Graduate Program in Genetics, Genomics, & Bioinformatics

University of Colorado Anschutz Medical Campus

Cherokee Nation

The Social and Biological Ecology of Chronic Disease in Indigenous People:

Development of a New Multi-Dimensional Model

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Faculty/Presenter Disclosure

- In the past 24 months, neither James N. Jarvis nor Meagan Chriswell have had relevant financial relationships with the manufacturer(s) of commercial services discussed in this CME activity
- We do not intend to discuss an unapproved/investigative use of a commercial product/device in our presentation.

10th International Meeting on Indigenous Child Health
March 24-26, 2023 – Tulsa, Oklahoma

Acknowledgment

Even before European contact, Oklahoma was home to indigenous people. Caddo, Apache, Wichita, and Quawpaw people were all present here. We gratefully acknowledge the suffering and sacrifices of the many indigenous nations who were forcibly removed here and have yet continued to thrive.

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Indigenous Peoples in NY State

New York and Michigan have the largest indigenous populations east of the Mississippi River. Niagara Falls has a higher percentage of Native American than any city east of the Mississippi. More than 2,000 American Indians live in Buffalo proper.

Outline

1. A brief discussion of the concept of health inequities using rheumatic diseases in indigenous populations as an example.
2. The Adverse Childhood Experiences (ACE) study and how it informs our understanding of health inequities.
3. Biological considerations: effects of stress and chronic disease.
4. Effects of dietary changes and altered microbiome.

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Part 1:

Rheumatic Disease Rates in Indigenous North American People

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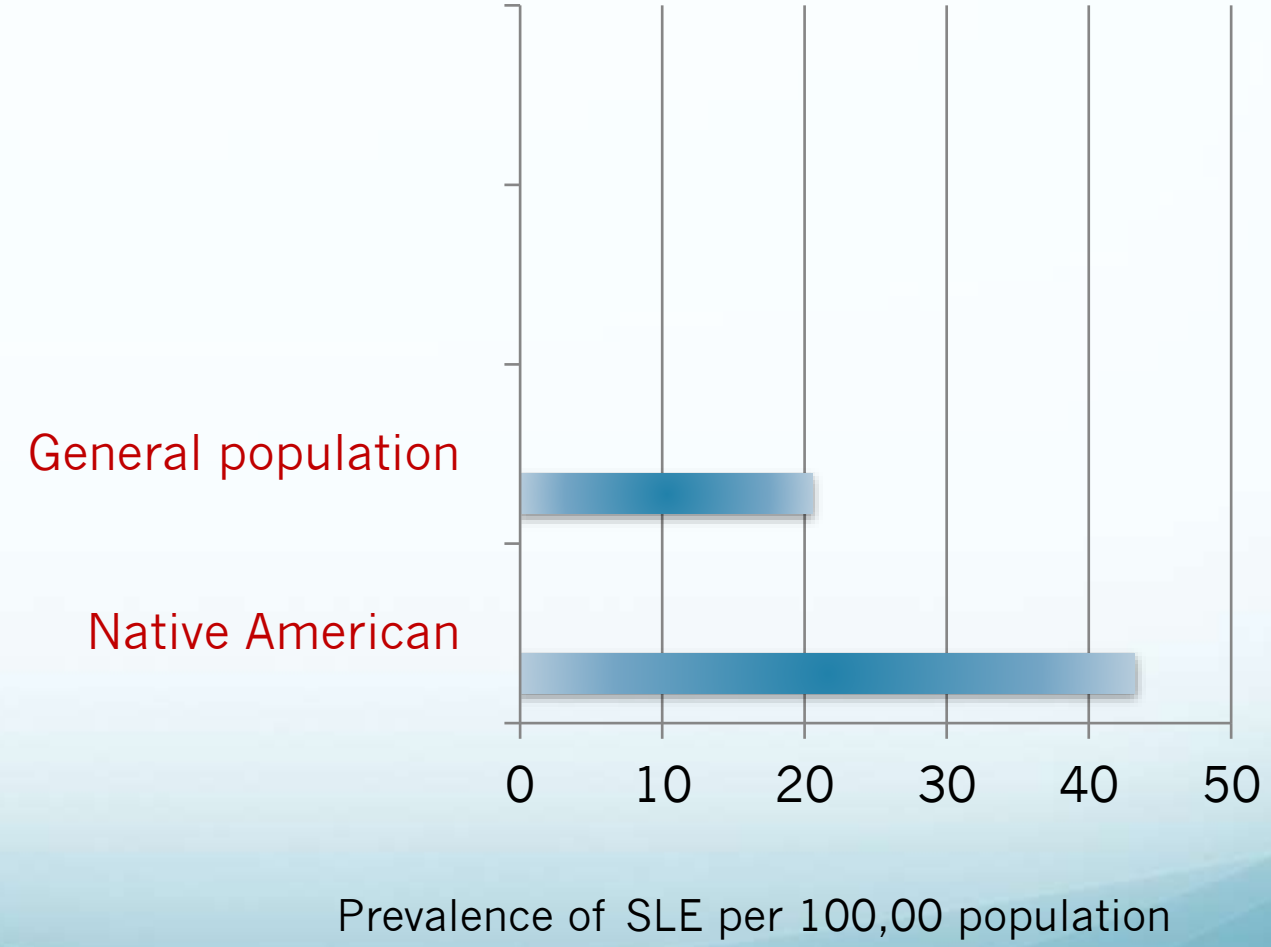
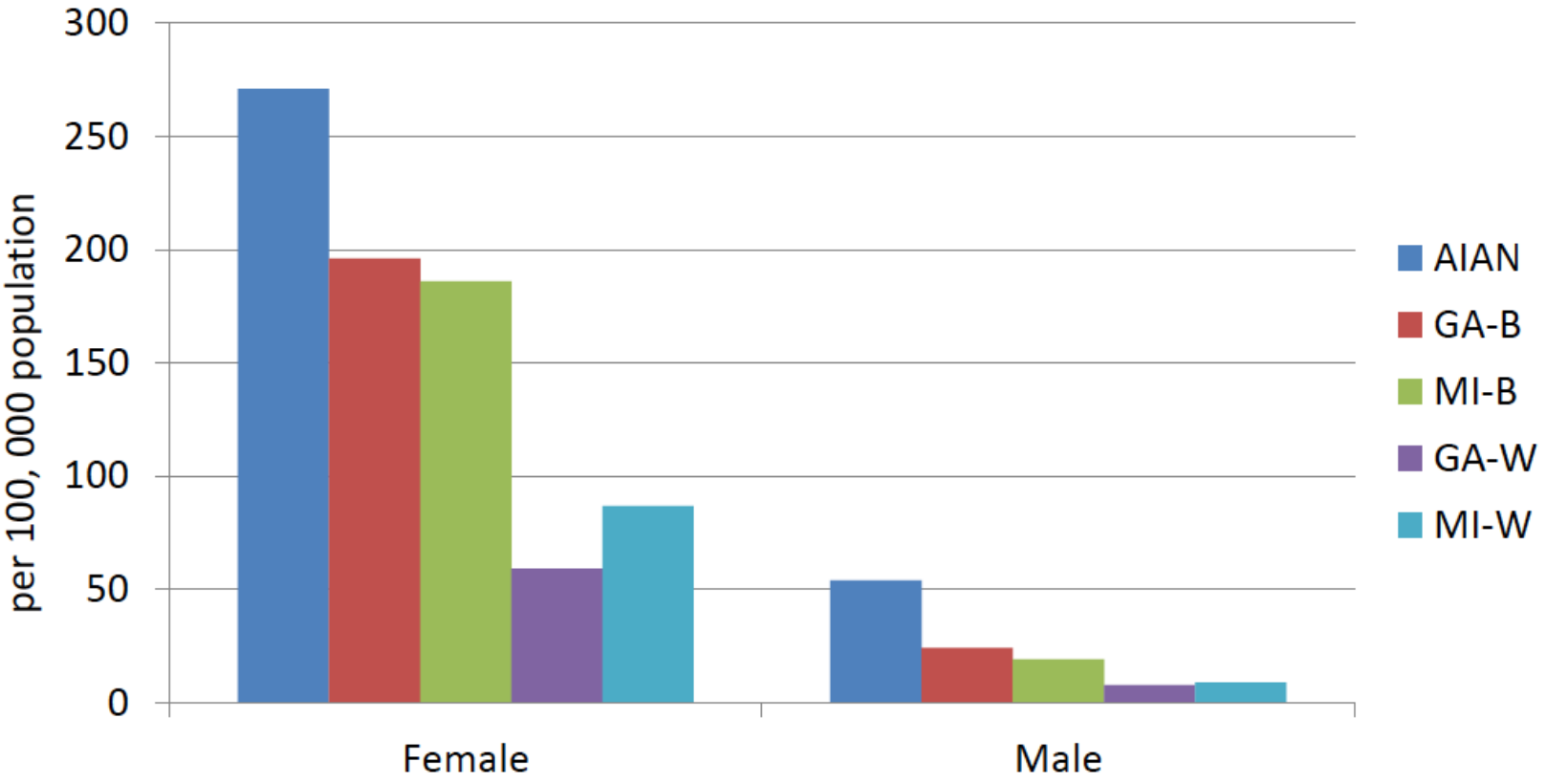
Health Inequities: Rates of Systemic Lupus in Native Americans



Prevalence of SLE in CDC registries



AIAN: American Indian/Alaska Native from IHS registry; GA-B: Georgia Registry—Black; MI-B: Michigan Registry—Black; GA- W: Georgia Registry—White; MI-W: Michigan Registry—White

