FRIDAY			
8:30 – 9:15	Alie	Bioethics/ Implementation	Bioethical principles in genetic epidemiology,deciding whether to implement genetic testing
BREAK			
9:30-10:15	Sara	Rare variation	Strategies to analyze rare genetic variants
BREAK			
10:30-11:15	Sara	GxE interactions	Gene x Environment interactions analyses
LUNCH BREAK			
11:45 – 12:30	Alie	Risk prediction	Polygenic risk scores and population screening
BREAK			
12:45-1:30	Sara	Mendelian Randomization	Mendelian Randomization studies
BREAK			
1:45 – 2:30	Sara/Alie	Office Hours	Stop by to ask questions from the day, or schedule time to discuss your own project.

Bioethics, legal issues

Session 9

Learning objectives

- Understand principles of bioethics and engaging stakeholders in study design and implementation.
- Frame genetic epidemiology within legal framework.

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).

Zoom chat: what is happening here?

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.

Zoom chat: what type of information do you have that is relevant for the lawsuit?

What is happening with the genetics?

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

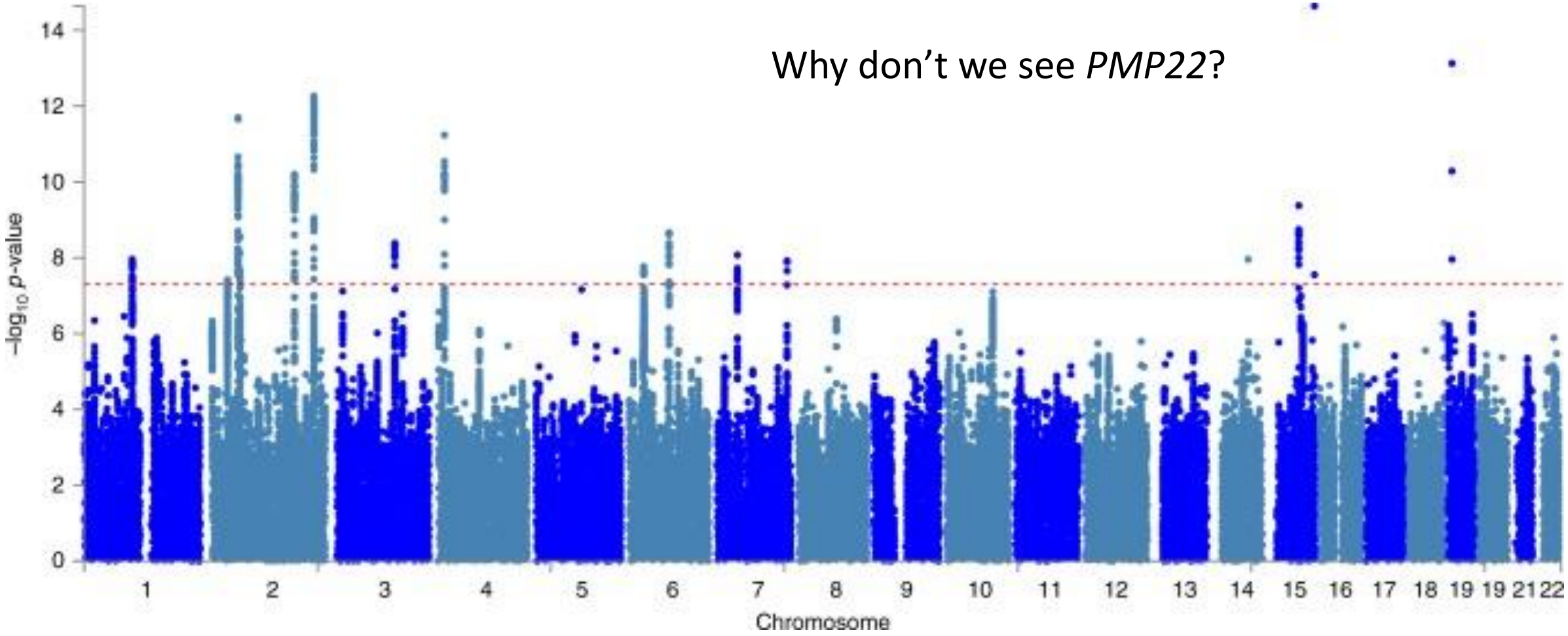
Genetics may be responsible for just 1-4% of carpal tunnel syndrome.

