ACT Matching Events – Gender Dimension ERA Priority Groups

Hosted by *Karolinska Institutet*

Reflections on sex and gender in clinical practice and research: towards precision medicine

Valeria Raparelli, MD, PhD

October 20, 2020

On behalf of the GOING-FWD Consortium

OUTLINE

Why Am I Here?

- Sharing my experience as physician (internist) and clinical scientist
- Sex- and Gender-Informed Medicine (Precision Medicine)
- How to deal with the integration of sex and gender in clinical studies (what I have learned) – “my warning signs”
- Get inspired by sex and gender experts

GOING+FWD
GENDER OUTCOMES INTERNATIONAL GROUP: TO FURTHER WELL-BEING DEVELOPMENT

INTRODUCTION
WHO Health Definition

A state of complete

PHYSICAL, MENTAL and SOCIAL

WELL-BEING

and not merely the absence of disease or infirmity

1948

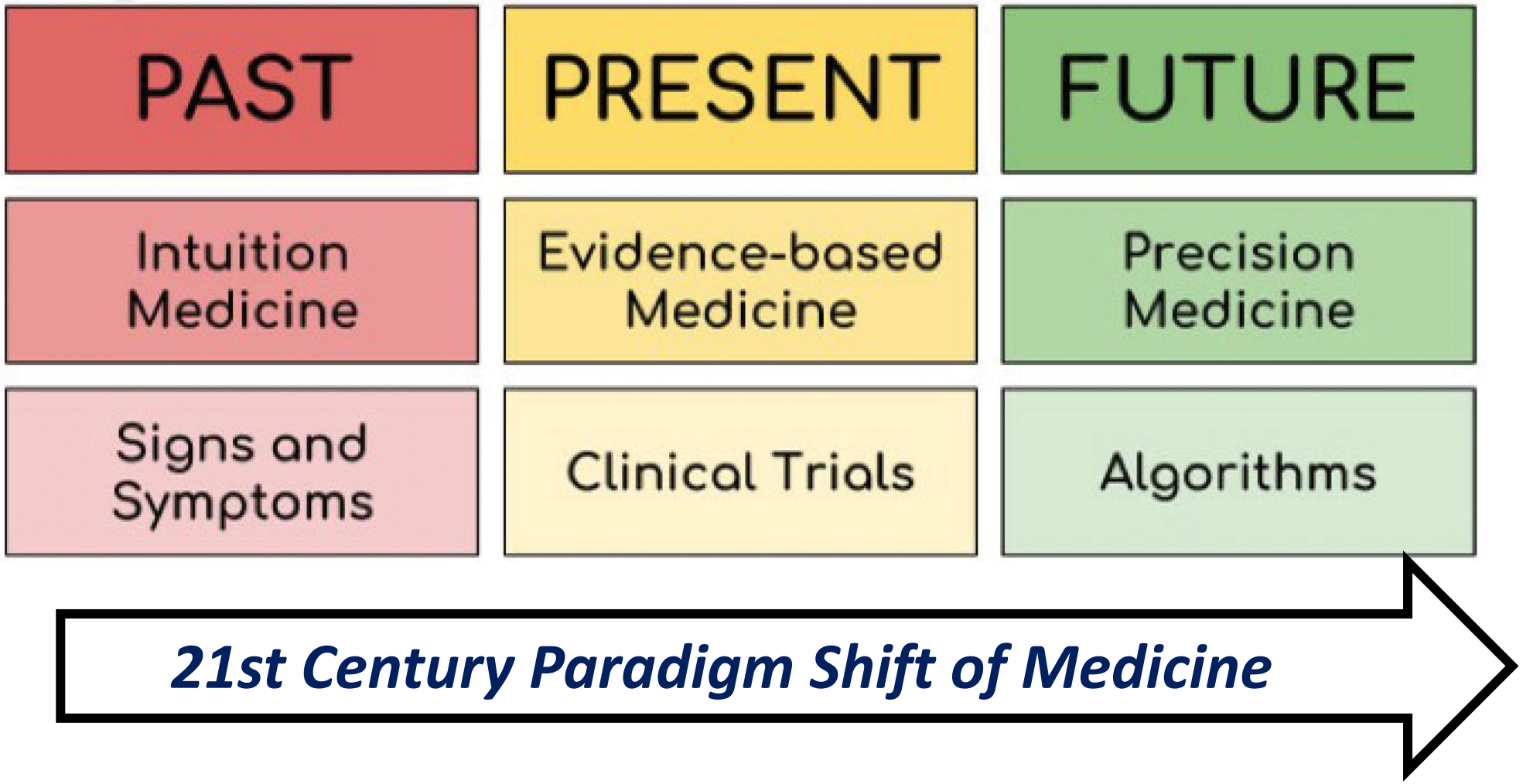
World Health Organization

INTERNAL MEDICINE
= «IN UNO OMNIA»

Holistic Approach of Care

INTRODUCTION

How is medicine changing over time?

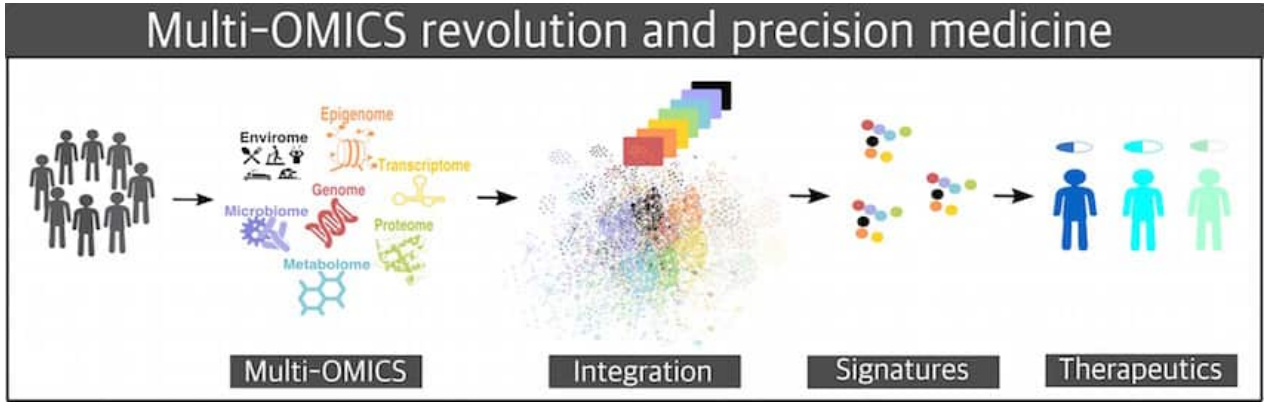


Gameiro, Gustavo Rosa, et al. *Clinics* (2018).