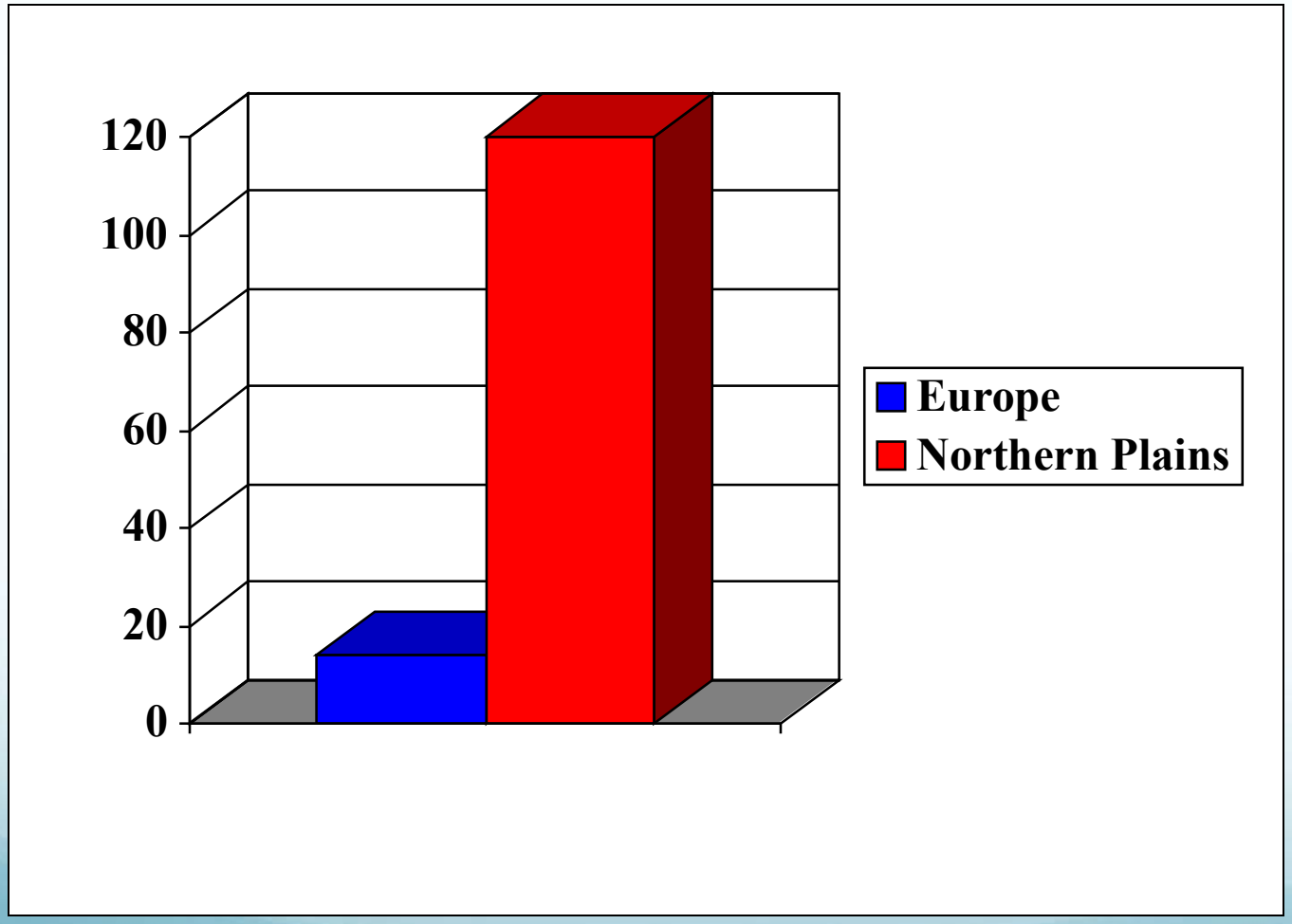
Note that indigenous SLE rates exceed all other groups....contrary to what the textbooks say.

RA in Indigenous Communities

Table 1: Prevalence and Incidence Rates of Rheumatoid Arthritis in Caucasians and Native North Americans

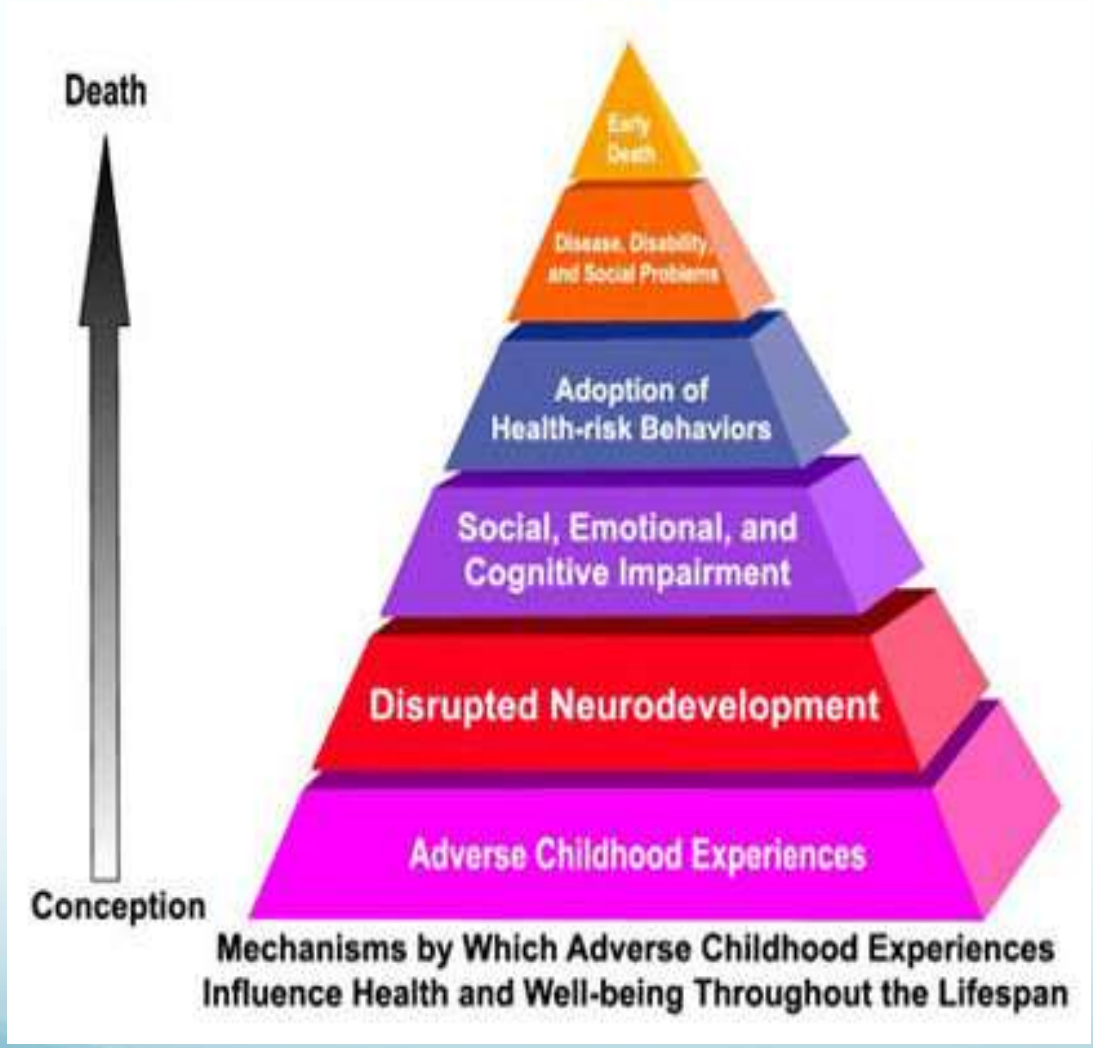
Population	Geographic Region	Prevalence	Annual Incidence
Pima Indians (22, 41, 54)	Arizona	2.5-5.3%	422/100,000
Chippewa Indians (4)	Central Minnesota	5.3%	—
Blackfeet Indians (40)	Montana	5% females, 4% males	—
Yakima Indians (43)	Central Washington	3.4% females	—
Tlingit, Tsimshian, & Haida Indians (6)	Southeast Alaska	2.4%	122/100,000 women 46/100,000 men
Algonkian Indians (44)	Central Canada	2.0%	—
Nuu-Chah-Nulth (12)	Vancouver Island	1.4%	—
Haida Indians (46)	Queen Charlotte Islands	1-1.5% females, 0.5-1% males	—
Inupiat Eskimos (6)	Northwest Alaska	1.0%	—
Yupik Eskimos (13)	Southwest Alaska	1.1%	—
Inuit Eskimos (11)	Northwest Territories	0.6%	48/100,000
National Health Examination Survey (37)	USA	1.6% females, 0.7% males, 0.9% total	—
Rochester (38)	Minnesota	1.0%	22/100,000 men 48/100,000 women
England (39)	England	1.1%	—

Polyarticular Juvenile Idiopathic Arthritis: Northern Plains vs. Europe



Part II
The link between health inequities and childhood experiences

Adverse Childhood Experiences: Where Physical Health and Community Health Are Joined



1. Recurrent physical or emotional abuse.
2. Sexual abuse.
3. ETOH or other substance abuser in the home.
4. Incarcerated household member.
5. Someone who is chronically depressed, suicidal, or otherwise mentally ill.
6. Mother being treated violently.
7. One or no parents.
8. Emotional or physical neglect.

