

In Education, Research, & Clinical Care: SeXX Makes a Difference

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Disclosure

- ✓ No financial disclosures
- ✓ Representative of Texas Tech Univ HSC
- ✓ The information provided by the speaker are her own and not meant to represent official statements of U.S. Food and Drug Administration



Learning Objectives

- ✓ Understand the unique terms sex and gender
- ✓ Recognize the limitations of applying a onesex lens in research, education and clinical care
- ✓ Apply a sex and gender lens to achieve personalized patient-centered care



Starting on the same page

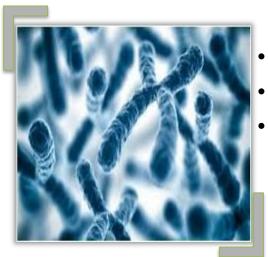
Definitions



Institute of Medicine Definitions

Source: Exploring the Biological Contributions to Human Health: Does Sex Matter (2001)





SEX

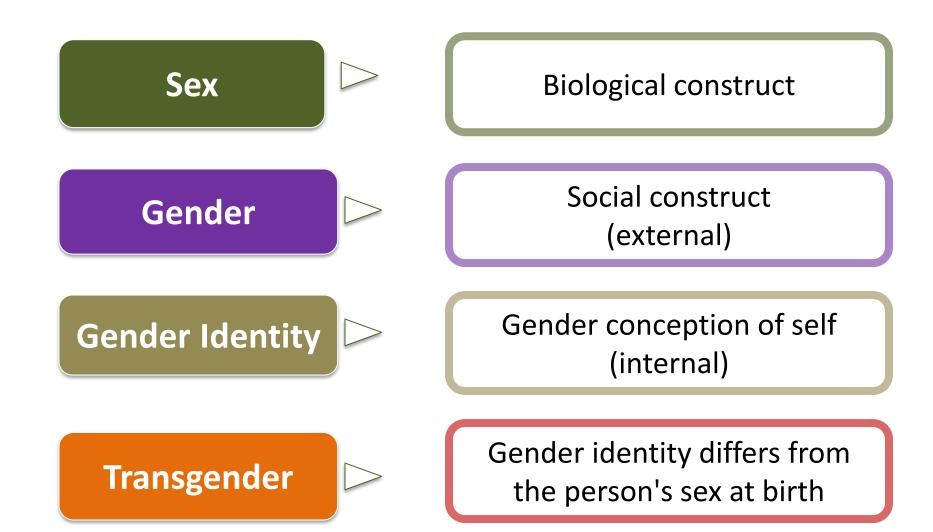
- Chromosomal
- Physiological
- Typically binary
 - Male/Female

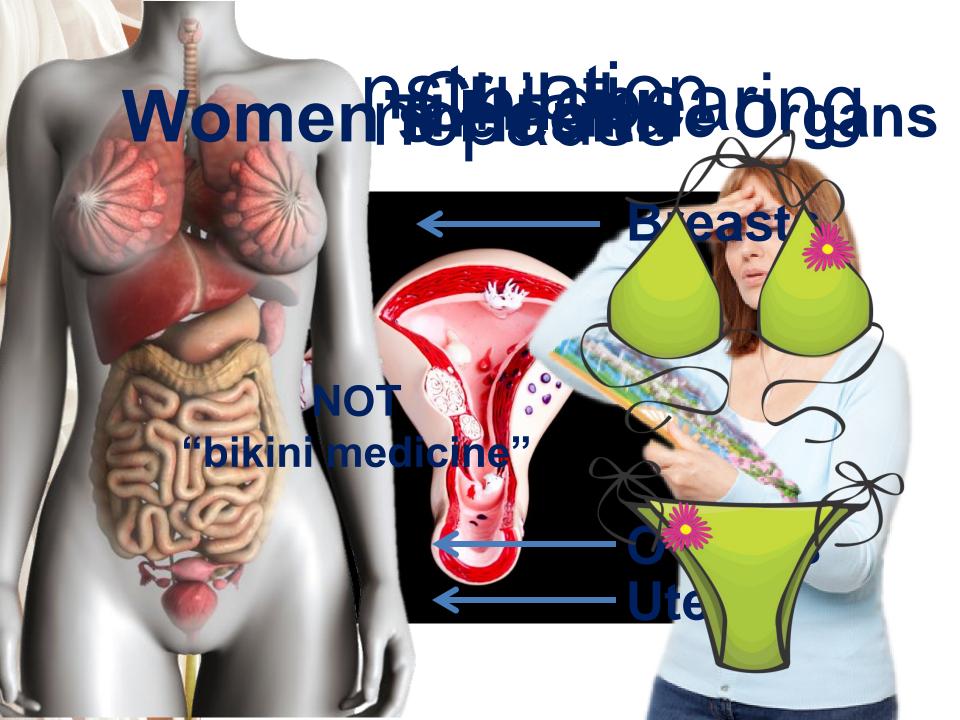
GENDER

- Environmental
- Society
- Spectrum
 - Masculine/Feminine
 - Man/Woman
 - Both
 - Neither











Sex and Gender in Biomedical Research and Health Policy





1977

FDA Mandate: Women of childbearing age in clinical trials

In 1977, the FDA recommended that premenopausal women capable of becoming pregnant be excluded from early phases of drug trials.

(Including all women using reliable methods of contraception, women whose male partners had had vasectomies or used condoms, and women who were "single.")

