Friday	8:30-9:15	**Sara/Alie**	Journal Club	Benonisdottir, S et al. "Epigenetic and genetic components of height regulation"
	9:15-10:00	**Alie**	Bioethics and Implementation	PPV, NPV, sensitivity, specificity, principles of bioethics
	10:30-12:00	**Sara**	Gene-Environment Interactions	Definitions, methods, practical issues
	1:30-2:15	**Sara**	Mendelian Randomization	Concept, methods
	2:15-3:00	**Alie**	Pharmacogenetics	Pathways and analysis
	3:30-4:30	**Sara**	Risk prediction	Methods, applications
	4:30-5:00	**Alie/Sara**	Wrap-up	

Bioethics and implementation

Section 9

(45 minutes)

Learning objectives

- Understand four principles of bioethics and framework for implementing genetic testing in clinical care.
- Frame difference between moral and legal.
- Apply bioethics framework to genetic epidemiology questions.
- Translate odds ratios and allele frequencies into public health screening metrics.

Burlington Northern Sante Fe Railroad (BNSF)

- US Equal Employment Opportunity Commission settled with BNSF for $2.2 million for secretly testing employees for deletion of *PMP22*.
- Hereditary Neuropathy with liability to pressure palsies (HNPP), a cause of carpal tunnel syndrome.
- The railroad was repairing a stretch of track that required extensive repetitive movements.

Burlington Northern Sante Fe Railroad (BNSF)

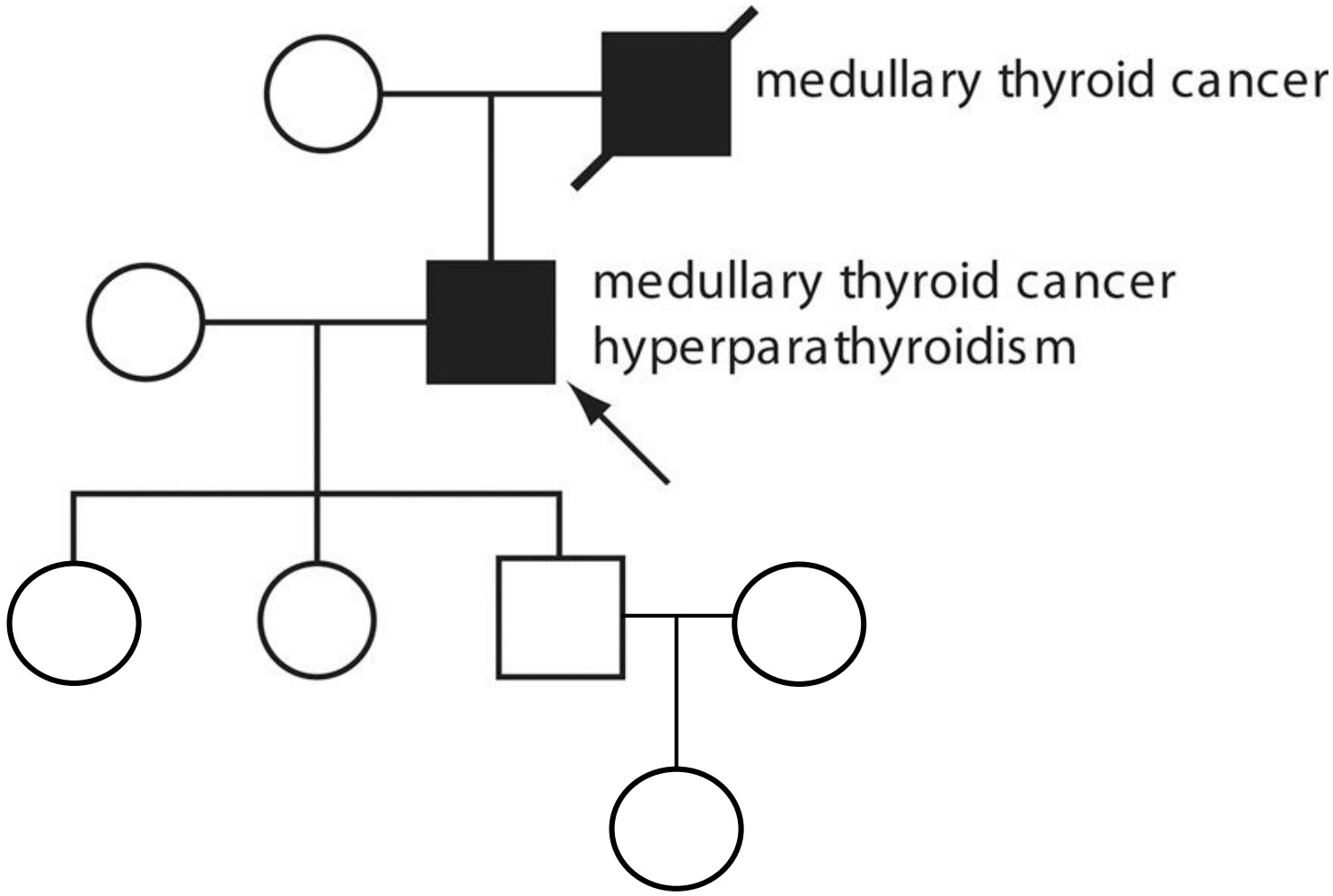
- 6% of US adults have a carpal tunnel diagnosis.
- 0.02% of US population has the *PMP22* deletion.
- Railroad claimed to need testing to show whether carpal tunnel was a work-related injury.
- None of the workers they tested had the variant.
- Settled out of court, but deemed genetic discrimination.