Table 2.

STATEWIDE PREVALENCE OF ADVERSE CHILDHOOD EXPERIENCES BY AMERICAN INDIAN RACE/ETHNICITY COMPARED WITH NON-AMERICAN INDIAN RESPONDENTS

	American Indian (n = 516)	Non-American Indian (n = 7078)	Significance
Abuse			
Emotional Abuse	30.10%	17.41%	.0008*
Physical Abuse	24.51%	12.31%	.0002*
Sexual Abuse	15.53%	9.60%	.0263*
Neglect			
Emotional Neglect	25.87%	14.00%	.0005*
Physical Neglect	15.89%	2.78%	<.0001*
Household Dysfunction			
Mother Treated Violently	23.76%	5.31%	<.0001*
Household Substance Abuse	50.04%	21.49%	<.0001*
Household Mental Illness	24.36%	13.89%	.0032*
Parental Separation or Divorce	39.34%	20.17%	<.0001*
Incarcerated Household Member	22.57%	3.73%	<.0001*
Number of ACEs (Score)			<.0001*
0	16.84%	50.02%	
1	21.59%	23.02%	
2	16.20%	9.60%	
3	12.99%	6.09%	
4–5	13.10%	7.38%	
≥6	19.28%	3.89%	

Note
*statistically significant

Dr. Donald Warne
University of North Dakota

ACE Scores and Rheumatic Disease Risk

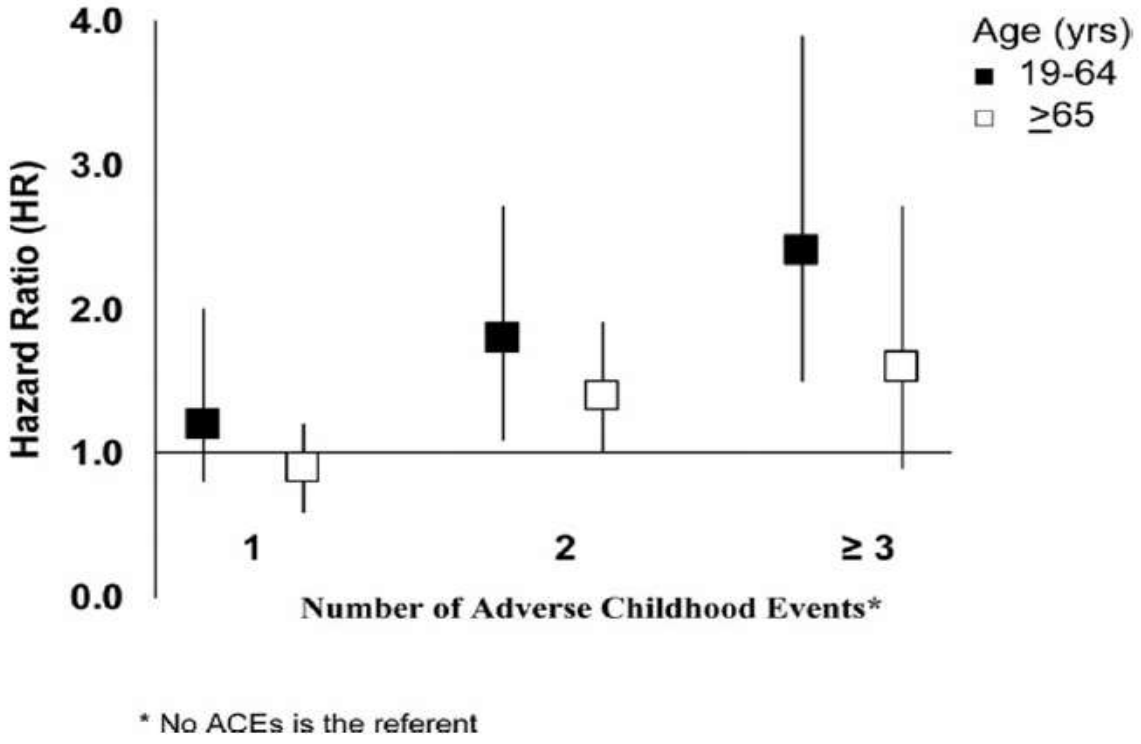


Figure 1.
Adjusted hazard ratios and 95% confidence intervals for the association of adverse childhood events with the development of any auto-immune disease, by age groups: Adverse Childhood Experiences Study 1995-2005.

From Dube et al *Psychosom Med* 2009; 7: 243-250.

ACEs and Lupus Severity

Outcomes	0 (n=52)	1 (n=26)	2-3 (n=28)	≥4 (n=20)	p-value
SLE activity (SLAQ)	5.4 (5.3)	6.3 (5.4)	12.9 (7.5)	12.6 (8.8)	<0.001
SLE damage (BILD)	1.9 (2.1)	1.5 (1.6)	1.9 (2.3)	3.3 (3.1)	0.05
Quality of life (SF36 PCS)	45.6 (10.6)	44.8 (9.0)	38.8 (11.0)	27.4 (8.9)	<0.001
Depressive symptoms (PHQ-8)	4.4 (4.1)	4.1 (3.7)	8.5 (5.2)	8.3 (4.2)	<0.001

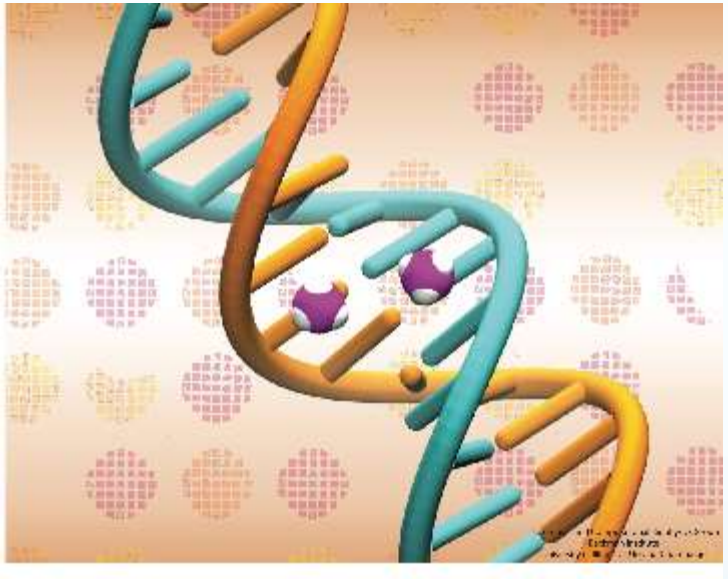
Table values are mean (sd) of outcome measure.

Data from Trupin et al, abstract #1968 presented at the American College of Rheumatology annual meeting Washington, DC, November 14, 2016.