Although the FDA guidelines pertained only to early phases of drug development, in practice the participation of women in all phases was affected





1985

Women's
Health: Report
of the Public
Health Service
Task Force

"the historical lack of research focus on women's health concerns had compromised the quality of health information available to women as well as the health care they receive"

T

- <u>Consider</u> the inclusion of women in the study populations for all clinical research efforts.
 - Exceptions would be studies of diseases which exclusively affect males or where involvement of pregnant women may expose the fetus to undue risks.
- General differences <u>should be</u> noted and evaluated.
- If women are not to be included, a clear rationale <u>should be</u> provided for their exclusion.



1986

NIH Inclusion Policy: *voluntary*

Source: NIH Guide for Grants and Contracts (Vol. 16, pp. 2).





Women were significantly underrepresented in drug trials

Even when women were included, data were not analyzed sufficiently

Recommended ensuring drug companies consistently include "sufficient numbers of women in drug testing"





1993

NIH Reformation Act NIH Office of Research in Women's Health established

1993 NIH REVITALIZATION ACT

Women & minorities to be included in clinical research

Ensure that valid scientific analysis <u>could be</u> performed in determining whether differences existed between women and minorities in relation to other study subjects

Include both sexes in adequate numbers to ensure data <u>could be</u> analyzed for an effect of gender on safety and efficacy of proposed intervention or drug.



Food and Drug Modernization Act:

Congress directs FDA to develop guidance on inclusion of women and minorities in clinical trials

Demographic Rule requires sponsors:

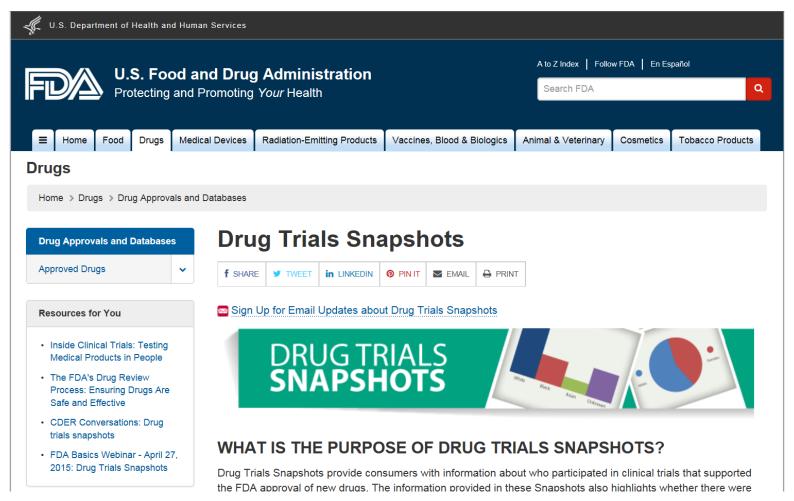
- Tabulate the trial population by age group, sex, and race in Investigational New Drug (IND) applications
- Analyze safety and efficacy by age group, sex, race, and other variables as appropriate in New Drug Applications (NDA)



1997

FDA:
Modernization
Act
Demographic
Rule





http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm



% Women Reported in FDA Drug Trial Snapshots

(cardiovascular drugs approved since Jan 2014)

BRAND NAME	INDICATION	WOMEN
UPTRAVI	Pulmonary arterial hypertension	80%
REPATHA	Hypercholesterolemia (HoFH)	50%
SAVAYSA	Reduce risk of pulmonary embolism in VTE patients	43%
PRALUENT	Hyperlipidemia	40%
SAVAYSA	Reduce the risk of stroke in a Afib patients	38%
KENGREAL	Blood thinner following heart procedure	28%
CORLANOR	Heart failure	24%
ENTRESTO	Heart failure	22%

Source: http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm





Report to Congressional Requesters

October 2015

NATIONAL INSTITUTES OF HEALTH

Better Oversight
Needed to Help
Ensure Continued
Progress Including
Women in Health
Research



- 57% of 2014 NIH-funded clinical trials subjects were women
- No data element in NIH's data system to indicate whether an awardee's study should or does include plans for an analysis in research outcomes by sex
- NIH <u>lacks summary data</u>, such as the percentage of awardees in a given year with trials designed to identify potential differences in clinical outcomes by sex
 - <u>Compromises</u> NIH's monitoring of Inclusion Policy implementation
 - <u>Limits</u> NIH's assurance that it is supporting research that can be used to shape improved medical practice for both women and men



NEW RESEARCH POLICY January 2016





NIH to balance sex in cell and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