PRECISION MEDICINE

What is Precision Medicine?

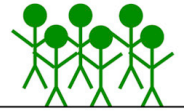
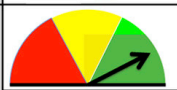
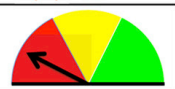
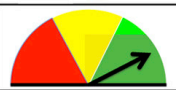
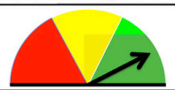
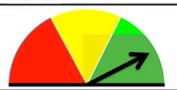
- An extension to existing medical care
  - Research disciplines and clinical practice
  - Builds a knowledge base to better guide individualized patient care
- A model for health care delivery relying on:
  - *Data*
  - *Analytics*
  - *Information*
- Improvement of patient outcomes:
  - Patients
  - Health care delivery systems
  - Research and research participants



Opportunity *to capture the whole picture of BIOLOGICAL systems* in a hypothesis-free and unbiased models

PRECISION MEDICINE

Disease Treatment and Prevention Strategies – Different Approach

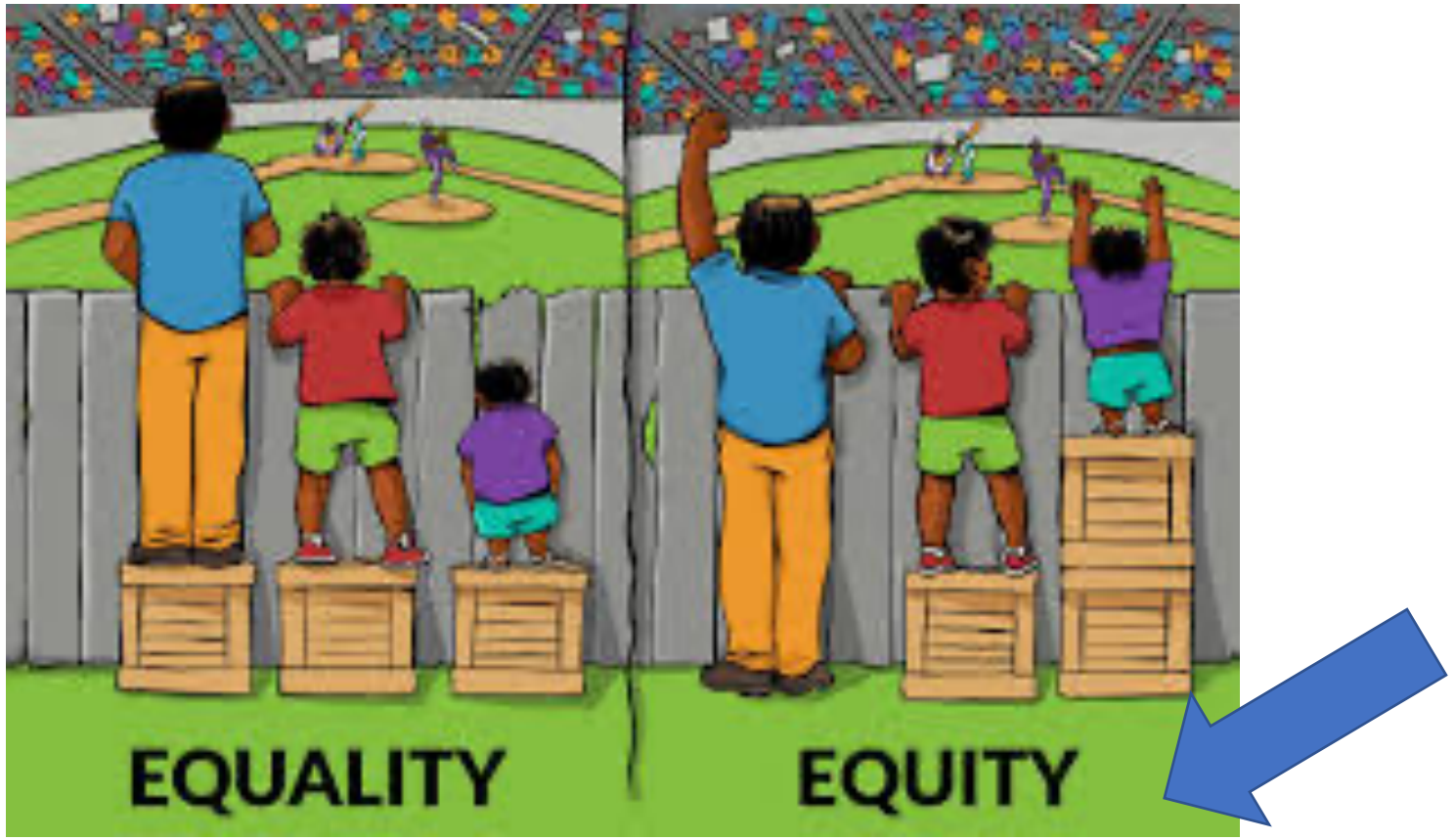
	Traditional Approach			*Precision Medicine Approach*		
Population of Individuals						
Classify by Risk						
Surveillance for Preclinical Disease						
Signs or Symptoms						
Treat with						
Strategy	**"One Size Fits All" Leads to Overall Mixed Results**			**Focus Existing**	**Repurpose FDA Approval**	**Invent New**
						
Outcome						
	Benefit	**No Effect**	**Adverse**	**Benefit**	**Benefit**	**Benefit**

…are developed for the AVERAGE PERSON , with less consideration for the differences between individuals

….take into account INDIVIDUAL VARIABILITY in genes, environment, and lifestyle for each person… provides strategies that will work in which groups of people

PRECISION MEDICINE

Disease Treatment and Prevention Strategies – Different Approach



…are developed for the AVERAGE PERSON , with less consideration for the differences between individuals

….take into account INDIVIDUAL VARIABILITY in genes, environment, and lifestyle for each person… provides strategies that will work in which groups of people

Precision Medicine
is more than
Genetics and Omics

SEX AND GENDER

Who are our patients?