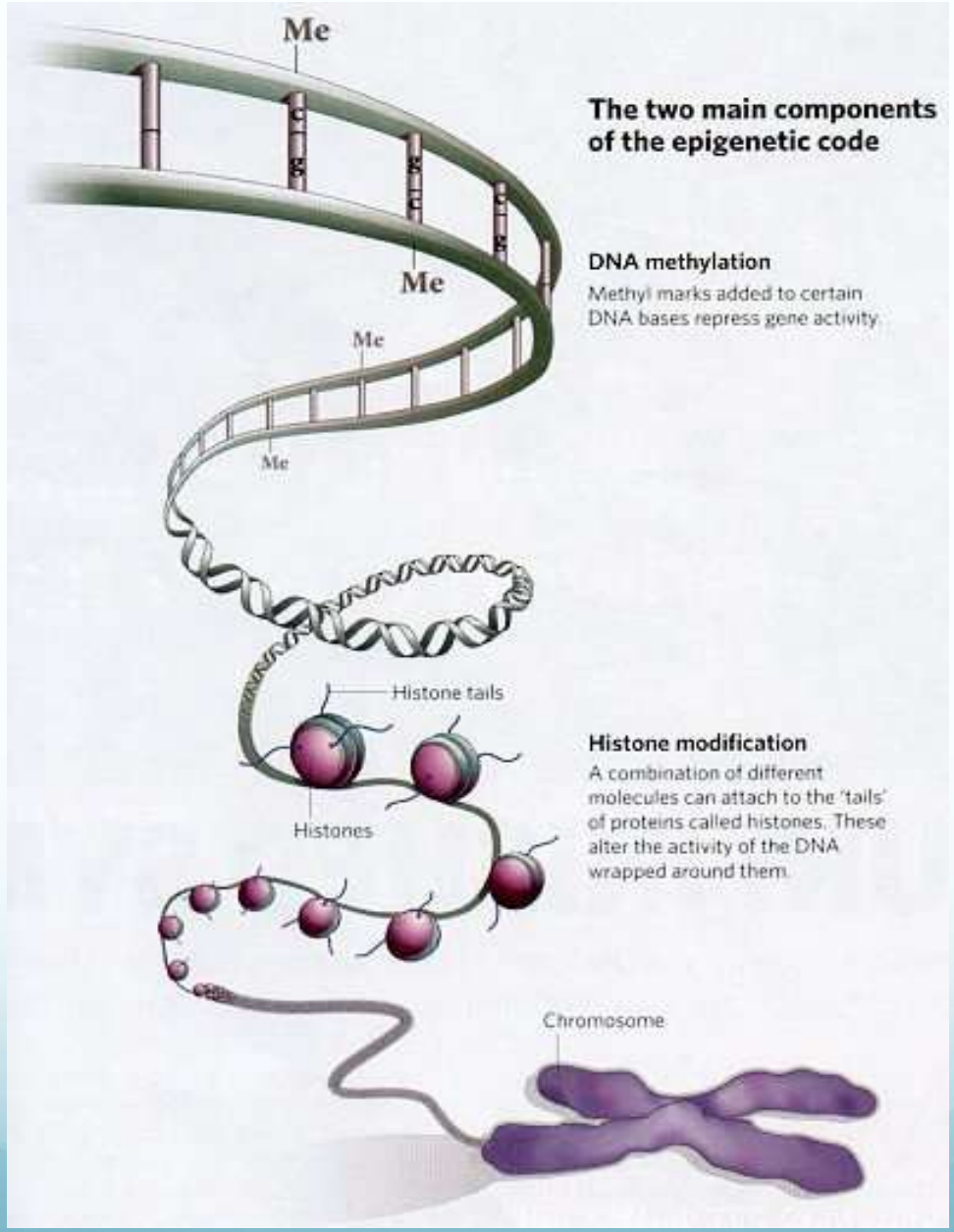
Epigenetics: Genes and Environment

Epigenetics-Definition

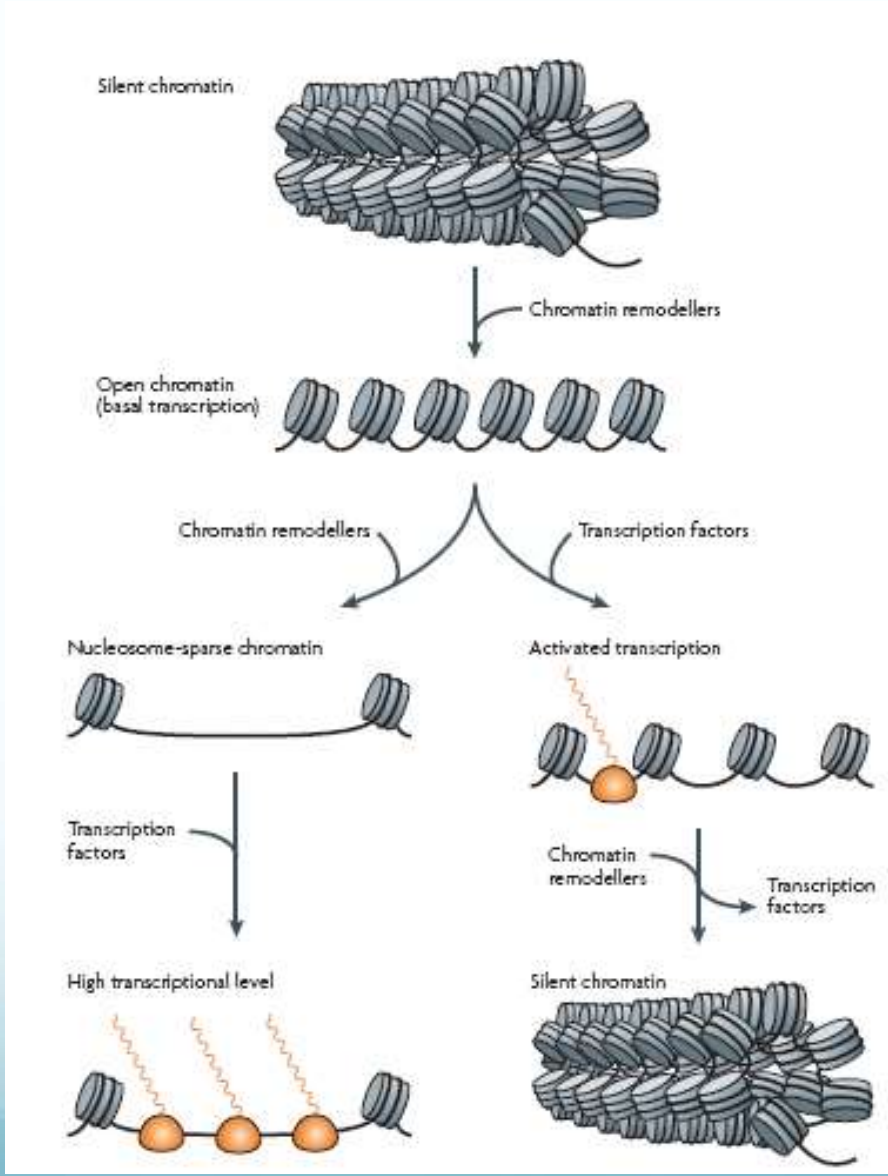
Alterations to DNA or its associated proteins that do not change the actual coding sequence of the DNA but which may have effects on DNA function.



Epigenetic Alterations



Regulation of Transcription



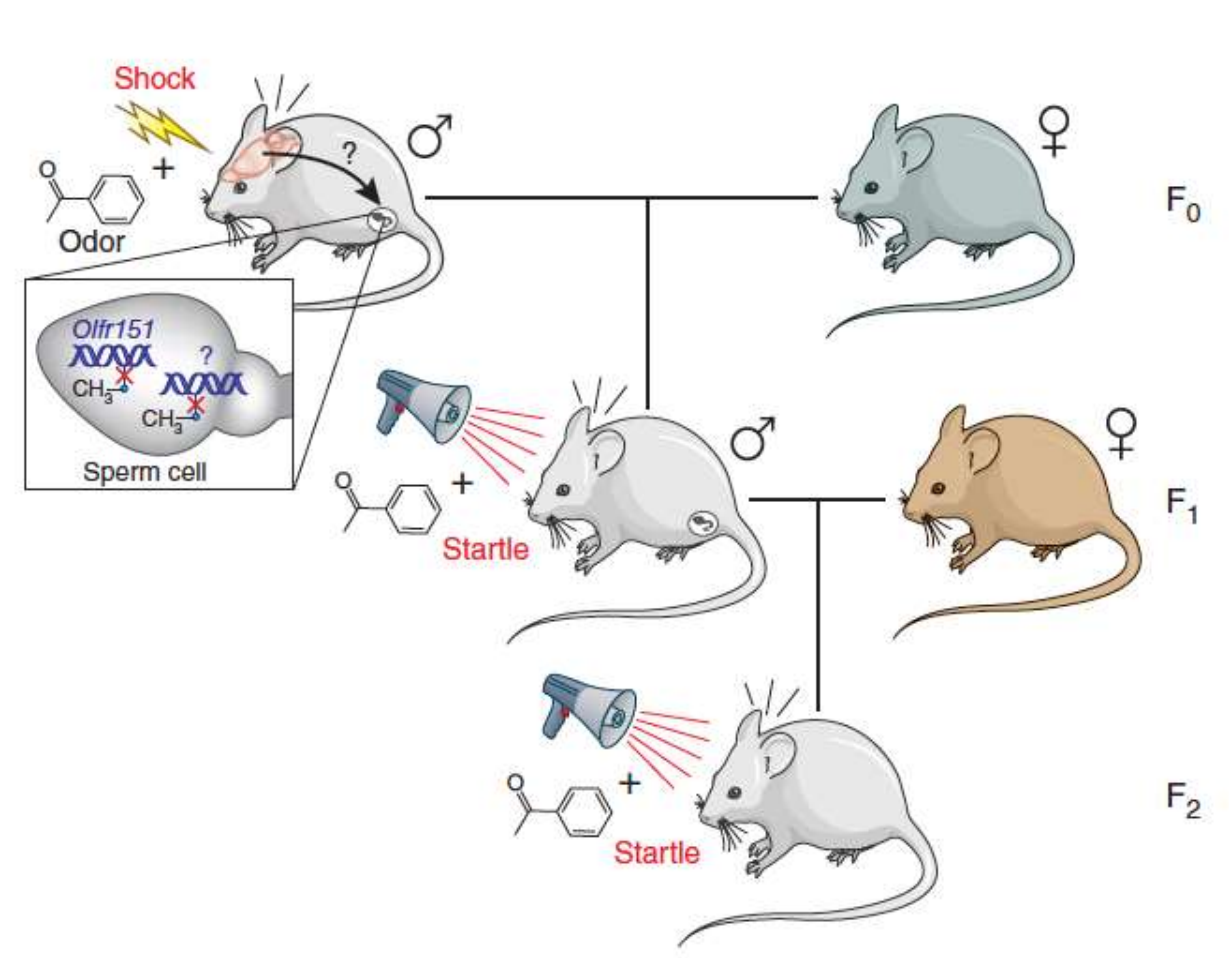
Importance of Epigenetic Changes:
The Key to "Gene-Environment Interactions" ?

1. Can be environmentally-induced (e.g., by diet, stress hormones, etc)
2. Can be passed on trans-generationally.

Source: Randy Jirtle, Ph.D., Duke University Medical Center. Used with permission.