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)

Why don't we see *PMP22*?



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

Laws vs Ethics

Bioethics implementation:

Beneficence: Maximize benefit

Non-maleficence: Minimize harm

Autonomy: ability of individuals to make their own decisions

Justice: equitable access, benefit, and harms.

Stakeholders

All parties who may be impacted or affected by a decision or program.

Stakeholder analysis: process of assessing a decision or program as it relates to all relevant and interested parties.

Bioethical evaluation

Bioethical category	Considerations
Beneficence	
Non-maleficence	
Autonomy	
Justice	

NIH funded research and data sharing

- Zoom breakout: Conduct a bioethical evaluation case study.

Evaluation of genetic testing

Analytic validity: does the test give you the right result?

Clinical validity: does the test result correlate strongly with the phenotype?

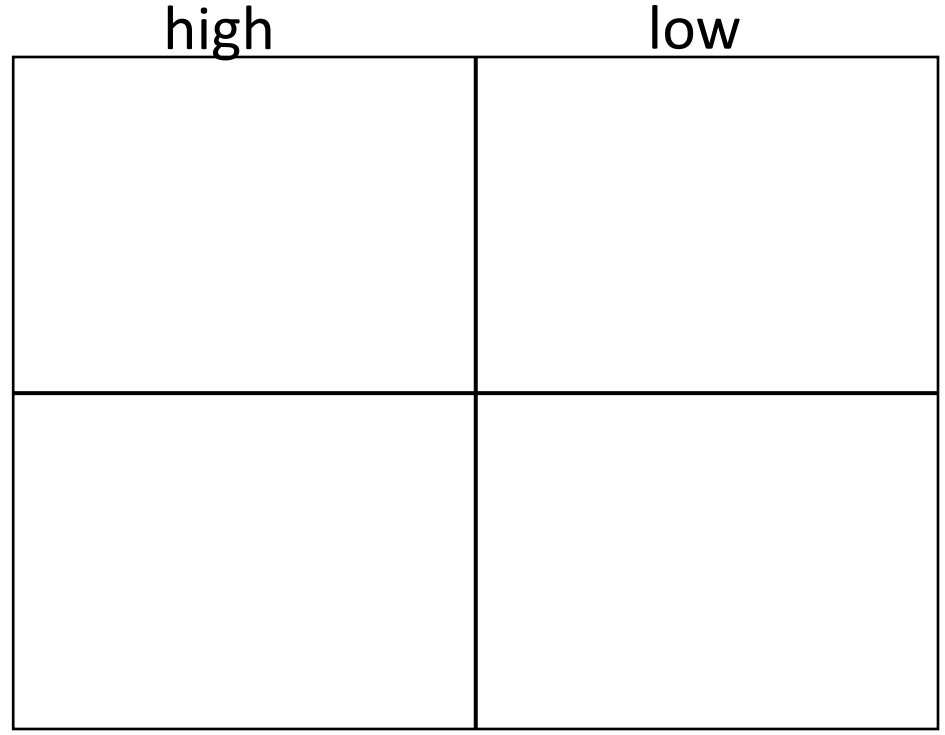
Clinical utility: does knowing the result help you? Is there a treatment? Is it a good treatment? Are there harms from the treatment?