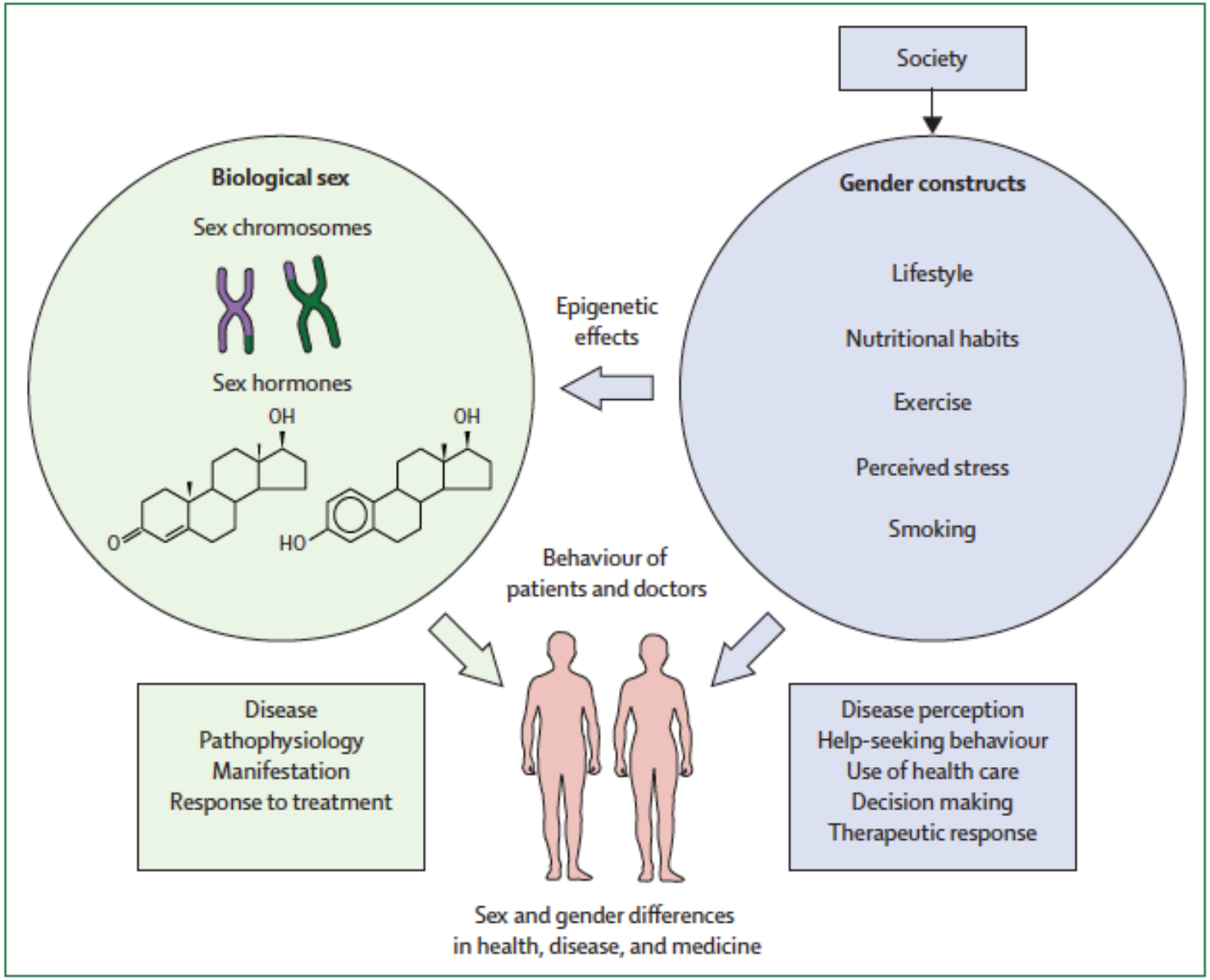
EVERY CELL IS SEXED AND
EVERY PERSON IS GENDERED

CIHR IRSC
Institute of Gender and Health
Institut de la santé des femmes et des hommes

SEX AND GENDER IN PRECISION MEDICINE

Sex and gender: modifiers of health, disease and medicine

EQUALLY RELEVANT FOR HEALTH

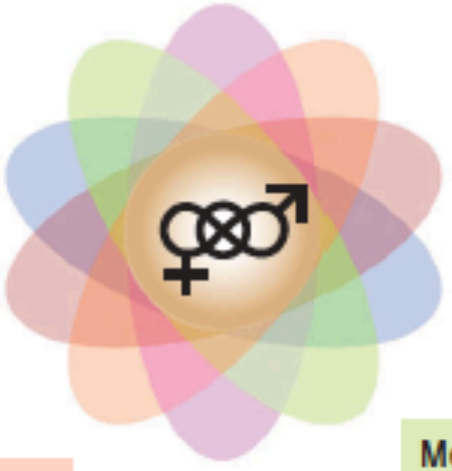


Mauvais-Jarvis et al. Lancet 2020; 396: 565–82

SEX AND GENDER IN PRECISION MEDICINE

How sex modifies the response to drugs

Figure 4. Parameters Through Which Sex May Affect an Individual's Response to Pharmaceuticals



Absorption
- Enterohepatic and renal handling
- Gastric enzymes
- Pulmonary function
- Transport proteins

Distribution
- Body fat composition
- Cardiac output, regional blood flow
- Total blood, plasma, and RBC volumes
- Total body, intracellular, and extracellular water

Pharmacodynamics
- Membrane receptor sensitivity
- Interactions with macromolecules (eg, hormones, enzymes)
- Target organ response, adverse events

Metabolism
- Dose
- Lipid solubility
- Protein binding and cytochromes P450
- Route of exposure

Elimination
- Glomerular filtration rate
- Renal blood flow
- Tubular secretion, reabsorption

Bartz D et al. JAMA Intern Med. 2020 Apr 1;180(4):574-583.