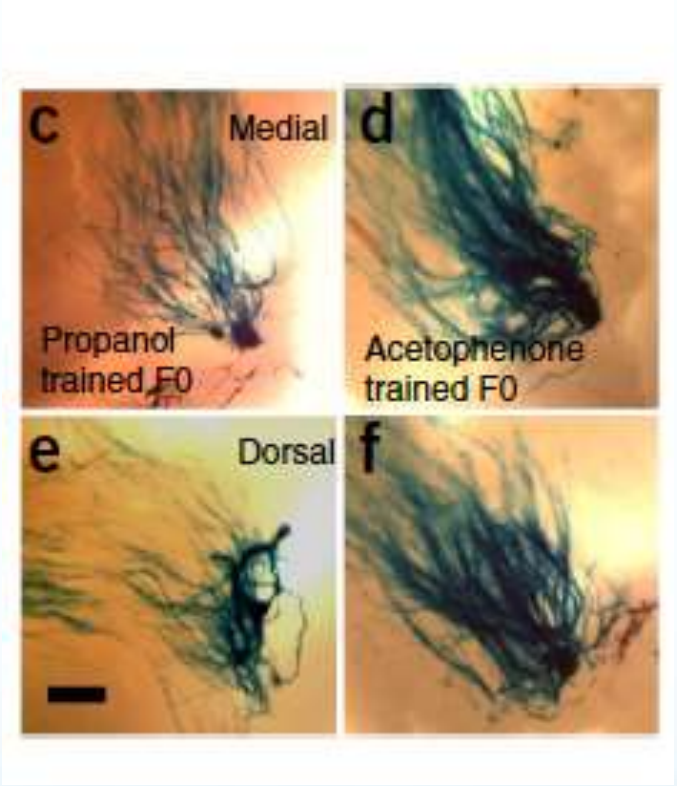
These inbred mice are genetically identical. They are each about a year old and both are female. Their different characteristics result from differences in the epigenome. The mother of the mouse on the left received a normal mouse diet. The mother of the mouse on the right received a diet supplemented with genistein, the phytoestrogen found in soy products. Genistein increases the incidence of brown offspring by altering the epigenome rather than mutating the genome — an example of nature via nurture.

Epigenetics and Behavior



Dias BG and Ressler K, Nature Neurosci 2014; 17: 89

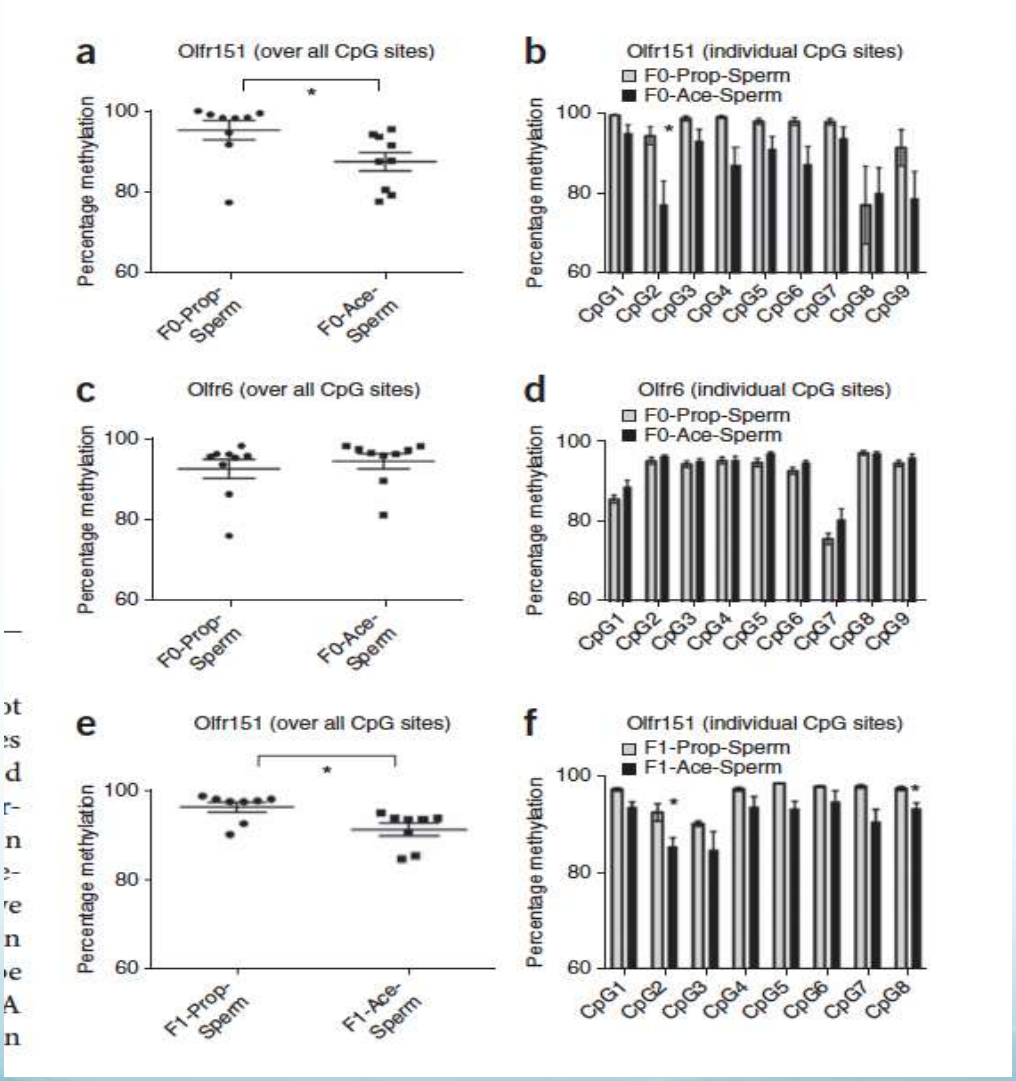
Epigenetics and Behavior: Brain Rewiring



Beta galactosidase staining of select olfactory regions: F1 offspring

Dias BG and Ressler K, Nature Neurosci 2014; 17: 89

Epigenetics and Behavior: Methylation of *Olfr51*



Transgenerational Epigenetic Inheritance

No Longer Controversy

REVIEWS

Molecular mechanisms of transgenerational epigenetic inheritance

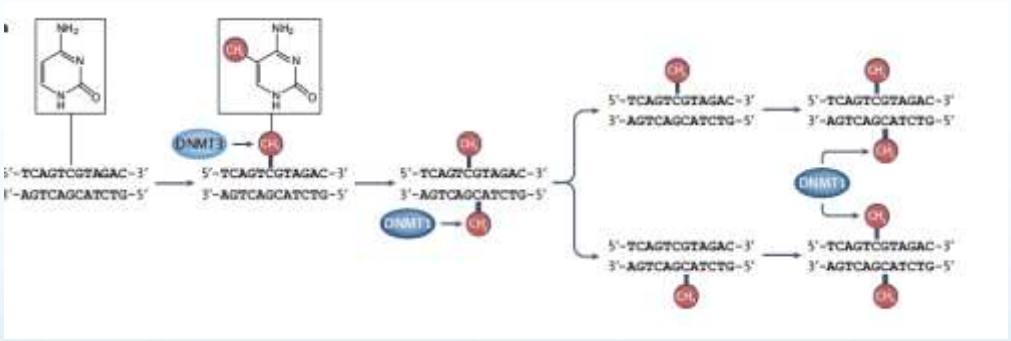
Maximilian H. Fitz-James and Giacomo Cavalli

nature cell biology

FOCUS | REVIEW ARTICLE

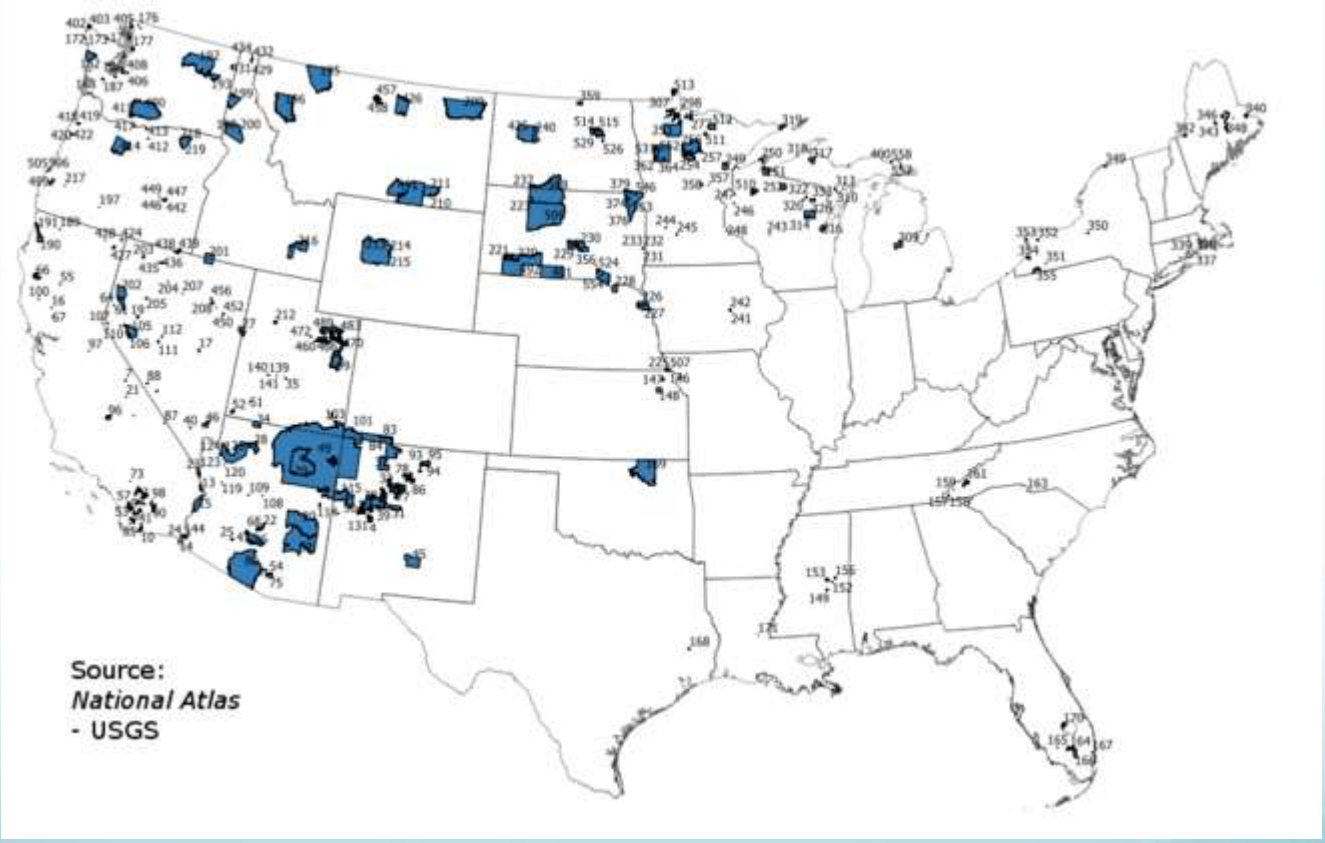
Intergenerational and transgenerational epigenetic inheritance in animals

