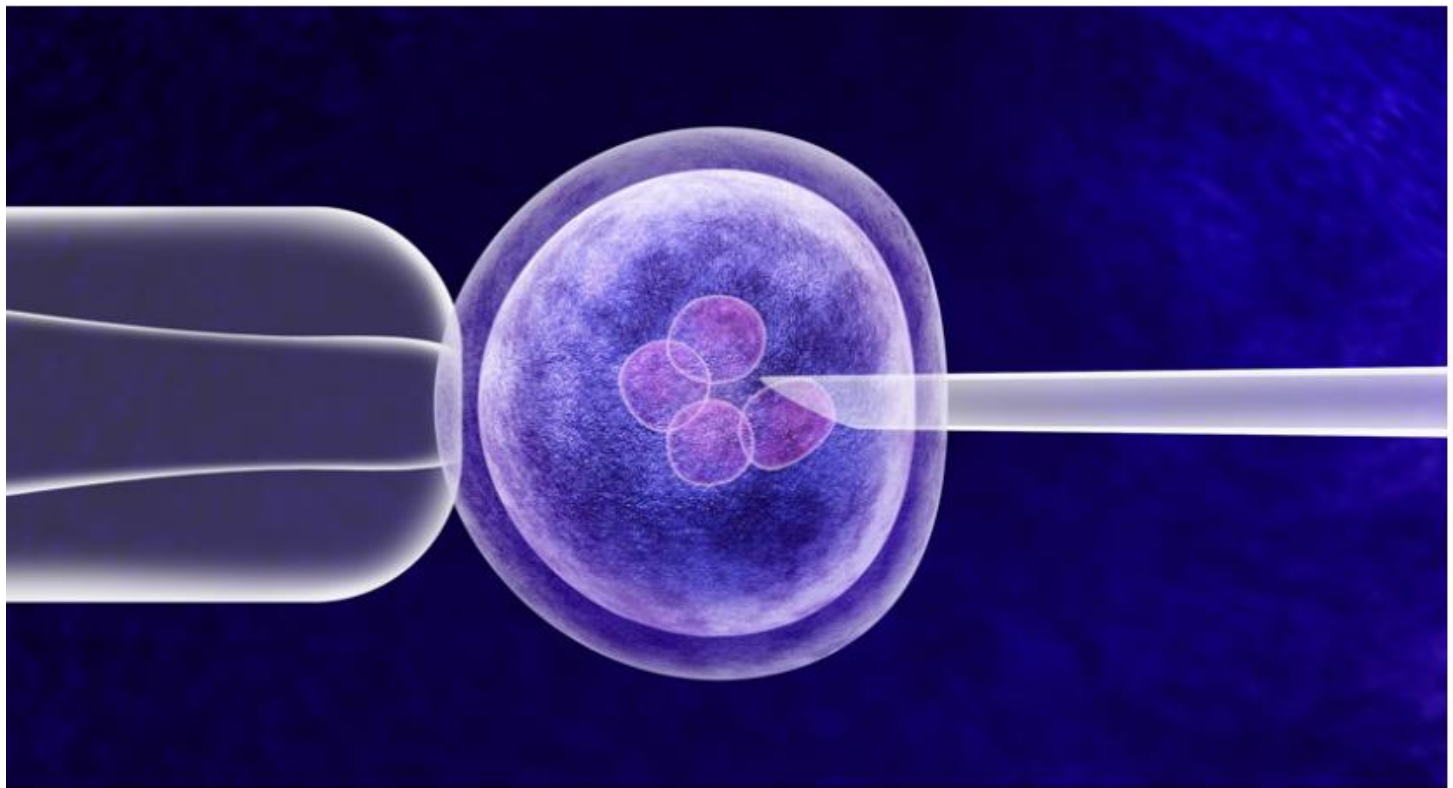
https://www.sciencenews.org/article/geneticists-push-5-year-global-ban-gene-edited-babies

NEWS GENETICS, SCIENCE & SOCIETY

Geneticists push for a 5-year global ban on gene-edited babies

Previous attempts to discourage the experiments with somewhat softer lingo haven't worked

BY TINA HESMAN SAEY 2:00PM, MARCH 13, 2019



NO-NO Scientists have said that editing DNA in eggs, sperm or embryos to make babies with altered genes is neither safe nor acceptable. But that hasn't stopped it from happening.

LIGHTSPRING/SHUTTERSTOCK

Magazine issue: Vol. 195, No. 7, April 13, 2019, p. 12

https://www.sciencenews.org/article/nobel-prize-winner-david-baltimore-crispr-babies-ban

NEWS GENETICS SCIENCE & SOCIETY

A Nobel Prize winner argues banning CRISPR babies won't work

A registry could keep human gene editing aboveboard, David Baltimore says

BY TINA HESMAN SAEY 7:00AM, APRIL 2, 2019

NO BAN Nobel laureate David Baltimore is a proponent of doing research to make human gene editing safer, but says the technique isn't ready for producing genetically modified babies. He talked with *Science News* about how gene editing should be regulated.

> "With a science that's moving forward as rapidly as this science is, you want to be able to adapt to new discoveries."
>
> — David Baltimore

The fertility center in Dubai was interested in offering CRISPR embryo editing to its patients. Its opening line is, “Congratulations on your recent achievement of the first gene editing baby delivered by your application!”

HEALTH

Fertility clinics around the world asked ‘CRISPR babies’ scientist for how-to help

By SHARON BEGLEY @sxbegle / MAY 28, 2019

He Jiankui speaks during the International Summit on Human Genome Editing in Hong Kong on Nov. 28, 2018.

KIN CHEUNG/AP

https://news.berkeley.edu/2019/06/03/crispr-baby-mutation-significantly-increases-mortality/

nature medicine

Brief Communication | Published: 03 June 2019

CCR5-Δ32 is deleterious in the homozygous state in humans

Xinzhu Wei & Rasmus Nielsen

Nature Medicine (2019) | Download Citation

Abstract

We use the genotyping and death register information of 409,693 individuals of British ancestry to investigate fitness effects of the CCR5-Δ32 mutation. We estimate a 21% increase in the all-cause mortality rate in individuals who are homozygous for the Δ32 allele. A deleterious effect of the Δ32/Δ32 mutation is also independently supported by a significant deviation from the Hardy–Weinberg equilibrium (HWE) due to a deficiency of Δ32/Δ32 individuals at the time of recruitment.

What is our obligation as genetic epidemiologists? As scientists? As global citizens?