SEX AND GENDER IN PRECISION MEDICINE

How sex modifies the response to cardiovascular drugs

Parameter	Sex differences
Drug bioavailability	
Absorption	M > W
Gastric acid secretion	M > W > P. Decreases absorption of weak acids but increases absorption of weak bases in M
Gastric emptying	M > W > P. E inhibit gastric empting
Gastrointestinal transit times	
Gut metabolism	M = W
Body composition	
Body surface area	M > P > W. Absorption increases when body surface is larger
Organ (heart) size	M > W
Organ blood flow	Greater blood flow to skeletal muscle and liver in M; greater to adipose tissue in W. Blood flow increases during P
Total body water	M > P > W
Plasma volume	P > M > W. Varies during the menstrual cycle and P
Body fat content	W > M
Cardiac output	M > P > W. Increase rate of distribution in M
Pulmonary function	M > P > W. Increase pulmonary elimination in M
Drug distribution	
Volume of distribution	W > M. Higher Vd for lipophilic drugs in W M > W. Higher Vd for hydrophilic drugs in M
Plasma protein binding to	
Albumin	M = W. P and OCP reduce plasma albumin and increases free drug plasma levels
α1-acid glycoprotein	M > W. E, OC and P decrease its plasma levels
Globulins	E increase sex-hormone binding, corticosteroid-binding and thyroxine-binding globulins
Drug transporters	
Hepatic P-glycoprotein	M > W
OCT2	M > W. E downregulates OCT2
OATP1B1-3	M > W
Drug metabolizing enzymes and transporters	
Phase I metabolic reactions (hydrolysis, oxidation, reduction) mediated via cytochrome P450 (CYP) isoforms	CYP1A2: M > W. Decreased in pregnancy and by OCP CYP2B6: W > M CYP2C9: M = W CYP2C19: M = W Decreases in pregnancy and by OCP CYP3A4: W > M. Increases by OCP CYP2D6: M > W. E induces and OCP decreases CYP2D6 activity CYP2E1: M > W. Increases by OCP
Phase II metabolism	
Uridine diphosphate glucuronosyltransferases (UGTs 1/2)	M > W. Increase by OCP and E and during pregnancy
N-Acetyltransferases	M = W
Catechol-O-methyltransferase	M > W
Acetyl-/Butyryl-cholinesterase	M > W
Xantine-oxidase	W > M
Gastric alcohol dehydrogenase	M > W. Higher alcohol plasma levels in W
Drug excretion	
Renal blood flow	M > W. Renal Cl increases during P
Glomerular filtration rate	Drugs actively secreted by the kidney may show sex differences in renal excretion
Tubular secretion/reabsorption	

Drug class	Outcomes in females
Anaesthetics: propofol	Plasma propofol levels decline more rapidly in W at the end of infusion
Alcohol	Lower gastric alcohol dehydrogenase activity in W. Higher plasma concentrations in W as compared with M following an equivalent drink
Antidepressants	Higher AUC and C_{max} in W
H1-antihistamines	Slower metabolism and elimination in W
Antipsychotic drugs[a]	Higher plasma levels and Vd and lower Cl in W. Reduce the dosage in W or increase dosage in M. Olanzapine is more rapidly eliminated in M than in W
Aspirin	Bioavailability and plasma levels of aspirin and salicylate are higher in W possibly due to lower activity of aspirin esterase, larger Vd and lower Cl in W than in M. Differences disappear with OCP
Benzodiazepines	Lower initial plasma levels due to larger Vd, and possibly higher Cl, in W. OC reduce their Cl. Higher plasma levels of free diazepam in W
Beta-receptor agonists	W are less sensitive
Beta blockers: metoprolol, propranolol	W have higher plasma levels due to a smaller Vd and slower Cl. Drug exposure to metoprolol increases by OC Renal Cl of atenolol and metoprolol increases during P due to enhanced hepatic metabolism
Calcium channel blockers	Faster Cl of verapamil, and nifedipine in W. Increased bioavailability and decreased clearance of oral verapamil in W compared with M
Digoxin	W have higher serum digoxin concentrations due to reduced Vd and lower Cl. Drug Cl increases during P
Glucocorticoids	Oral Cl and Vd of prednisolone are higher in M. Prednisolone clearance was reduced by OC
Heparin	W had higher plasma levels and APTT values than M due to a lower Cl
Iron	Oral absorption of iron is greater in W than in M
Isosorbide mononitrate	W had significantly higher serum plasma concentrations compared with men, probably due to the lower body weights in females
Labetalol	Labetalol concentrations are 80% higher in W
Lidocaine	W has a larger Vd and may require a higher i.v. bolus dose than M. Higher free plasma levels in W receiving OCP, as alpha 1-acid glycoprotein levels are reduced by oestrogens
μ-opioid (OP3) receptor agonists[b]	Slower onset and offset of action in W
Neuromuscular blocking drugs[c]	Lower Vd, higher plasma levels, faster onset and prolonged duration in W due to the higher body fat and lower Vd
Paracetamol	Lower plasma levels and higher Cl in M due to increased activity of the glucuronidation pathway. OCP increase drug clearance
Procainamide	Plasma levels are higher (30%) in W due to a lower BMI and Vd
Quinidine	Plasma protein binding decreases during P
Selective serotonin reuptake inhibitors[d]	W present higher plasma levels, probably related to sex-related activity of various CYP enzymes
Statins	Higher plasma levels of lovastatin and simvastatin in W
Theophylline	Metabolism is faster and half-life is shorter in W than in M. Plasma protein binding decreases and the Vd increases during P
Torasemide	Higher C_{max} and lower Cl in W than in M
Tricyclic antidepressants	Free plasma concentrations of imipramine, clomipramine, and nortriptyline are higher during pregnancy
Verapamil	W display faster Cl of verapamil after i.v. administration probably due to the higher activity of CYP3A4 or lower activity of P-gp; lower Cl in W after oral administration
Vorapaxar	C_{max} and AUC are 30% higher in women but no dose adjustment is required
Warfarin	Higher free plasma levels in W
Zolpidem	Plasma levels and AUC are higher, and Cl is lower in W

