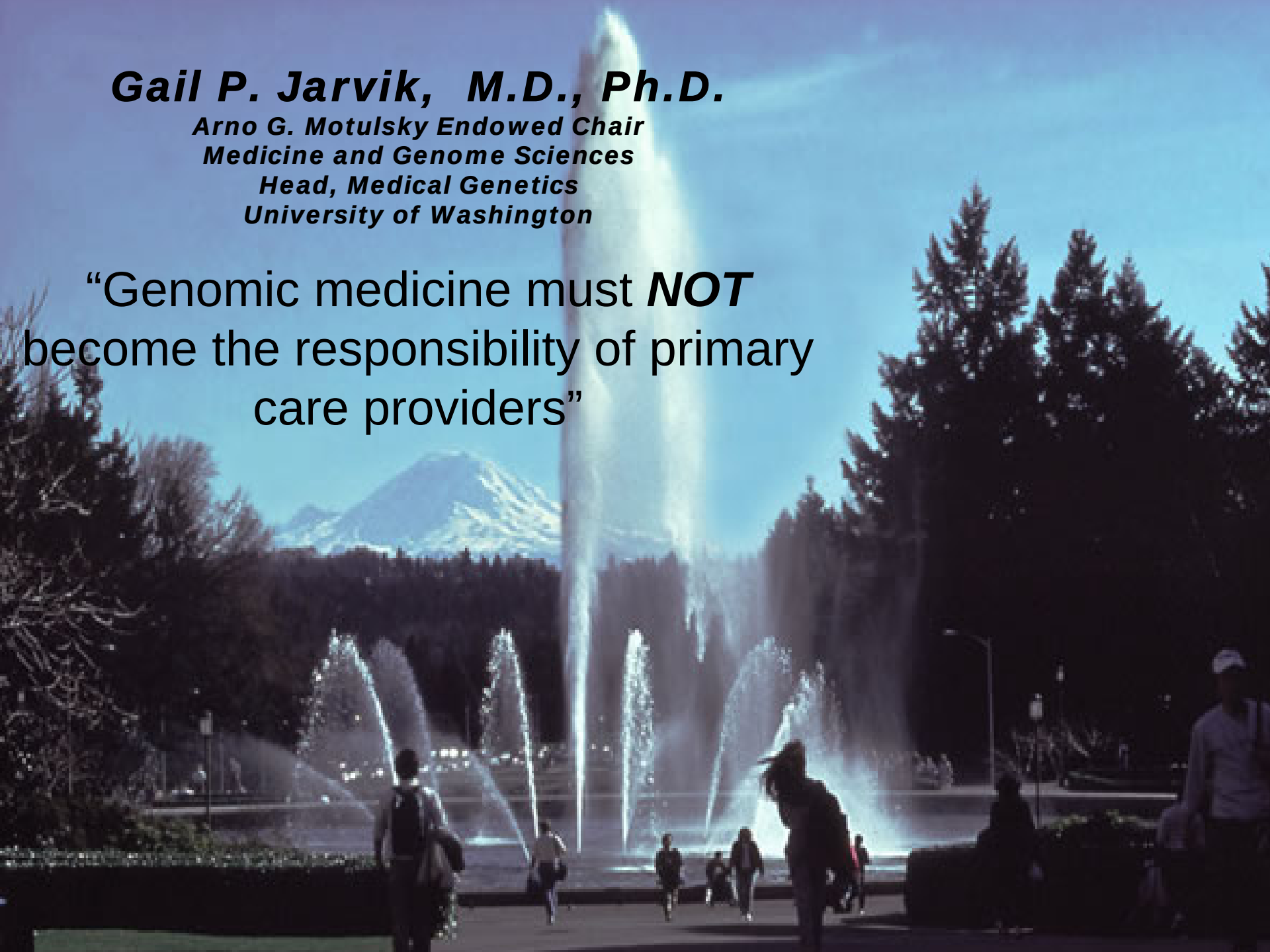

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"Genomic medicine must ***NOT*** become the responsibility of primary care providers"