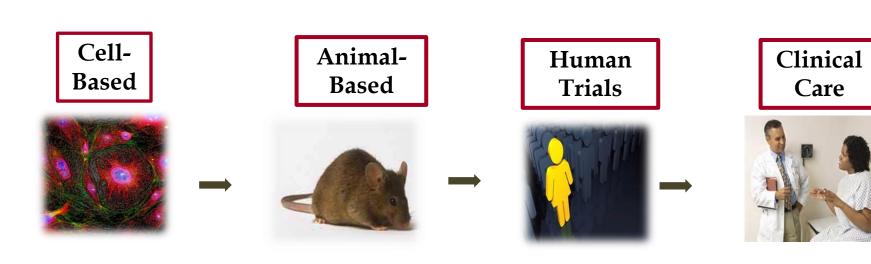
THE COLBERT REPORT





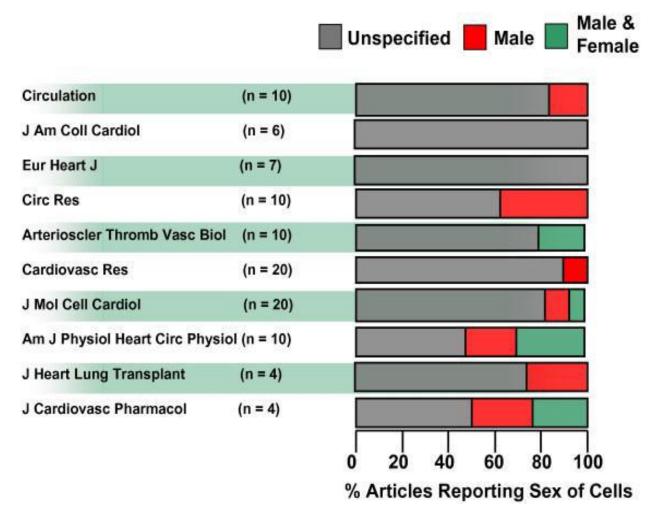


BIAS in the RESEARCH PIPELINE



Taylor, K. et al. (2011). Reporting of Sex as a Variable in Cardiovascular Studies using Cultured Cells. *Biology of Sex Differences, 2 (11),* 1-7.

Percentage of articles reporting sex of cells in experiments





BIAS in the RESEARCH PIPELINE





Animal-Based

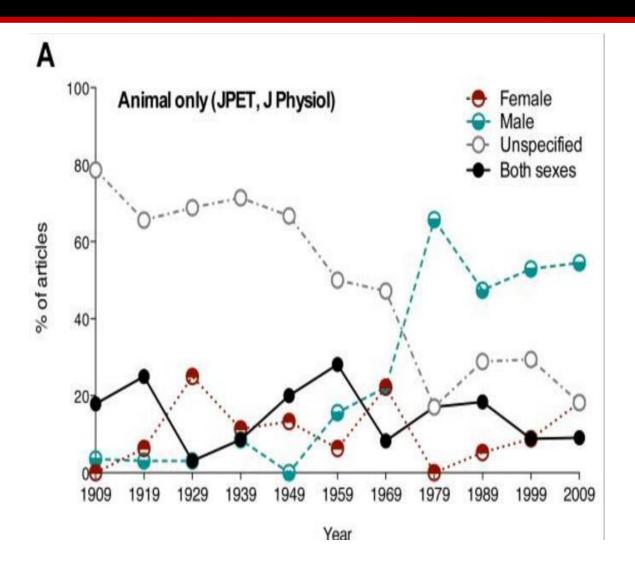


Human Trials



Clinical Care





Beery AK, Zucker I. Sex Bias in Neuroscience and Biomedical Research. *Neuroscience and biobehavioral reviews*. 2011;35(3):565-572.

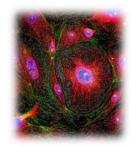
The American Physiological Society



BIAS in the RESEARCH PIPELINE

Cell-Based Animal-Based

Human Trials Clinical Care











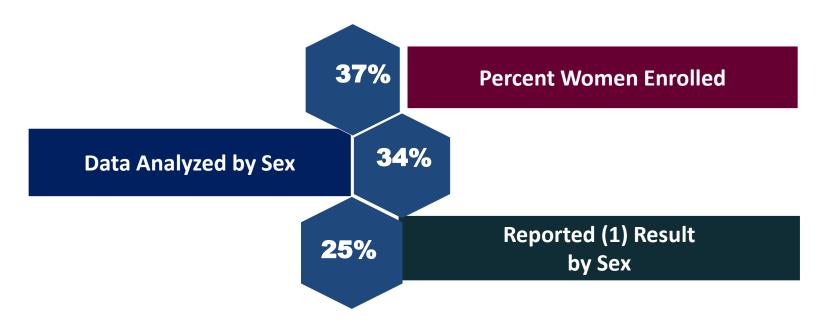
Review of Federally Funded RCTs 9 Major Scientific Journals in 2009

- 1. New England Journal of Medicine
- Journal of the American Medical Association
- 3. Annals of Internal Medicine
- 4. American Journal of Medicine
- 5. Journal of Clinical Oncology
- 6. Circulation
- 7. Clinical Infectious Disease
- 8. Obstetrics and Gynecology
- 9. American Journal of Obstetrics and Gynecology

Geller S et al. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? J Womens Health 2011;20(3):315-320.



Sex in Clinical Trials: Inclusion, Analysis and Reporting: n= 87



Geller S et al. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? J Womens Health. 2011;20(3):315-320.



Coronary Drug Project

To determine whether regular administration of lipid modifying drugs (clofibrate, nicotinic acid, *estrogen*, dextrothyroxine) to men with a documented myocardial infarction would result in significant reduction in total mortality over a 5 year period.

Source: ClinicalTrials.gov



Flibanserin

- Drug for treatment of hypoactive sexual desire disorder in women
- Safety studies conducted determine interaction of drug with ETOH
 - 18 of 20 subjects were men
- Post-marketing safety studies in women were required by FDA at the time of drug approval

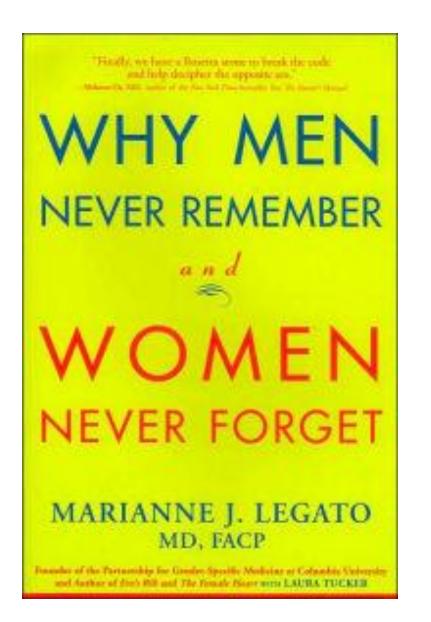


The Issue

When biomedical research is biased our abilities are limited when teaching future clinicians evidence-based care for all



Are men and women really the same?