European Heart Journal - Cardiovascular Pharmacotherapy (2017) 3, 163–182

SEX AND GENDER IN PRECISION MEDICINE

Low participation of Women in Clinical Trials

- ✓ ***36*** *pivotal cardiovascular drugs trials (**2005-2015**) for FDA approval*
- ✓ *Overall percentage of women enrolled **36%** (from 22 to 81%) across different areas*
- ✓ *Percentage of women per trial/percentage of women with the disease in the population **(Participation Prevalence)** – **LOW for Heart Failure and Ischemic Heart Disease***
- ✓ *Even though progress has been made toward a higher participation of women in pivotal clinical trials, **it still not time to rest on our laurels.***

TABLE 1 Interventions to Address the Low Inclusion of Women in Trials and to Obtain Women-Specific Results

Pitfalls in Drug Clinical Trials	Proposed Interventions
Knowledge and awareness of sex and gender	
Knowledge gap in terminology, use of sex and gender as synonymous	Clarify the use of the terms sex and gender though educational intervention among health providers, researchers, and general population
Pre-screening/screening	
Gender-related barriers for screening Day care Elderly Access to care	Promote awareness on gender-dimension Policies to support women in day-life (e.g., adequate child care during time spent as a research participant, assistance for elderly included in the study)
Inclusion male-pattern criteria	Inclusion criteria that consider sex differences in pathophysiology Age Glomerular filtration rate Body size Biomarkers/diagnostic criteria
Study methodology/analysis of data	
No adjustment for relevant covariates Sample size lead to unpowered results	Pre-specified subgroup analyses Adjusted analyses with term for sex*drug interaction in all trials Adequate power for efficacy and safety analyses
Editorial policy/research output dissemination	
Lack of specific editorial requirements for sex-specific reporting in clinical trials	Journal-specific checklist for sex-specific reporting (i.e., specify the number of women in the trial, all primary and secondary endpoints by sex, discuss generalizability in both sexes)

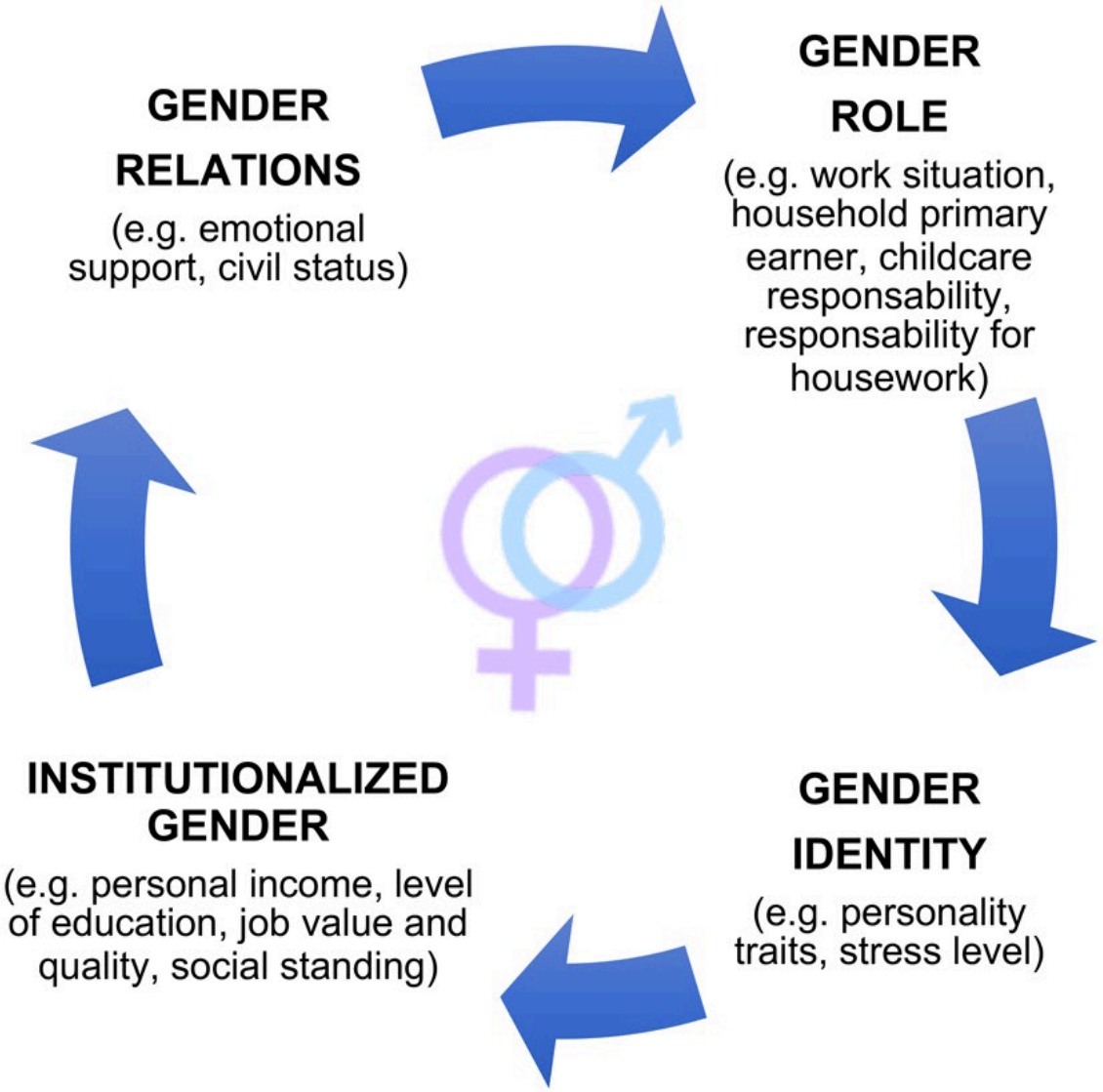
THE REPRESENTATION OF WOMEN IN RCT?