Lack of Medical Student Genetics Training

Genetics is *part* of 34 days

UW Medicine
SCHOOL OF MEDICINE

Academic Year 2018 – 2019
Autumn, Winter, and Spring Quarters

2 wk	9/4-10/19, 2018	1 wk	10/29-12/14, 2018	3 wk	1/2-3/8, 2019	1 wk	1 wk	3/25 – 5/3/2019	1 wk	5/13/19-5/24/19	5/28-6/14/19
Immersion, Foundations of Clinical Medicine & Orientation, Sea. 8/20-8/30/18	**Molecular & Cellular Basis of Disease** • Cell Physiology & Function • Genes, Molecules, and Signaling • Genetic Diseases Human Form & Function* Pathology/Histology Pharmacology Themes†	Ecology of Health & Medicine§ (10/23/18-10/26/18)	**Invaders & Defenders** • Immune System • Microbial Biology • Infectious Diseases • Inflammation & Repair • Skin Human Form & Function* Pathology/Histology Pharmacology Themes†	Winter Break (12/17/18 – 1/1/19)	**Circulatory Systems (CPR)** • Cardiovascular System • Respiratory System • Renal-Urinary System • Multisystem Fluid Balance Human Form & Function* Pathology/Histology Pharmacology Themes†	Spring Break (3/11/19 – 3/15/19)	Ecology of Health & Medicine§ (3/19/19-3/22/19)	**Energetics & Homeostasis** • Metabolism & Nutrition • Obesity & Diabetes • Gastrointestinal Physiology • Endocrinology Human Form & Function* Pathology/Histology Pharmacology Themes†	Ecology of Health & Medicine§ (5/7/19-5/10/19)	**MSK** • Musculo-skeletal Systems: Anatomy & Function • Rheuma-tologic Diseases Human Form & Function* Pathology/ Histology Pharma-cology Themes†	**Blood & Cancer** • Cancers • Heme/ Lymph Human Form & Function* Pathology/ Histology Pharmacology Themes†
	Foundations of Clinical Medicine‡		Foundations of Clinical Medicine‡		Foundations of Clinical Medicine‡			Foundations of Clinical Medicine‡		Foundations of Clinical Medicine‡	

What do you need to know?

- Thousands of genetic diseases; where to get reliable information
- Who needs or does not need genetic testing?
- Test affected first
- Explain the test and possible outcomes (including VUS, IF)
- Test limits and follow-up intervals
- Genetic test preauthorization
- Management changes
- Implications for the family

$50,000,000 award

- Known unbalanced translocation in family
- Valley Medical Center in Renton, WA. No genetic counselor or medical geneticist involved (Valley had reduced GC staff)
- Sent prenatal test, but did not specify the known condition in family (Lab did not f/u)
- Test missed unbalanced fetus
- Will need lifetime 24/7 care

Physician knowledge of clinical implications of VUS

- Mayo clinic FL, 92/488 nongenticists responded to survey.
- Asked 3 multiple choice questions about variants of uncertain significance (VUS)
- VUS detected over 30% of the time when a 25 gene panel is ordered to assess cancer susceptibility (PMID: 4872307)

- Over half of the physicians stated that they did not feel comfortable disclosing a VUS to a patient

PMID: 29721668

Physician response to case examples

Case example	N (%)	N (%)	N (%)	N (%)
Case 2: Your patient has no personal history of cancer. Her sister was diagnosed with breast cancer at age 45. Her sister completed comprehensive genetic testing and was found to carry a variant of uncertain significance in the BRCA1 gene. Which of the following recommendations do you make to your patient?	Recommend that she proceed with com- prehensive genetic testing for hereditary cancer syndromes 20 (23.8%)	Recommend that she proceed with targeted genetic testing for the BRCA1 variant of uncertain significance 44 (52.4%)	Recommend that she not proceed with genetic testing for the BRCA1 variant of uncertain significance at this time 20 (23.8%)	
Case 3: Your patient was diagnosed with breast cancer at age 45. She was found to carry a variant of uncertain signifi- cance in the BRCA1 gene. How do you explain her result?	This BRCA1 variant is responsible for your personal history of breast cancer 2 (2.4%)	This BRCA1 variant is very likely responsible for your personal history of breast cancer 27 (32.1%)	This BRCA1 variant is not responsible for your personal history of breast cancer 10 (11.9%)	None of the above 45 (53.6%)