Marcos Francisco Perez and Ben Lehner



Part III: Environmental Effects on Health and Disease

And the molecular basis of social determinants of health



Dietary Changes During Transitions to Reservations

Disparities in Nutrition Sources for Native American Youth lead to Metabolic Disease

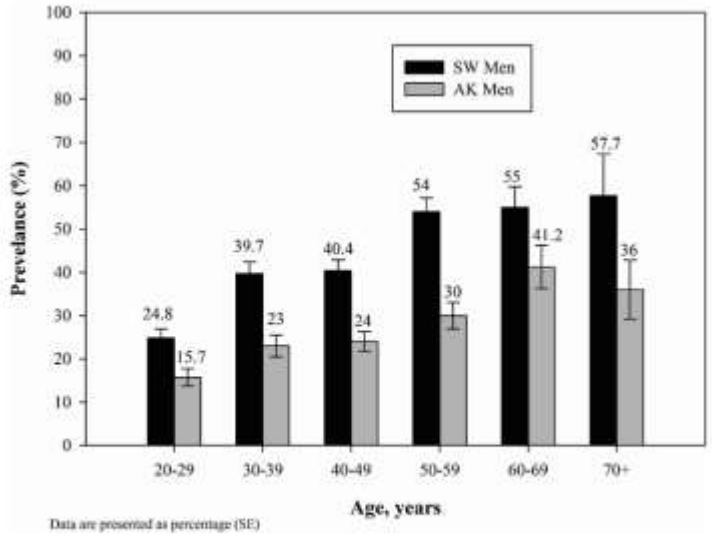


FIG. 1. Age-specific prevalence of metabolic syndrome among American Indian and Alaska Native men.

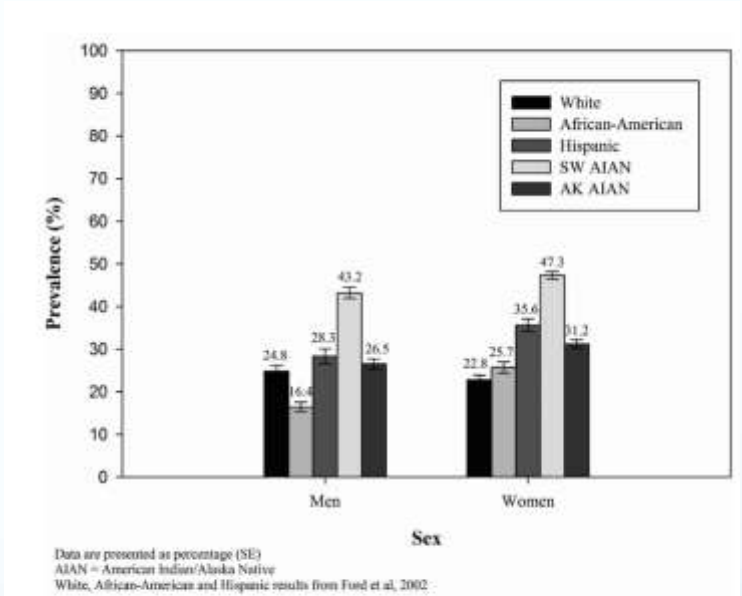


FIG. 3. Age-adjusted prevalence of metabolic syndrome by race and sex.

Comparative Study > Ethn Dis. 2005 Autumn;15(4):705-12.

Dietary patterns of reservation and non-reservation Native American youths

Jennifer Di Noia [1], Steven P Schinke, Isobel R Contento

Dietary sources of nutrients among rural Native American and white children

Metabolic Syndrome: Prevalence among American Indian and Alaska Native People Living in the Southwestern United States and in Alaska

Microbiome Differences in Oklahoma Natives

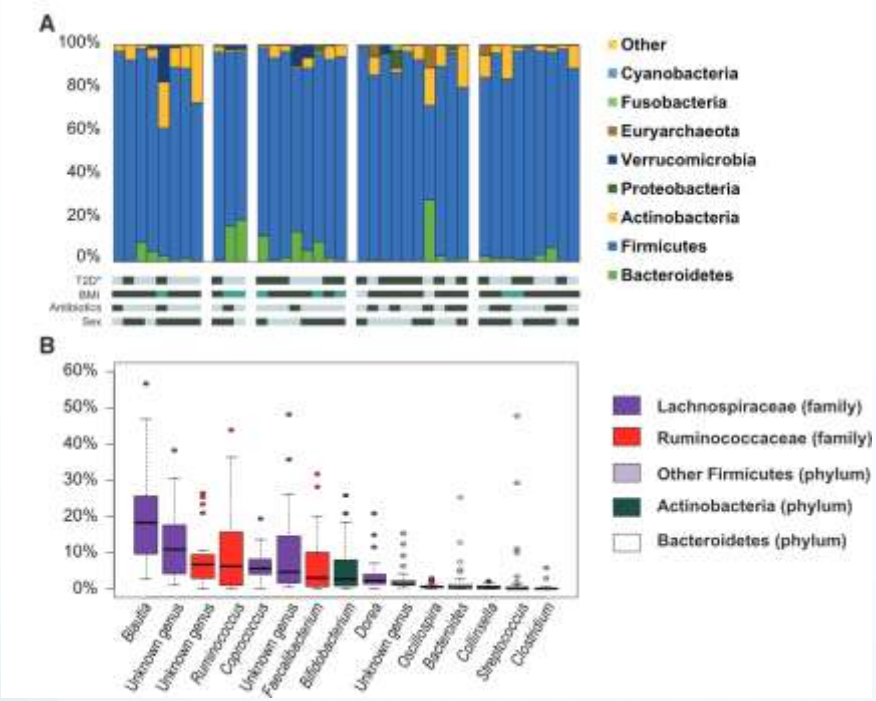


Table 1. Random Forest Supervised Classification Results, OTU Level

		Oklahoma		South America		Classification
True \ Predicted		C&A	NNIs	Matses	Tunapuco	Accuracy
Oklahoma	C&A	38	0	0	0	100%
	NNIs	11	9	0	0	45%
South America	Matses	0	0	10	0	100%
	Tunapuco	0	0	0	11	100%

Current Biology

Gut Microbiome Diversity among Cheyenne and Arapaho Individuals from Western Oklahoma