JACC JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Pilote L and Raparelli V. J Am CoLl Cardiol 2018, 71 (18):1970-2

GENDER

GENDER IS A MULTIDIMENSIONAL PSYCHOSOCIAL CONCEPT: HOW DO WE MEASURE IT?



COMPOSITE vs INDIVIDUAL MEASURES?

Lack of standard measurement

How can we measure such psycho-socio-cultural complexity?

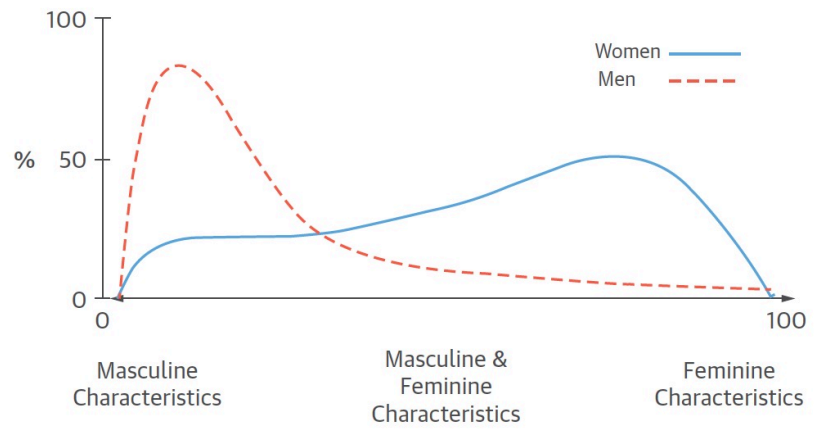
Raparelli V, Proietti M, Basili S. Heart. 2018 Dec;104(23):1900-01

GOING+FWD
GENDER OUTCOMES INTERNATIONAL GROUP: TO FURTHER WELL-BEING DEVELOPMENT

SEX AND GENDER IN PRECISION MEDICINE

Beyond sex, gender predicts better clinical outcomes

FIGURE 1 Gender Score Distribution in Men and Women With Premature Acute Coronary Syndrome



Adapted with permission from Pelletier et al. (22).

GENDER SCORE

1. Primary household earner status
2. Personal income
3. Number of hours per week doing housework
4. Primary responsibility for doing housework
5. Level of stress at home
6. Bem Sex Role Inventory masculinity score
7. Bem Sex Role Inventory femininity score

GENESIS PRA

Sex Versus Gender-Related Characteristics

Which Predicts Outcome After Acute Coronary Syndrome in the Young?

Pelletier, R. et al. *J Am Coll Cardiol*. 2016; 67(2):127–35.

Pelletier et. Al 2015. Methods and Statistics. *A composite Measure of Gender and Its Association with Risk Factors in Patients with Premature Acute Coronary Syndrome*

SCIENTIFIC CARDIOVASCULAR SOCIETIES PERSPECTIVE

Social Determinants of Health in Cardiovascular Disease – SODH SHOULD INFORM OPTIMAL IMPLEMENTATION OF TREATMENT

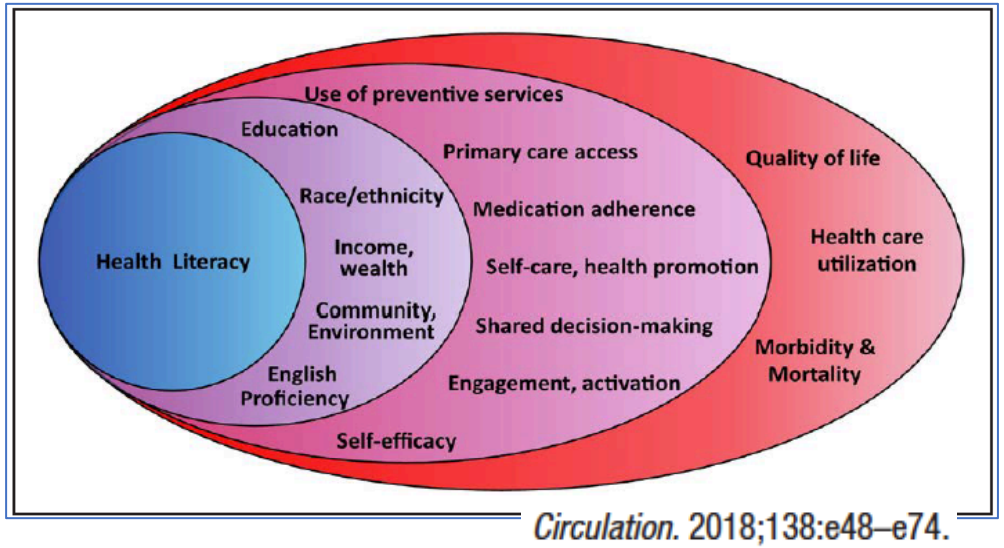
AHA Scientific Statement

Social Determinants of Risk and Outcomes for Cardiovascular Disease

A Scientific Statement From the American Heart Association

Circulation. 2015;132:873-898.