Macklin, S. K., Jackson, J. L., Atwal, P. S., & Hines, S. L. (2018). Physician interpretation of variants of uncertain significance. *Familial Cancer*. doi:10.1007/s10689-018-0086-2

Percentage of OB/GYN residents selecting each answer to pretest questions regarding hereditary breast-ovarian cancer (N=65)

Question	Answer (%) [a]		
	Yes	No	Unsure
Are the following features associated with HBOC...			
Early age of cancer onset	***92*** [b]	3	5
Dominant inheritance pattern	***51***	31	19
Recessive inheritance pattern	30	***35***	28
More than 1 primary cancer	***83***	5	8
Can be inherited from the father's side of the family	***62***	14	25
Can be inherited from the mother's side of the family	***91***	2	8
Bilateral breast cancer	***77***	8	14
Are the following cancers associated with HBOC...			
Ovarian	***97***	0	3
Lung	2	82	14
Breast	***99***	0	2
Endometrial	29	***52***	19
Colorectal	51	***30***	20
Cervix	0	***85***	12

[a]Some totals do not equal 100% because not all participants answered the question
[b]Bold and italic text indicates the percentage who answered the question correctly

Ready, K. J., Daniels, M. S., Sun, C. C., Peterson, S. K., Northrup, H., and Lu, K. H. (2010) Obstetrics/Gynecology residents' knowledge of hereditary breast and ovarian cancer and Lynch Syndrome. *Journal of Cancer Education* 25:401-404. doi: 10.1007/s13187-010-0063-4 PMID: 20186516

Table 1 Physician responses to questions about *BRCA1* and *2* mutations, by specialty and practice characteristics