Implementation of genetic testing

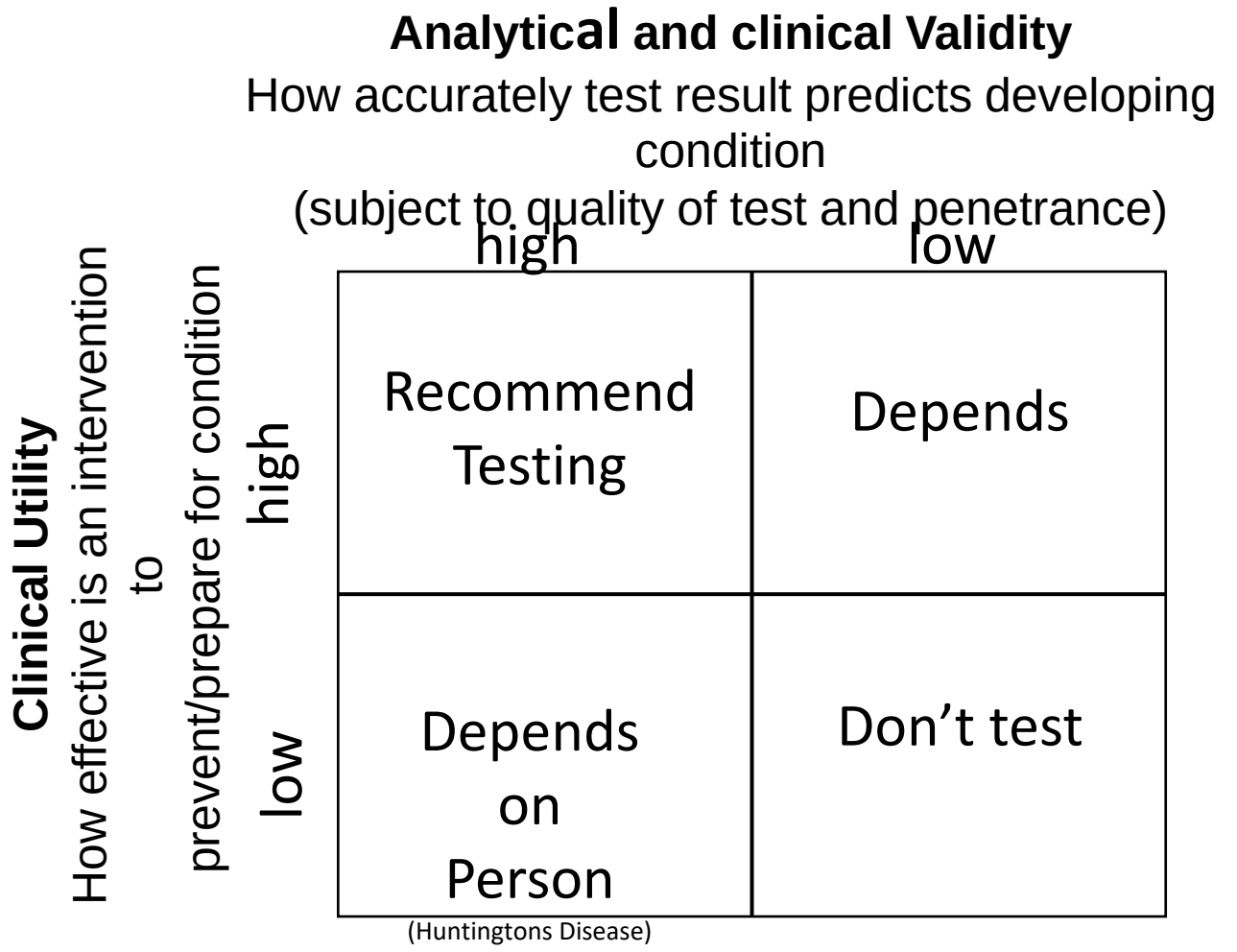
Analytical and clinical Validity

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



Implementation of genetic testing



Actionability decision table

Clinical Utility	Analytical/Clinical validity: High	Analytical/Clinical validity: Low
Good	**Test!**	Depends
Bad	Depends	**Don’t test!**

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

- Odds ratio is a comparison of odds -- there is often still a risk among people who don’t have the variant
- Penetrance – some people with the genetics will not develop the outcome

Considerations of genetic tests and interventions: Clinical Utility

- Severity of preventative actions (Mastectomy? Improved diet?)
- Costs of testing, intervention, recovery.
- Window of error (do you have early warning signs that are good enough?)
- Age of onset

What is our obligation as genetic epidemiologists? As scientists? As global citizens? to ensure ethical research and use of genetic testing?