Social determinants of health are associated with a range of intermediate- and long-term healthcare outcomes



Circulation. 2018;138:e48–e74.

2.1. Patient-Centered Approaches to Comprehensive ASCVD Prevention

JACC VOL. 74, NO. 10, 2019
SEPTEMBER 10, 2019:1376-414

Recommendations for Patient-Centered Approaches to Comprehensive ASCVD Prevention
Referenced studies that support recommendations are summarized in Online Data Supplements 1 and 2.

COR	LOE	RECOMMENDATIONS
I	A	1. A team-based care approach is recommended for the control of risk factors associated with ASCVD (S2.1-1–S2.1-14).
I	B-R	2. Shared decision-making should guide discussions about the best strategies to reduce ASCVD risk (S2.1-15–S2.1-18).
I	B-NR	3. Social determinants of health should inform optimal implementation of treatment recommendations for the prevention of ASCVD (S2.1-19–S2.1-25).

AHA SCIENTIFIC STATEMENT

Addressing Social Determinants of Health in the Care of Patients With Heart Failure

A Scientific Statement From the American Heart Association

Circulation. 2020;141:e841–e863.

ASSESS AND ADDRESS SOCIAL DETERMINANTS OF HEALTH (GENDER):

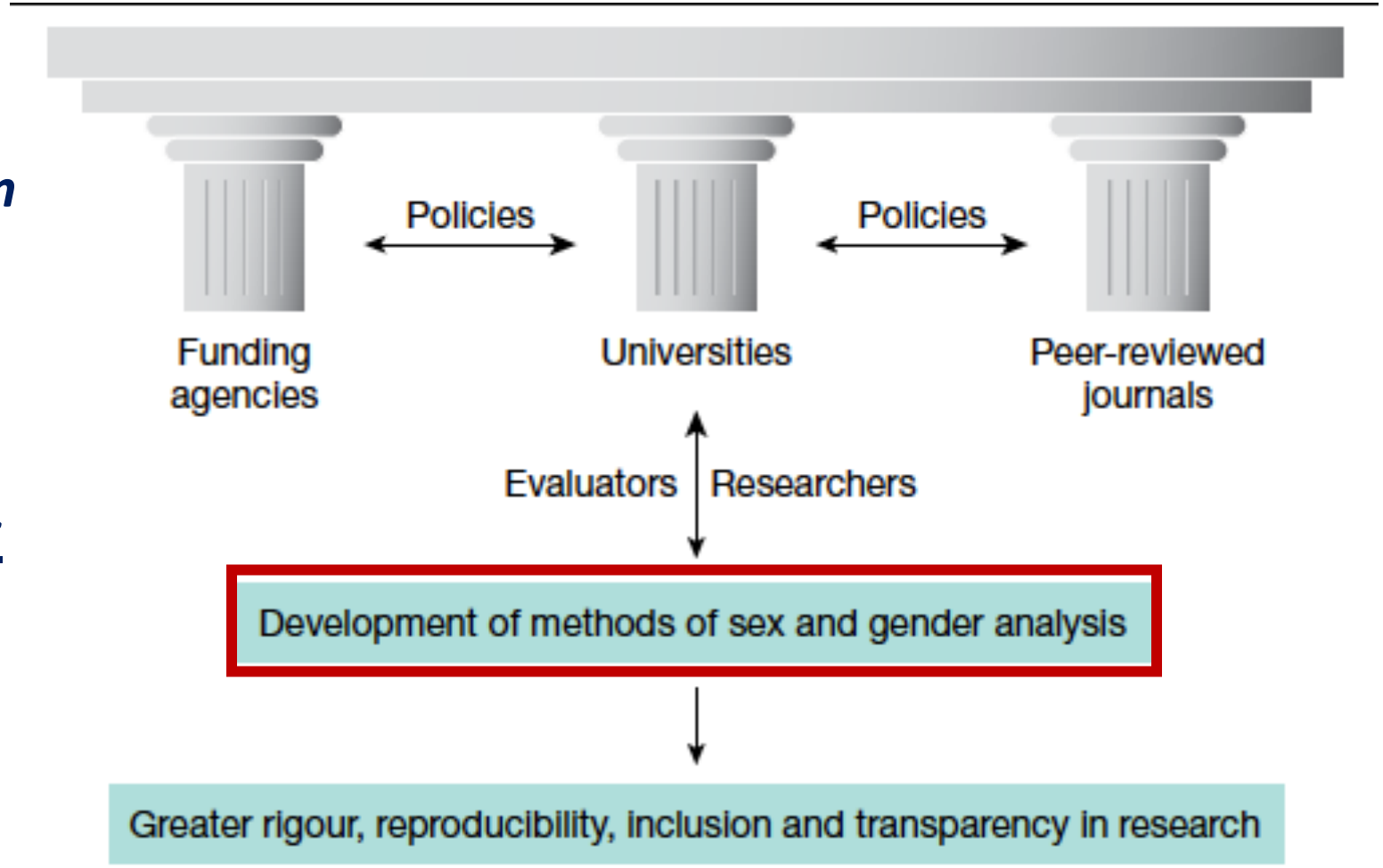
Gender-Sensitive Interventions

HOW TO IMPLEMENT SEX AND GENDER IN PRECISION MEDICINE

Three pillars of science and engineering infrastructure

STRUCTURAL CHANGE

Implementation of gender dimension in practice and research a priority but it is challenging



Tannenbaum C. et al Nature 2019; 575: 137–146

HOW TO IMPLEMENT SEX AND GENDER IN PRECISION MEDICINE

Italian Law for the Implementation of Gender-specific Medicine

POLICY?