Characteristics	Suppose you had a patient whose aunt or grandmother on her father's side carries the *BRCA1* gene mutation for breast/ovarian cancer syndrome. In your opinion, could your patient also be a carrier of this mutation?*					In your opinion, what percentage of female breast cancer patients have a *BRCA1* or *BRCA2* gene mutation?*				
	Yes (%)	No (%)	Not sure (%)	OR†	95% CI	<10 (%)	10–100 (%)	Not sure (%)	OR‡	95% CI
Total	37.5	10.6	49.0			33.8	27.4	36.7		
Medical specialty										
Family/general practice	28.1	10.8	58.0	1.0	–	21.8	26.7	49.1	1.0	–
Internal medicine	37.3	11.3	47.7	1.3	0.9 to 1.8	29.5	30.8	36.6	1.4	0.9 to 2.0
Obstetricians/gynaecologist	51.9	11.9	34.4	2.0	1.3 to 3.0	53.6	29.3	16.5	3.0	1.9 to 4.6
Oncologists	66.8	7.6	21.8	3.4	2.2 to 5.3	71.0	21.5	4.2	5.7	3.6 to 9.0
General surgeons	45.0	13.7	38.8	1.7	1.1 to 2.7	57.8	20.5	20.9	4.6	2.9 to 7.4
Gastroenterologists	24.8	6.7	68.5	0.6	0.3 to 1.4	22.4	19.9	57.9	0.9	0.4 to 2.2
Age										
≥60	37.3	5.8	53.4	1.0	–	28.7	19.7	49.2	1.0	–
40–59	36.7	11.6	48.5	0.9	0.6 to 1.3	34.7	27.5	35.6	1.4	0.9 to 2.0
<40	40.2	11.0	46.6	1.1	0.7 to 1.8	34.8	33.7	29.8	1.6	0.9 to 2.6
Cancer genetics services provided in past 12 months										
None	33.3	9.2	54.5	1.0	–	27.6	28.3	41.8	1.0	–
Did not order breast/ovarian cancer genetics tests, but did order other cancer genetics tests or referred patients elsewhere for testing or risk assessment	45.3	12.6	40.6	1.2	0.8 to 1.6	45.2	27.5	26.4	1.4	1.0 to 1.9
Ordered breast/ovarian tests but did not refer patients elsewhere	54.6	17.0	25.0	1.6	0.8 to 3.3	55.8	21.3	19.5	2.3	1.1 to 4.7
Both ordered a breast/ovarian test and referred patients elsewhere	49.0	16.6	24.3	1.4	0.6 to 3.6	58.5	18.8	17.7	2.1	0.9 to 5.4
Local facilities for genetic counselling and testing for inherited cancer risk										
No	43.2	13.0	40.5	1.0	–	33.6	37.0	28.8	1.0	–
Yes	41.6	9.5	48.3	1.0	0.6 to 1.4	43.9	28.1	26.2	1.2	0.8 to 1.9
Not sure	28.6	7.7	61.4	0.7	0.4 to 1.0	20.6	24.4	52.7	0.6	0.4 to 1.0
Clear guidelines or strategies are not available for managing patients with inherited cancer susceptibility mutations										
Agreed with statement, somewhat or strongly	40.8	12.4	45.9	1.0	–	37.1	31.1	31.6	1.0	–
Disagreed, somewhat or strongly	42.1	6.5	47.5	1.1	0.7 to 1.7	39.9	26.4	33.7	1.0	0.6 to 1.6
Not sure	22.7	5.4	72.0	0.5	0.3 to 0.8	17.1	13.1	69.1	0.5	0.3 to 0.8
Received cancer genetic test advertising										
No or not sure				1.0	–	29.3	26.8	41.8	1.0	–
Yes				1.3	0.9 to 1.8	45.7	29.8	23.7	1.2	0.8 to 1.6
Academic affiliation										
No	36.6	9.8	51.0	1.0	–	31.8	26.3	40.0	1.0	–
Yes	39.8	11.9	45.3	1.0	0.8 to 1.3	37.4	30.0	31.1	1.0	0.7 to 1.3
Specialties in the practice										
Single specialty	36.9	10.9	49.3	1.0	–	33.9	27.0	37.2	1.0	–
Multispecialty	40.8	9.9	47.6	1.1	0.8 to 1.6	34.8	29.4	34.9	0.9	0.6 to 1.4
Practice arrangement										
Full or part owner	37.6	10.1	49.6	1.0	–	33.7	26.6	37.4	1.0	–
Employee of physician practice, HMO, hospital, university, or clinic	38.0	11.0	48.5	1.0	0.8 to 1.4	33.9	28.4	36.5	1.1	0.8 to 1.6

Practicing Physician Responses on BRCA1/2

Year 2000
N=1251

*Unadjusted percentages representing physician responses are weighted to the U.S. population of physicians in the selected specialties. Row percentages may not add to 100% due to nonresponse to some items.

Wideroff, L., Vadaparampil, S. T., Greene, M. H., Taplkin, S., Olson, L., & Freedman, A. N. (2005). Hereditary breast/ovarian and colorectal cancer genetics knowledge in a national sample of US physicians. *J Med Genet, 42*, 749-755. doi:10.1136/jmg.2004.030296

PMID: 15784723

A 2018 case

A patient with several teenage children was found to have a BRCA pathogenic variant by COLOR testing sent by her oncologist. She reports that she requested testing for her children and was told “we do not test children”. No explanation was given.

The patient sent COLOR testing on her children. Only after that did she learn that her children’ health care management would not change until the age of 25 and that life, disability, and long term care insurance are not protected by GINA.

GC only patients: cost effective

- In general, no exam needed or diagnosis issue
- familial cancer;
- cardiac genetics
- neurodegenerative conditions (including offering presymptomatic testing);
- chromosomal abnormalities;
- multiple miscarriage;
- single-gene disorders including hemoglobinopathy, cystic fibrosis, metabolic disorders, hemachromatosis disease;
- counselling for neural tube defect, advanced maternal age, or abnormal prenatal screening results
- test results

- “Practice at the top of your license”. GC salary ~1/2 to 1/3 of MD.