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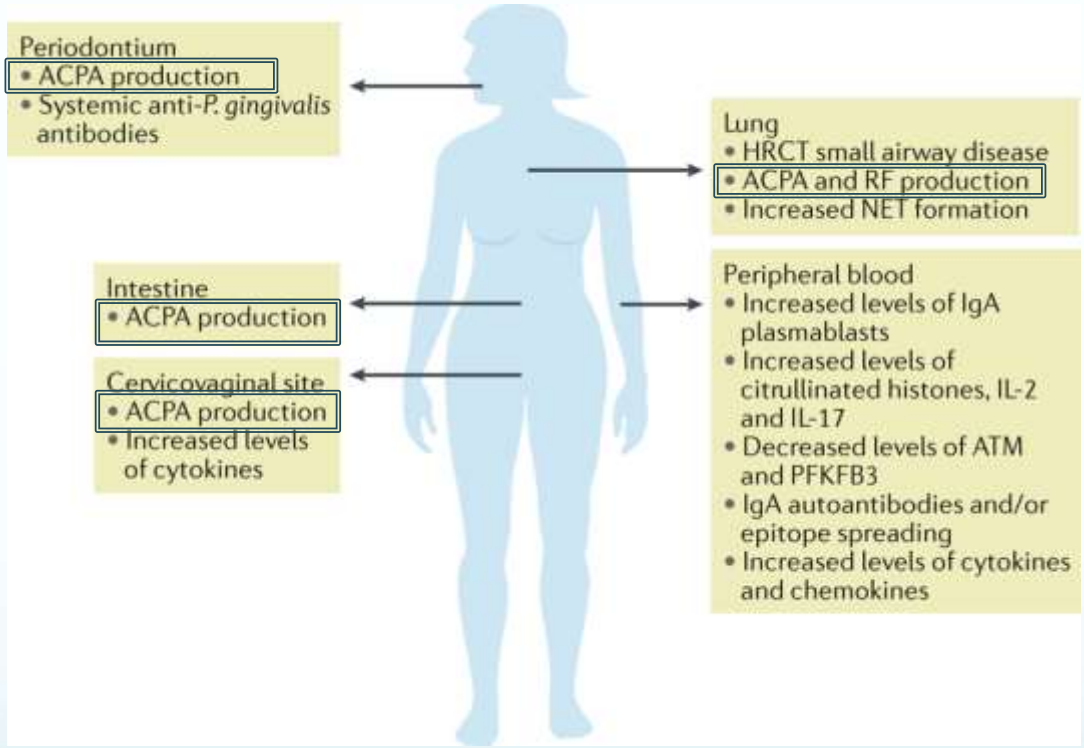
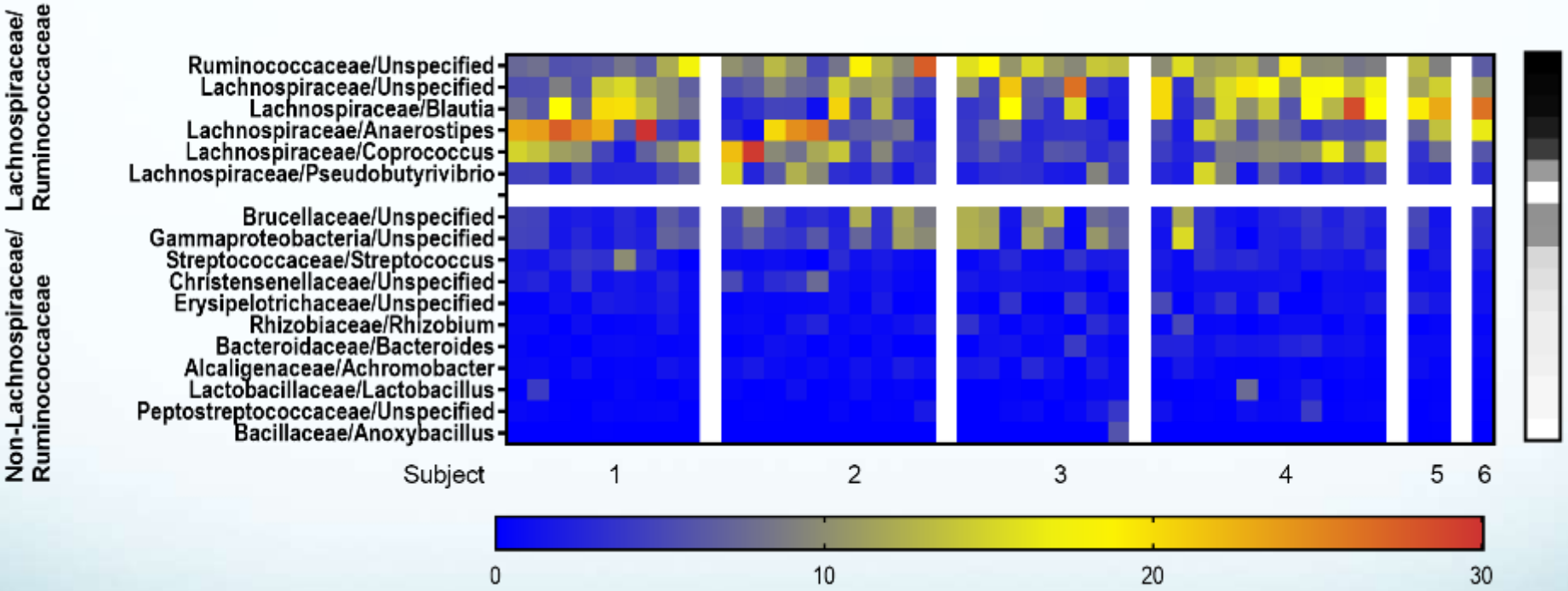
Gut Microbes and Rheumatoid Arthritis

The Mucosal Origins Hypothesis



Holers et al, 2018

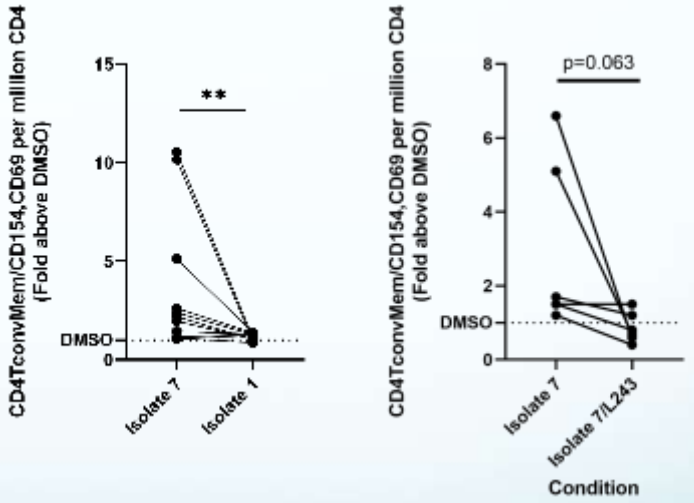
ACPA Antibodies Targeting *Lachnospiraceae/Ruminococcaceae*



Ruminococcaceae isolated from a human a target for ACPA binding and pro-inflammatory human T cell responses

Percent shared genomic identity among sequenced isolates

	Isolate 1	Isolate 3	Isolate 4	Isolate 5	Isolate 7	Reference Strain
Isolate 1	100					
Isolate 3	99.92512	100				
Isolate 4	96.10706	99.97949	100			
Isolate 5	99.23583	99.71826	99.97204	100		
Isolate 7	99.74642	99.96644	99.95963	99.69582	100	
Reference Strain	98.7268	98.67148	98.6949	98.72672	99.54811	100



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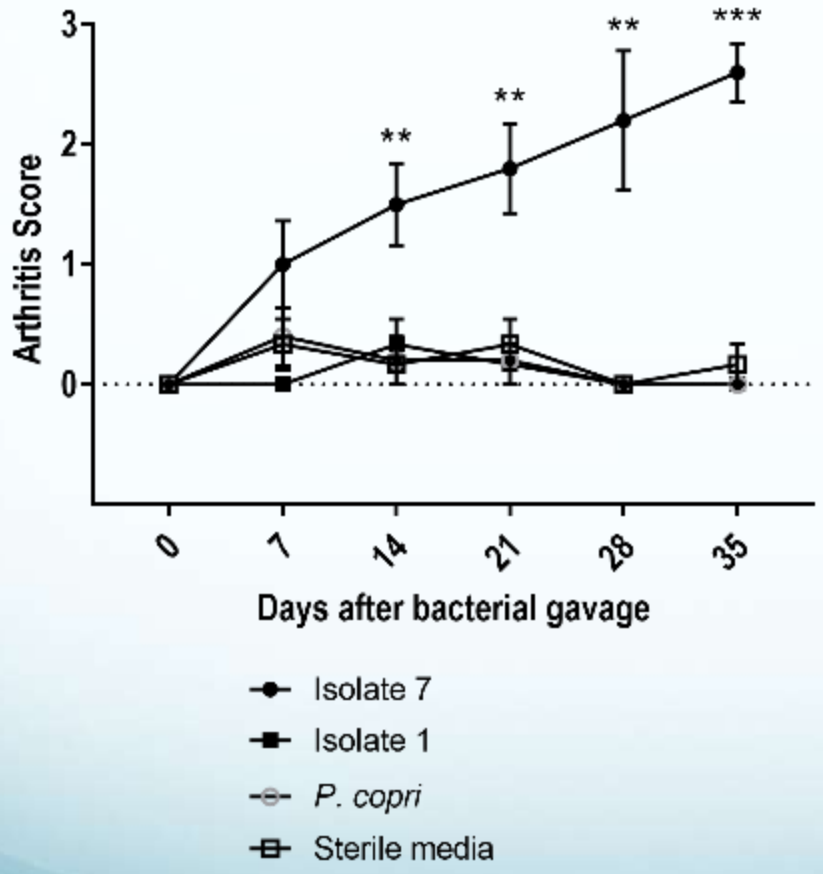
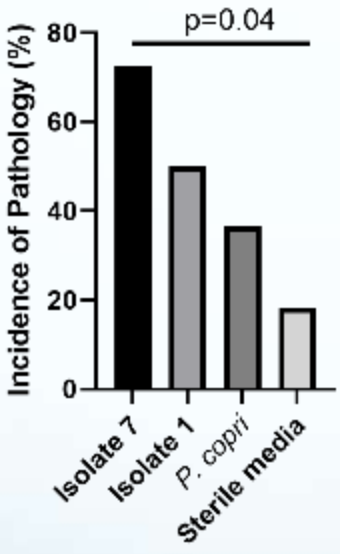
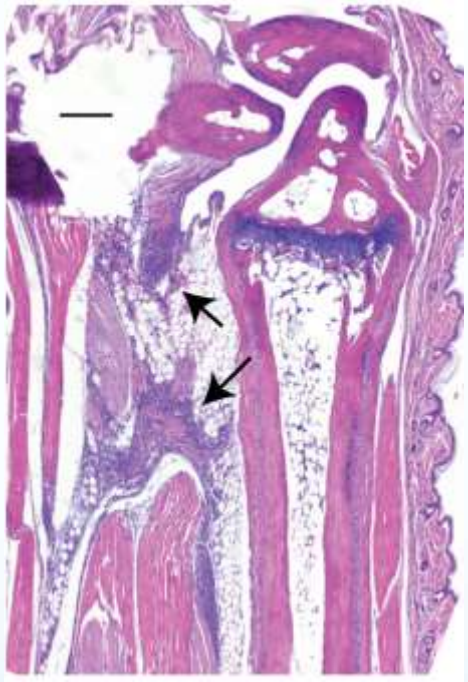
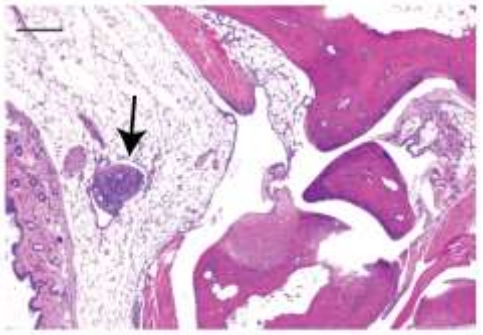
Ruminococcaceae Incites Arthritis in Mice