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

Multiple endocrine neoplasia (MEN2)

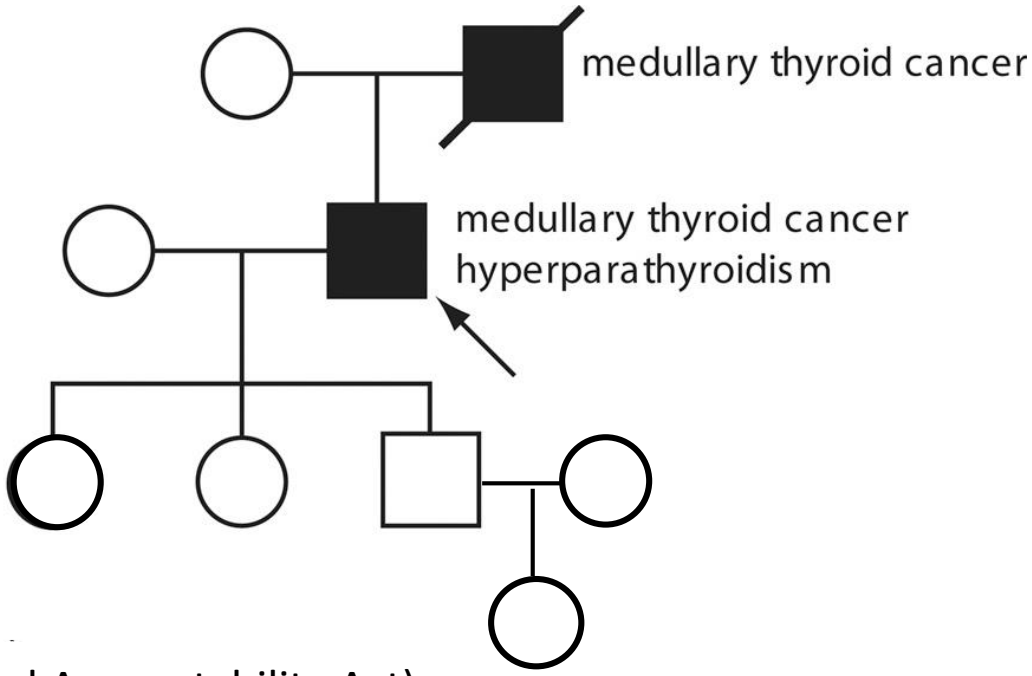


Adapted from Burke 2014

Case study – Family risk

50yr old man is diagnosed with advanced thyroid cancer. Genetic testing finds a known variant in *RET,* which causes MEN2 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?

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



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

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.

What about implementing *RET* screening for MEN2 across the whole population?

Implementing testing in clinical care

Test parameter	Definition
Sensitivity	Among people with a specific condition, 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

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 and genotype prevalence

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 MEN2 (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 is rare ~1/30,000 of the general population.

- Calculate positive and negative predictive values.