GCs assisted review of genetic tests cases sent in to ARUP.

Month in 2010	Cost Savings	Number of Tests Changed
February	$ 23,347	72
March	24,330	74
April	48,235	119
May	23,607	105
June	35,779	98
July	31,925	99
August	38,432	110
September	43,207	117
October	38,656	122
November	56,510	149
December	31,928	110
Total	**$ 395,956**	**1175**
Average per month	**$ 35,996**	**107**

Miller, C. E., Krautscheid, P., Baldwin, E. E., LaGrave, D., Openshaw, A., Hart, K., & Tvrdik, T. (2011). Value of genetic counselors in the laboratory. ARUP Laboratories, Salt Lake City, UT.

GC shortage

- **Genetic counseling jobs go unfilled and the demand is growing**
  - Anticipated national annual growth rate for jobs in genetic counseling is 30%.
  - Rural areas are underserved (e.g. Eastern and Southwestern WA, Skagit Valley, and the Peninsula).
  - Careers span a range of settings including clinical, industry, research & policy.
- **There are not enough training programs**
  - On average, there are over 107 applicants for every 8 new GC student slots.
  - In 2017 there were 41 GC programs in the USA (now~60)
  - 354 students matriculated in 2017, which did not meet the national need of over 500.

- It is easier to fix this than train MDs.

Commentary —What the Physician Needs to Know About Lynch Syndrome: An Update

- Stephen B. Gruber, MD, PhD, MPH; Joanne M. Jeter, MD; Julie A. Douglas, PhD Cancer Network Vol 9: Issue 4
- “The authors appropriately emphasize the "absolute necessity" of genetic counseling before and after testing; such counseling is critical to the care and management of patients and families at risk for hereditary cancer.”

Conclusions

- Medical Geneticists and GCs spend 2 years training in genetics, vs. weeks for other physicians
- Genetics is rapidly changing, which is poorly suited to primary care practice
  - Testing is particularly rapidly changing
- Physicians are not adequately trained for the most simple case in adult genetics, BRCA1/2
  - They do not understand the basics of inheritance
- Many tasks of genetics clinics are not suited to other MDs
  - Pre-auth, test limitations, inheritance pattern
  - Lack of compensation for these harms interest
- GCs can be cost effective, relative to MDs
  - Train more!

	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very Strong**
Population Data	MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact *BP4* Missense when only truncating cause disease *BP1* Silent variant with non predicted splice impact *BP7* In-frame indels in repeat w/out known function *BP3*	Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3*	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5* Protein length changing variant *PM4*	Same amino acid change as an established pathogenic variant *PS1*	Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1*
Functional Data	Well-established functional studies show no deleterious effect *BS3*		Missense in gene with low rate of benign missense variants and path. missenses common *PP2*	Mutational hot spot or well-studied functional domain without benign variation *PM1*	Well-established functional studies show a deleterious effect *PS3*	
Segregation Data	Non-segregation with disease *BS4*		N ≤ 1/8 if 1 family N ≤ 1/4 if > 1 family	N ≤ 1/16 if 1 family N ≤ 1/8 if > 1 family	N ≤ 1/32 if 1 family N ≤ 1/16 if > 1 family	
De novo Data				*De novo* (without paternity & maternity confirmed) *PM6*	*De novo* (paternity & maternity confirmed) *PS2*	
Allelic Data		Observed in *trans* with a dominant variant *BP2* Observed in *cis* with a pathogenic variant *BP2*		For recessive disorders, detected in *trans* with a pathogenic variant *PM3*		
Other Database		Reputable source w/out shared data = benign *BP6*	Reputable source = pathogenic *PP5*			
Other Data		Found in case with an alternate cause *BP5*	Patient's phenotype or FH highly specific for gene *PP4*			

Jarvik GP and Browning BL, AJHG 2016, PMID: 27236918