BMJ 2014;349:g7094 doi: 10.1136/bmj.g7094 (Published 11 December 2014)

Page 1 of 4

RESEARCH

CHRISTMAS 2014: GOING TO EXTREMES

The Darwin Awards: sex differences in idiotic behaviour

© OPEN ACCESS

Ben Alexander Daniel Lendrem *student*¹, Dennis William Lendrem *project manager, Institute of Cellular Medicine*², Andy Gray *consultant orthopaedic trauma surgeon*³, John Dudley Isaacs *director, Institute of Cellular Medicine*²





EVIDENCE OF DIFFERENCES

Cardiovascular
Suicide
Sudden Death
Aneurysms
Impulsivity
Cardiomyopathy
Autism
Antisocial





Autoimmune
Depression
Arrhythmia
Hip Fractures
Cholecystitis
Irritable Bowl
Migraine
Alzheimers



Cardiac Resynchronization Therapy in Women: US Food and Drug Administration Meta-analysis of Patient-Level Data

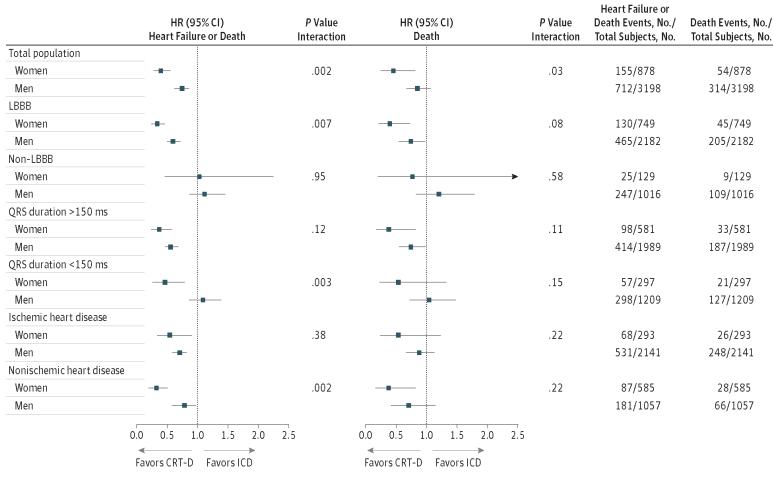
(Zusterzeel R., et al. JAMA Intern Med. 2014;174(8):1340-1348)



Cardiac Resynchronization Therapy

- Combined 3 clinical trials CRT-D vs.
 Implantable Cardioverter Defibrillator
 (ICD) in patients with mild heart failure
 (New York Heart Class II)
- 22% of the combined subjects were women

CRT-D to ICD HRs for Outcomes by Sex Combined Study Population



CRT-D indicates cardiac resynchronization therapy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; ms, milliseconds. *P* values represent sex-by-treatment interactions.



Results

- Overall, women benefited more than men.
- Neither group benefited with LBBB and QRS of <130 milliseconds.
- The majority benefited from LBBB with QRS of >150 milliseconds.



Results

- The main difference came in patients with LBBB and a QRS of 130 to 149 milliseconds.
- Women had a 76 percent reduction in heart failure (absolute difference 23%) or death and a 76 percent reduction in death alone (absolute difference 9%), but there was no significant benefit in men.



This finding matters because....

Cardiovascular clinical guidelines limit the Class I indication for CRT-D to patients with LBBB and QRS of 150 milliseconds or longer.

8 out of 10 discontinued medications between 1997-2001 Women experienced the majority of adverse events including death



Source: GAO FDA Study 2001

Prescription Drugs with Evidence of Greater Health Risks for Women

Pondimin (fenfluramine hydrochloride)	Appetite suppressant		Valvula r heart disease
Redux (dexfenfluramine hydrochloride)	Appetite suppressant		Valvula r heart disease
Seldane* (terfenadine)	Antihistamine		l'orsades de Pointes (potentially fatal irregular heartbeat)
Posicor (mibefradil dihydrochloride)	Cardiovascular	SHITTING OF	Lowered heart rate in elderly women and adverse interactions with 26 other drugs
Hismanal (astemizole)	Antihistamine		l'orsades de Pointes
Rezulin (troglitazone)	Diabetic		Liver failure
Propulsid ^b (cisapride monohydrate)	Gastrointestinal		Torsades de Pointes
Lotronex (alosetron hydrochloride)	Gastrointestinal	i	Ischemic colitis (intestinal inflammation due to lack of blood flow)

FDA GAO Report 2001 Slide courtesy of : McGregor A. Brown Univ.