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)
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

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)

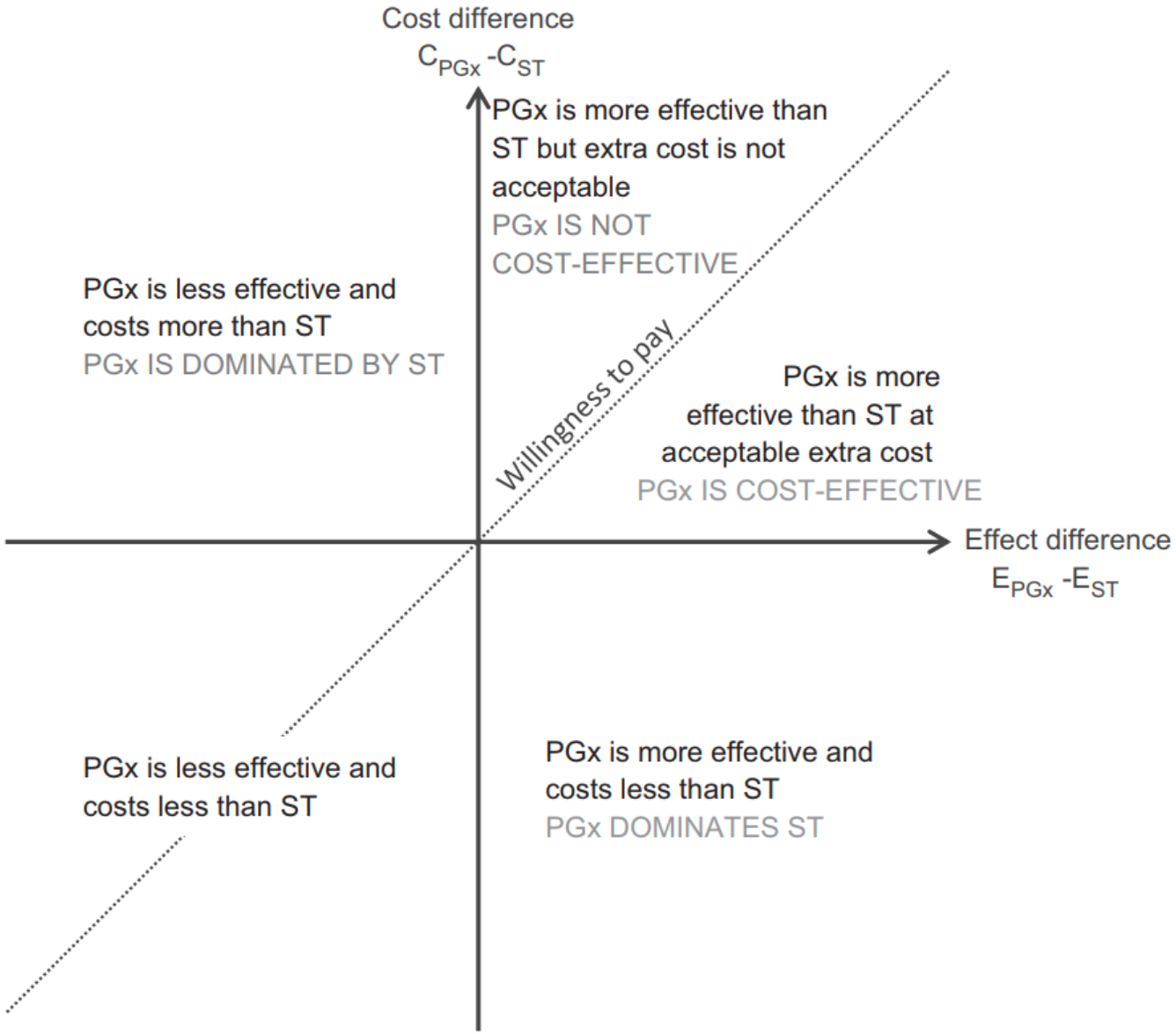
Specificity = d/(b+d) = 99% (people who will not have disease who test negative)

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	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