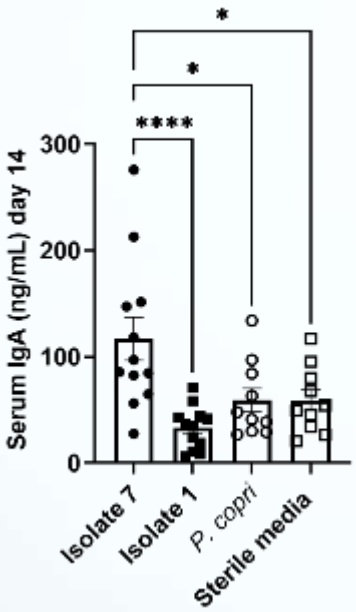
Ruminococcaceae Incites Arthritis in Mice

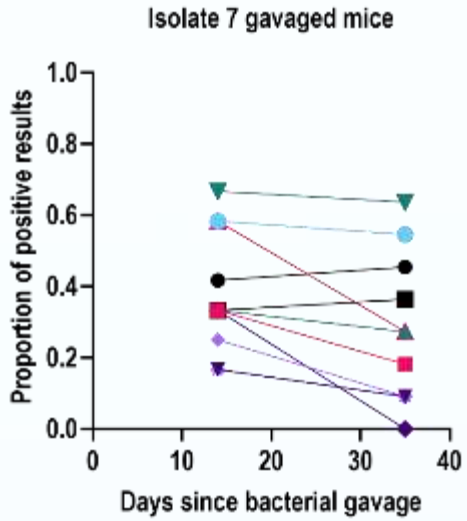


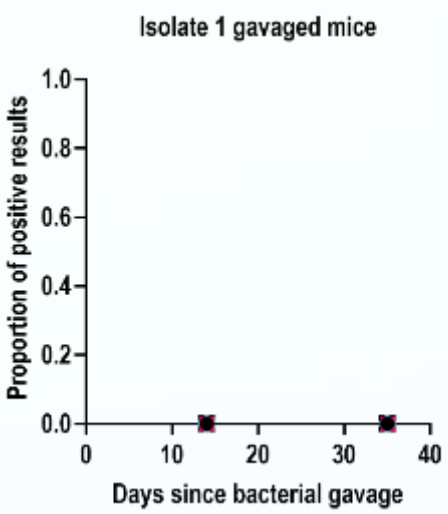


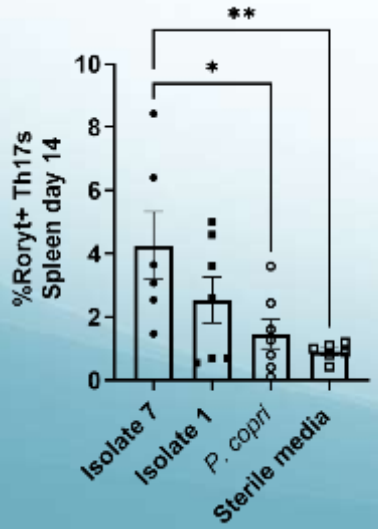


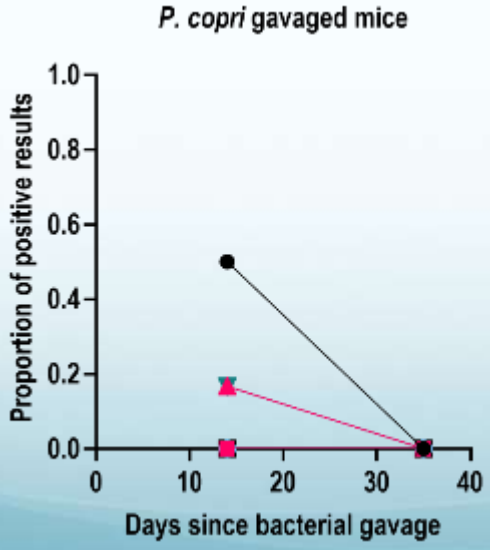
Ruminococcaceae Incites Proinflammatory T cells in mice and autoantibody development

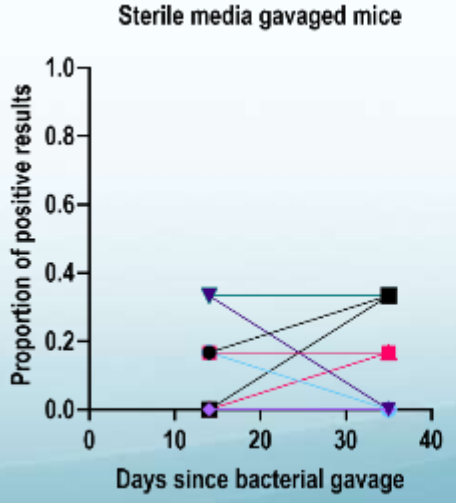


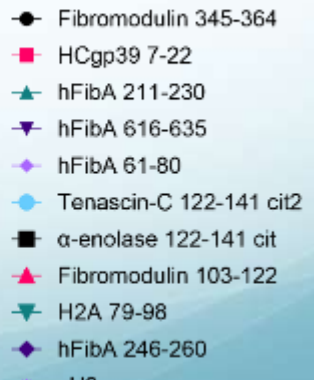






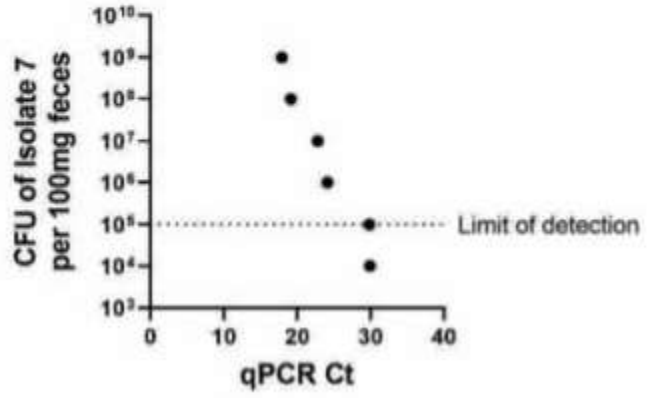






Ruminococcaceae isolate 7 detectable in people with and at-risk for RA

A



B

Group	Isolate 7 above limit of detection n (%)	No Isolate 7 above limit of detection n (%)	Total n (%)
Healthy Controls	0 (0%)	12 (100%)	12 (100%)
At-risk subjects	2 (16.7%)	10 (83.3%)	12 (100%)
Early RA subjects	2 (16.7%)	10 (83.3%)	12 (100%)
SPF Mice	0 (0%)	12 (100%)	12 (100%)
***, P<0.001, Chi-Square Test			

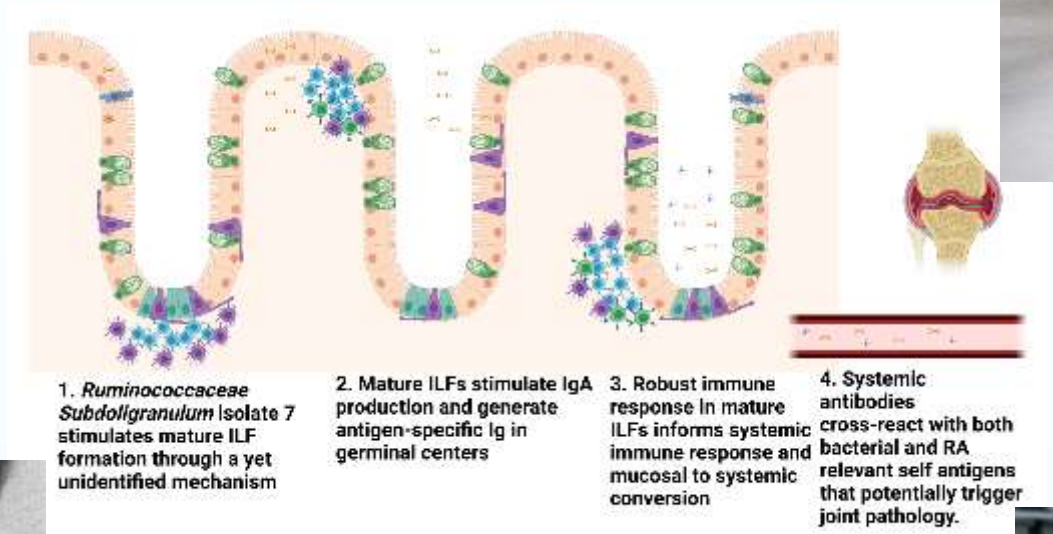
What could this mean in the context of rheumatologic health disparities?

1. *Ruminococcaceae* isolate 7 may play an important role in the stimulation of arthritis

2. This strain of *Ruminococcaceae* has only been detected in the feces of people with or at-risk for the development of RA

3. Some Native American populations have higher amounts of *Ruminococcaceae* in their microbiomes

Conclusions



Chronic diseases in indigenous North Americans, including adult diseases with pediatric origins, can only be understood in the context of the complex historical experiences and ongoing community challenges faced by indigenous peoples.

Blackfeet Saying

A child is sacred. And when that child comes into the home, the family must welcome it. And if the child is happy and feels the want, he will come into this world very, very strong. And not to know this is to know nothing.

Thanks to Dr. Don Warne for this slide.