AKE ONE MEAN AT BEDTIME AT SLEEP

AMBIEN 10M

QTY 30 NO REFILLS - Page





SEX & GENDER MEDICAL EDUCATION



The Issue

When medical education does not integrate evidence and awareness of sex and gender into curricula it creates a gap in knowledge which ultimately affects the treatment of patients



- Distributed to the 2011 AAMC New Horizons Group
 + 30 DO Schools (159)
- 70% of responding 46 US medical schools did not have formal sex and gender specific integrated medical curriculum
- 83.1% did not have and integrated women's health curricula outside of traditional Ob/Gyn
- Overall lack of coverage in health topics where sex and gender-based evidence exists



The Evidence

Endothelial

Dysfunction:

Normal Coronary MI

7X > women

Heart

Bones

Men are underscreened & undertreated for osteoporosis

Women:

>organ toxicity

<amounts over

<amount of time

ETOH

RX

2014 FDA recommends 1/2 -maximum zolpidem dosing in women



Perspective of Students and Faculty National Surveys

RESEARCH Open Access

CrossMark

Sex and gender in medical education: a national student survey

Marjorie R. Jenkins^{1*}, Alyssa Herrmann², Amanda Tashjian², Tina Ramineni², Rithika Ramakrishnan², Donna Raef¹, Tracy Rokas³ and John Shatzer⁴













DEMOGRAPHICS

- Students from a total of 205 schools including regional campuses participated
- 153 schools met the final inclusion criteria
- 1,191 students completed the survey
- 1,097 met the final inclusion criteria

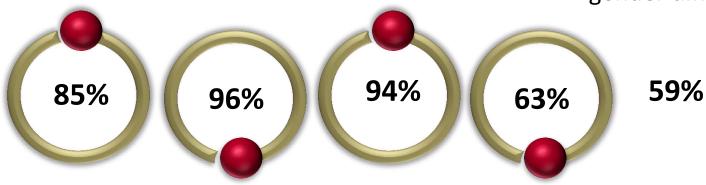
School Year	MS 1	MS 2	MS	3 MS 4	5+ Years
% of respondents	25.4	33.7	21.5	5 17.6	1.8
Gender		Fem	ale	Male	Other
% of respond	74.3		25.2	0.5	



MEDICAL STUDENT ATTITUDES AND PERCEPTIONS

I am familiar with the topic of sex and gender medicine Medical education should include teaching of sex and gender

My medical education includes teaching of sex and gender differences



Knowing sex and gender medicine improves one's ability to manage patients

The majority of medical knowledge is based on data obtained from males



Moderate to Extensive Coverage

	Medical History	Domestic Violence	Substance Use	Mental Health	Nutrition
Florida (59)	73.3	64.4	70.7	76.3	36.8
FSU (2)	100	0	100	100	0

	Pharm	Pulmonary	Cardiology	Rheum	ID	Endo
Florida (59)	56.9	59.3	68.4	69.1	62.7	80.7
FSU (2)	0	0	100	100	0	100

Survey Question:

Are there evidence-based health differences between men and women within these topics?

	Yes	
Topic	Male	Female
Presenting symptoms of MI	83.5	83.6
Dosing of Zolpidem	20.4	10.6
Outcomes after low impact fractures in adults	59	39.3
Risk factors for the development of osteoporosis	92.2	85.5

Jenkins, MR. et al. Biol Sex Diff. (2016)



There are evidence-based health differences between men and women in regard to....**YES**

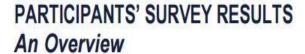
	MI	Aspirin	Domestic Violence	Zolpidem	Narcotic Addiction	Smoking Cessation
Florida (59)	95.2	58.7	71.0	12.9	37.1	46.0
FSU (2)	100	0	100	0	0	0



Surveys: Key Points

- Students perceive sex and gender differences are important to the ability to manage patient care: 96%
- There is <u>discordance</u> between expressed knowledge and perceived amount of exposure within curricular topics
- There is marked <u>inconsistency</u> across topics in regard to the reported and observes inclusion of sex and gender differences within medical education.

Formal approach to integration of sex and gender evidence into medical education is needed.



I am familiar with the topic of sex and gender differences in health and disease.

PRE-TEST: 81% Agree/Strongly Agree POST-TEST: 93% Agree/Strongly Agree

Does your institution require OSCEs or other simulated patient cases in women's health?

PRE-TEST: 28% No/Unsure/No, but Interested POST-TEST: 37% No/Unsure/No, but Interested

The FDA should consider recommending dosages based on the sex of the patient.

PRE-TEST: 69% Agree/Strongly Agree POST-TEST: 97% Agree/Strongly Agree

Sex and gender based medicine is a fundamental aspect of precision medicine.

PRE-TEST: 40% Strongly Agree POST-TEST: 81% Strongly Agree

"The resources that were made available to Summit participants are outstanding, and they will facilitate the promotion of additional curricular emphasis of this area."

"I will develop a proposal for our curriculum committee that we include sex- and gender-specific material in all our courses and clerkships...I will also request that student assessments include items about sex- and gender-based differences."

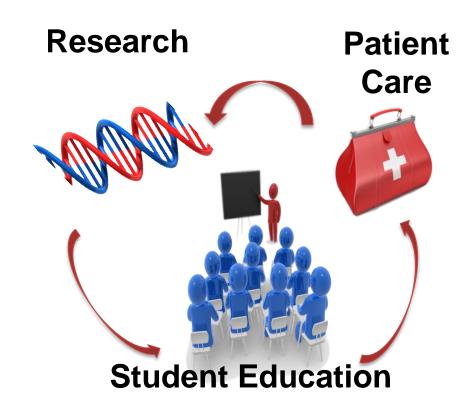
2015 US National Summit for Sex and Gender in Medical Education



Curricular Integration

"A scientific discovery, regardless of its potential, will ever impact patients, prevent deaths, or improve lives without first being transformed into clinical knowledge.