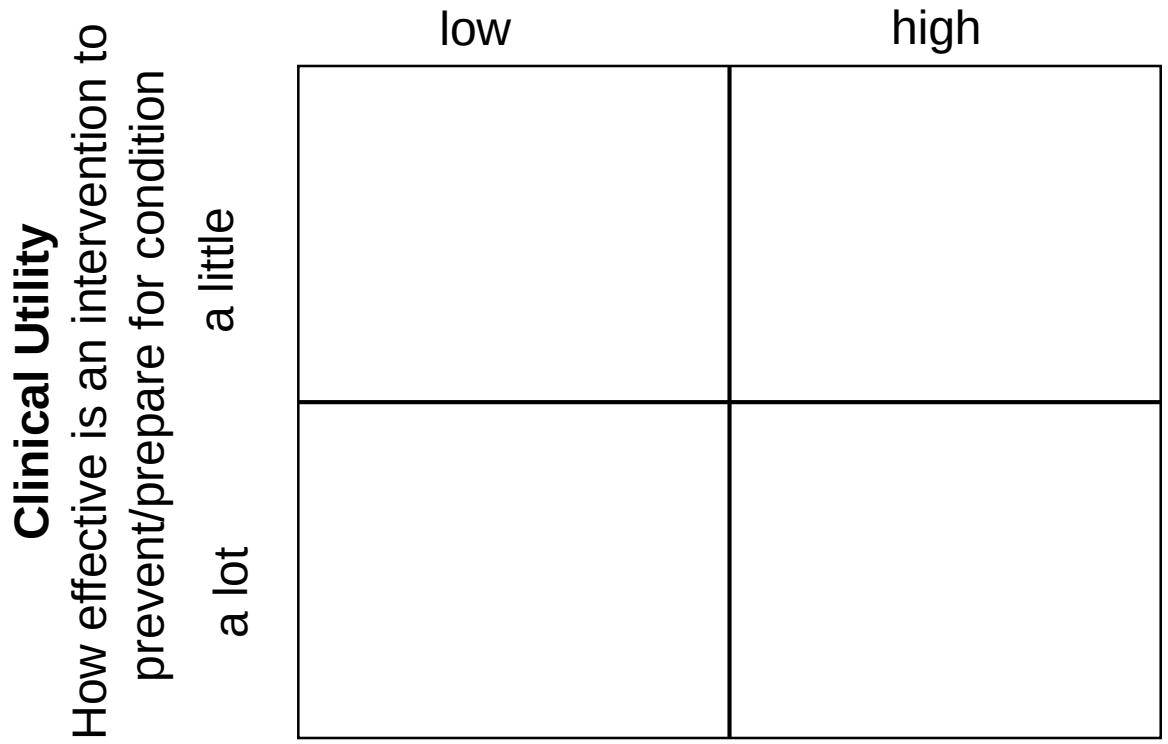


Verbelen 2017

PGx pharmacogenetic guided treatment
ST standard treatment

Implementation of genetic testing

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



Implementation of genetic testing

Analytics 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

Pesticide exposure and neurotoxicities

- The rs1785 variant in *MDR1* has an odds ratio of 2.9 for developing premature neurodegeneration with pesticide exposure.
- 20% of farm workers exposed to pesticides show signs of premature neurodegeneration (including those without the variant).
- FarmUSA wants to implement a screening program for rs1785.
- To protect workers from neurodegeneration, applicants with an rs1785 variant will be assigned to office work, making $15/hour.
- Applicants without an rs1785 variant will be assigned to the greenhouse where pesticides are used, making $25/hour.

For the break: Weigh issues according to 4 principles of bioethics

Should testing be allowed? What could change to make this situation more ethical?

Use the principles of bioethics to organize your answer.

We will re-convene after the break.

Bioethics and risk testing

Principles	Points to consider
Beneficence	• Workers most at risk would be protected from neurodegeneration. • Those workers most at risk will be financially compensated
Non-maleficence	• People without the variant are still exposed to pesticides and still are put at risk with exposure to pesticides and now are more likely than those with the variant to develop neurodegeneration (discrimination). • Identifying increased risk for neurodegeneration could be considered a “pre-existing condition” for health insurance purposes.
Justice	• Compensation is considerably less for those with the variant • While one genotype group is protected, another is put at greater risk.
Autonomy	• Workers should be able to decide whether they want to make more money and be exposed to pesticides. • Being employed by the company is contingent on testing (coercion)

Genetic Information Nondiscrimination Act (GINA)

- Federal law passed in 2008.
- Prohibits genetic discrimination (genetic testing or family history) in medical insurance coverage or employment decisions.
- 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”