Such transformation occurs in the learning environment!"



A Framework of Translation Education

T-0 Basic Scientific Discovery

Discovery

TEd-0 Sex & Gender Scientific Discovery

T-1 Translational research: To findings tested for clinical effect and/or applicability

Proof of Concept

TEd-1 Develop + test educational methodologies for threading SGBM evidence into medical education

T-2 Translational research:

T1 tested in controlled environment to support efficacy + optimal settings for guidelines

Develop Guidelines

TEd-2 Develop sex and gender curricular guidelines

T-3 Apply recommendations or guidelines to general practice

Dissemination

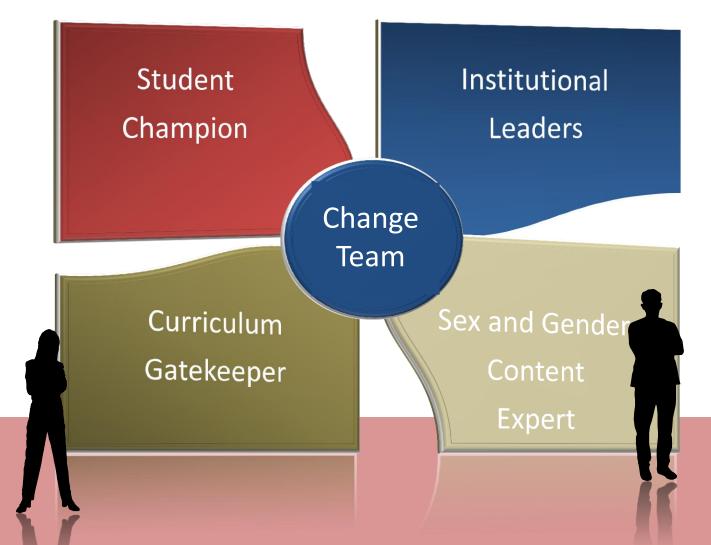
TEd-3 Implementation of SGBM curricular threads into real-world academic settings

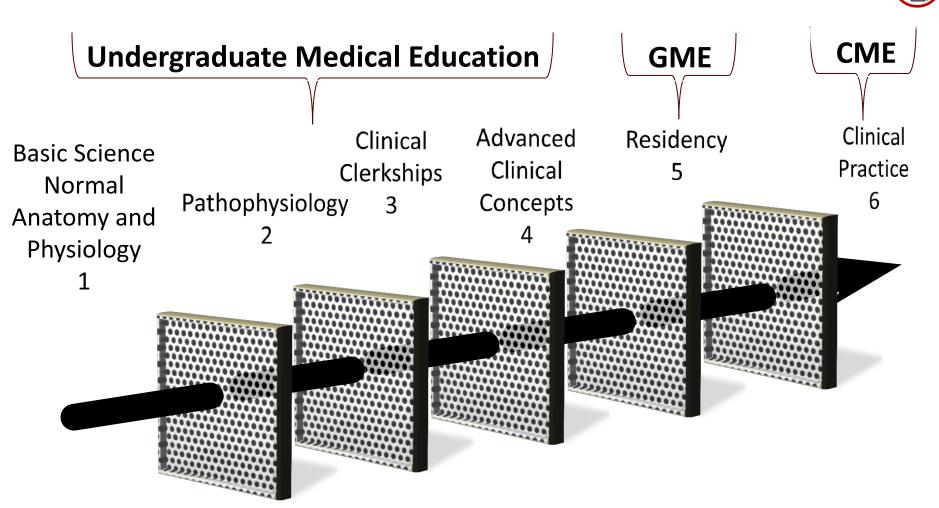
T-4 Apply recommendations to improve global health

Public Health

TEd-4 Global application of sex & gender health through public health integration

Team Model for Curricular Change





Sex and Gender Filter: UME to Clinical Practice

Source: TTUHSC SGSH Program



Common Barriers to Integrating New Information into Curricula

- Resources
- Time
- FacultyDevelopment



Resources and Time

JOURNAL OF WOMEN'S HEALTH Volume 00, Number 0, 2015

Development of a PubMed Based Search Tool for Identifying Sex and Gender Specific Health Literature

Michael M. Song, PharmD, Cheryl K. Simonsen, MLIS, Joanna D. Wilson, DO, and Marjorie R. Jenkins, MD3





<u>www.sexandgender</u> <u>health.org</u>

Username:

present_preview

Password:

Present_preview

Repository of Sex and Gender Tools for Health Professions



Slide Library

- Ready to use
- Speaking points
- Reference articles
- Level of evidence

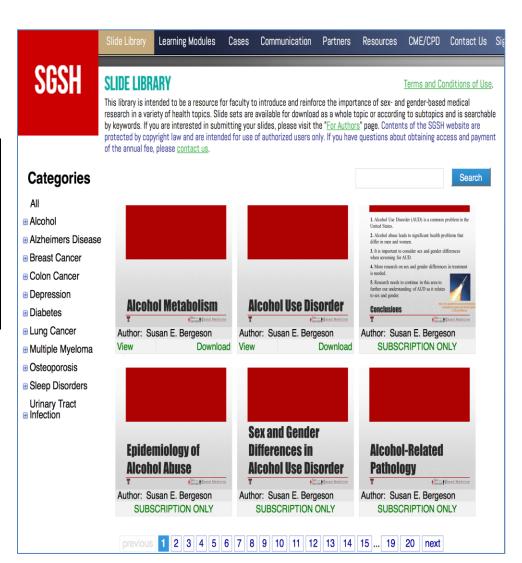
Indent More Metabolism:1 · Ethanol to Acetaldehyde via alcohol dehydrogenase · Aldehyde to Acetate via aldehyde dehydrogenase (ALDH). · Acetate used as energy for the body. **Alcohol Metabolism** Sex or Based Medicine At the liver, ethanol is broken down in several steps to produce energy for the body:¹ First, Ethanol is metabolized into Acetaldehyde via alcohol dehydrogenase (ADH) Next, Acetaldehyde is broken into Acetate via aldehyde dehydrogenase (ALDH). - Acetate is used as fuel for the body. Reference Citation w/ Level of Evidence: 1. Li, T.K., et al. (1986). Genetic variability of enzymes of alcohol metabolism in human beings. Annals of Emergency Medicine, 15(9), 997-1004. http://www.sciencedirect.com/science/article/pii/S0196064486801184# Patrick C. Marquardt TTUHSC School of Medicine Patrick.Marquardt@ttuhsc.edu Assistant Professor, Dept of Family & Community Medicine TTUHSC School of Medicine David.S.Edwards@ttuhsc.edu Assistant Professor, Dept of Family & Community Medicine TTUHSC School of Medicine David.Trotter@ttuhsc.edu Susan E. Bergeson Associate Dean, GSBS Associate Professor, Dept of Pharmacology & Neuroscience TTUHSC School of Medicine Susan.Bergeson@ttuhsc.edu Date Submitted 2/1/2016 Keywords for search engine - Alcohol Distribution and Metabolism

Jenkins M., Casanova R., et. al. www.sgsh.org



Slide Library

- Peer reviewed
- Add to existing lectures
- Searchable



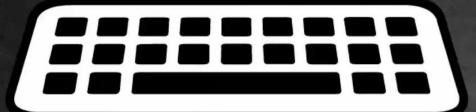








Slide Library Author Guide







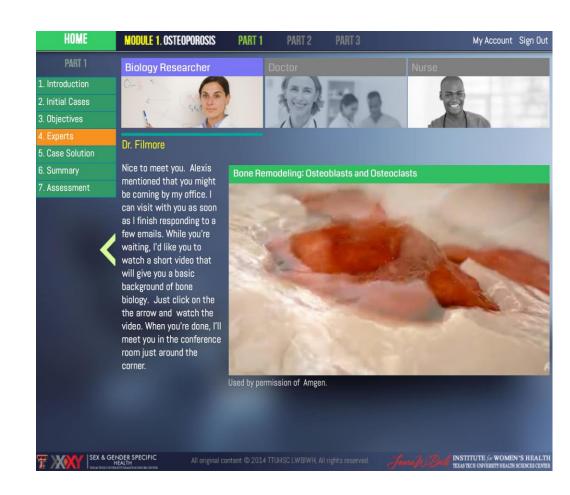






Learning Modules

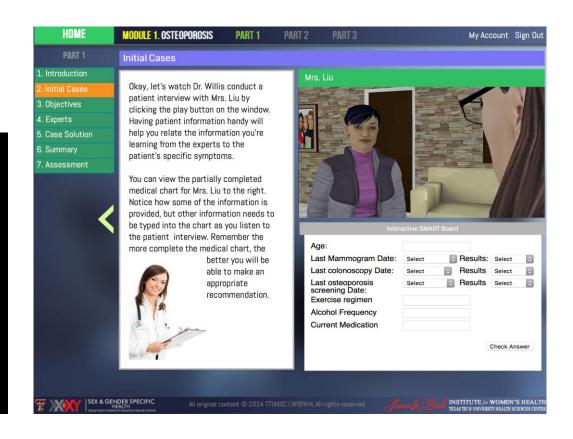
- IPE
 - Built in
 - SGSH





Learning Modules

 Cases follow male and female patient through disease process





Learning Modules

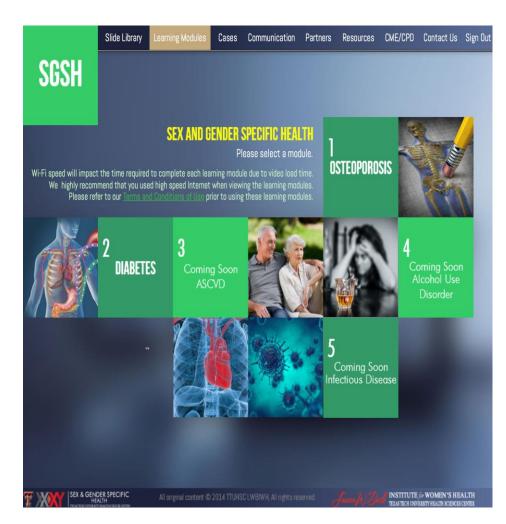
- Pre- and posttest
 - USMLE Type
 Questions
 - Attitudes
 - Knowledge

HOME MODULE 1. OSTEOPOROSIS	My Account Sign
etest	
As people age, which leads to bone resorption exceeding bone formation resulting in osteoporosis.	10. What percentage of adverse drug events can be prevented in the older adults ?
Osteoneogenesis exceeds osteoclastogenesis	∩ 12 %
Osteoclastogenesis exceeds osteoneogenesis	22 %
Osteoclastogenesis exceeds osteoblastogenesis	O 32 %
Osteoblastogenesis exceeds osteoclastogenesis	○ 42 %
2. The 3 phases of bone healing include:	11. Osteoblasts are derived from monocytes from the bone marrow.
Reactive, preparative and remodeling phases	↑ True
Reactive, regenerative and remodeling phases	False
Proactive, preparative and remodeling phases	
Reactive, preparative and regenerative phases	12. Women have higher morbidity than men after a hip fracture.
3. Which of the following medications increases the risks of	☐ True
osteoporosis?	False
Combination oral contraceptives	
Cephalosporins	13. There is valid evidence that most osteoporosis medications
Selective Serotonin Reuptake Inhibitors	do not work as well on women as on men.
Statins	
	☐ True☐ False
4. Most osteoporosis research is done on:	Faise
○ Middle seed mes	
SEX & GENDER SPECIFIC HEALTH All original content © 2014 TTUI	ASC I WRIWH All rights reserved INSTITUTE for WOMEN'S HE



Learning Modules

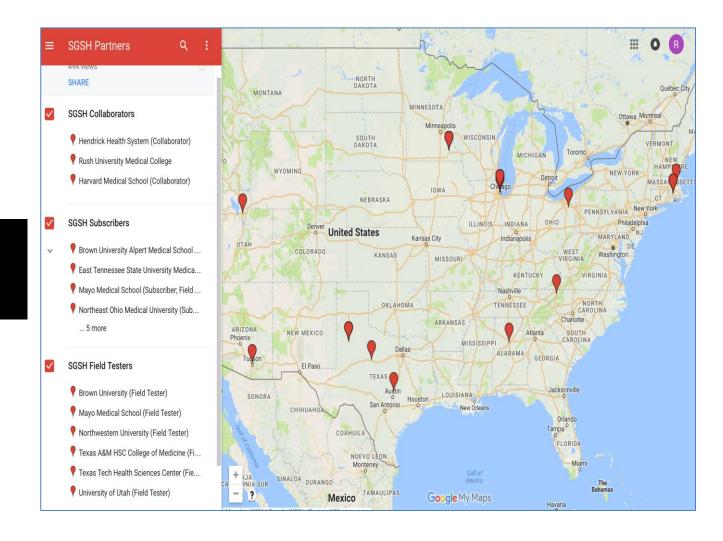
- Interactive
- Peer reviewed
- Stand alone
- Incorporate into existing course





Learning Modules

Field Tested





To access these curricular materials

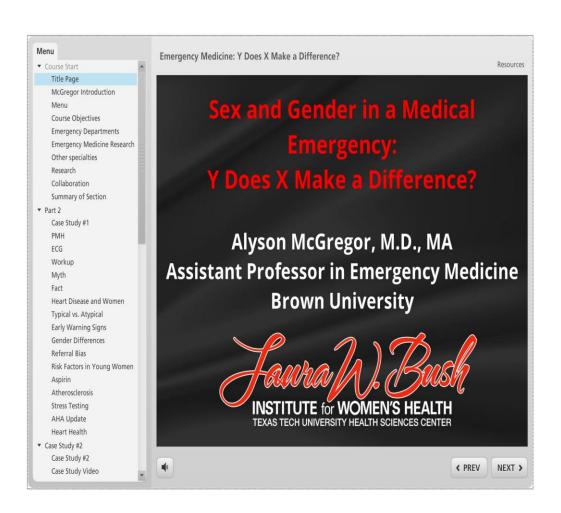
www.sexandgenderhealth.org

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Password: Present_preview



Continuing Professional Development





Publications



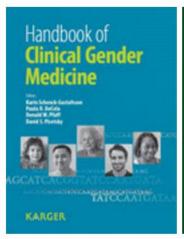


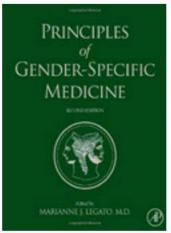
Journal Supplement

Sex and in Gender Medical Education October 2016

OPEN ACCESS

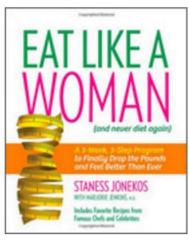




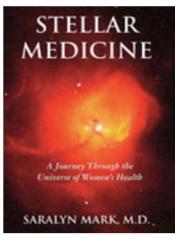


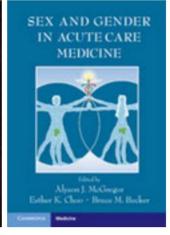






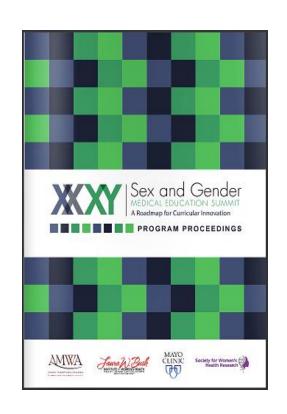


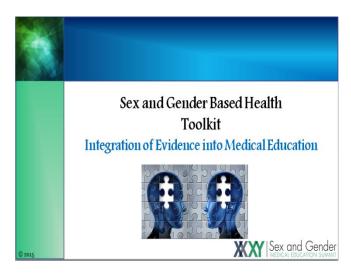












www.sgbmeducationsummit.org



2018 Sex & Gender Health Education Summit

Advancing Curricula through a Multidisciplinary Lens
April 8-10, 2018 University of Utah
Salt Lake City, Utah
www.sgbmeducationsummit.org

** faculty travel grants available **

Sponsors:











Not Knowing The Difference Doesn't Mean There Is No Difference





Thank you

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or

marjorie.jenkins@ttuhsc.edu