ITALY EXPERIENCE -

A law and a healthcare plan that promise the development of specificity and gender equity in health

(2018)


GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

LEGGE 11 gennaio 2018, n. 3

Delega al Governo in materia di sperimentazione clinica di medicinali nonche' disposizioni per il riordino delle professioni sanitarie e per la dirigenza sanitaria del Ministero della salute. (18G00019) (GU Serie Generale n.25 del 31-01-2018)

note: Entrata in vigore del provvedimento: 15/02/2018

Articoli

Capo I
SPERIMENTAZIONE CLINICA DEI MEDICINALI

1
2
3

Capo II
PROFESSIONI SANITARIE

La Camera dei deputati ed il Senato della Repubblica hanno approvato;

IL PRESIDENTE DELLA REPUBBLICA

Promulga

Article 3 *of this law, "Application and dissemination of gender medicine in the National Health System," required the preparation of "a plan aimed at spreading gender medicine through* ***dissemination, training and indication of health practices*** *that in research, prevention, diagnosis and treatment, take into account the differences arising from gender, in order* ***to ensure the quality and appropriateness of services*** *provided by the National Health System in a uniform manner throughout the country."*

The **second part** sets out the principles and **objectives of the Plan** and is divided into the following 4 areas:

(A) Clinical pathways,
(B) Research and innovation,
(C) Professional training and refresher courses,
(D) Communication and information.

Ital J Gender-Specific Med 2019;5(3):105-107

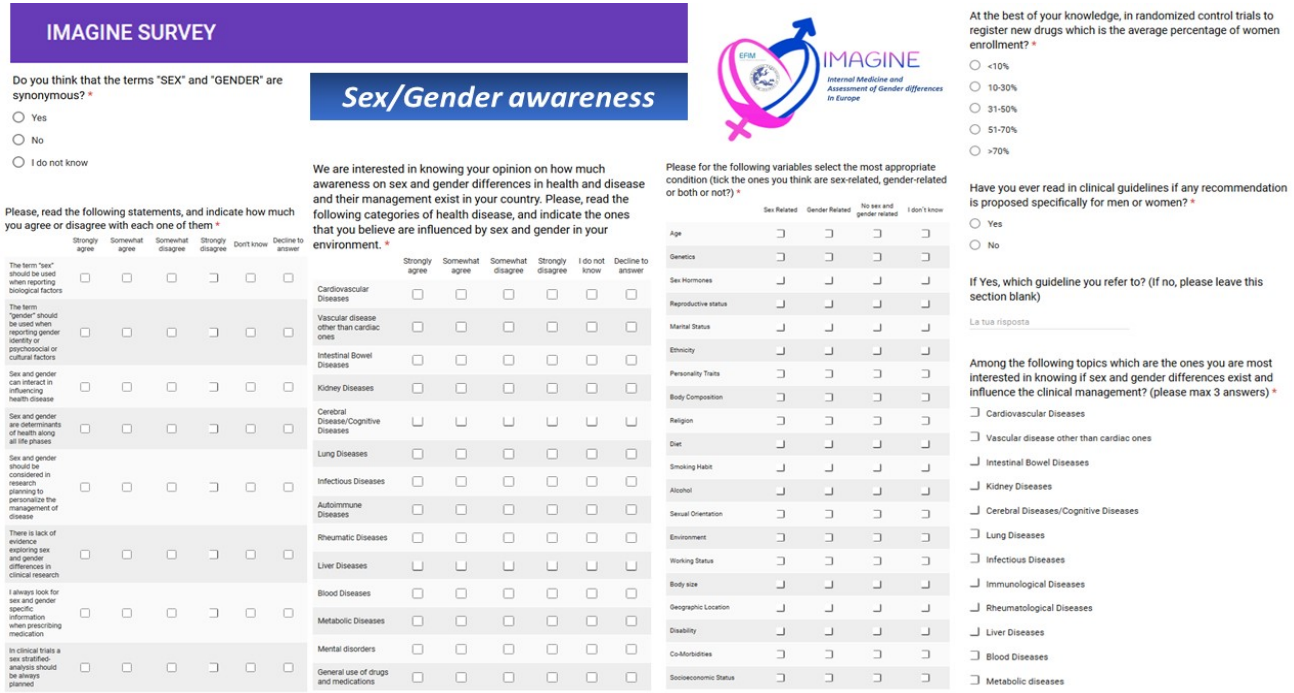
HOW TO IMPLEMENT SEX AND GENDER IN PRECISION MEDICINE

IMAGINE Working Group – to assess the awareness and knowledge of Europeans Internists

KNOWLEDGE GAP ?

A pilot electronic, anonymous survey consisted of *7 questions to explore awareness and knowledge on sex and gender in health among European Internists*

N=1323



IMAGINE SURVEY

Sex/Gender awareness

IMAGINE
Internal Medicine and Assessment of Gender differences In Europe

Do you think that the terms "SEX" and "GENDER" are synonymous? *
- Yes
- No
- I do not know

Please, read the following statements, and indicate how much you agree or disagree with each one of them *

	Strongly agree	Somewhat agree	Somewhat disagree	Strongly disagree	Don't know	Decline to answer
The term "sex" should be used when reporting biological factors						
The term "gender" should be used when reporting gender identity or psychosocial or cultural factors						
Sex and gender can interact in influencing health disease						
Sex and gender are determinants of health along all life phases						
Sex and gender should be considered in research planning to personalize the management of disease						
There is lack of evidence exploring sex and gender differences in clinical research						
I always look for sex and gender specific information when prescribing medication						
In clinical trials a sex stratified-analysis should be always planned						

We are interested in knowing your opinion on how much awareness on sex and gender differences in health and disease and their management exist in your country. Please, read the following categories of health disease, and indicate the ones that you believe are influenced by sex and gender in your environment. *

	Strongly agree	Somewhat agree	Somewhat disagree	Strongly disagree	I do not know	Decline to answer
Cardiovascular Diseases						
Vascular disease other than cardiac ones						
Intestinal Bowel Diseases						
Kidney Diseases						
Cerebral Disease/Cognitive Diseases						
Lung Diseases						
Infectious Diseases						
Autoimmune Diseases						
Rheumatic Diseases						
Liver Diseases						
Blood Diseases						
Metabolic Diseases						
Mental disorders						
General use of drugs and medications						

Please for the following variables select the most appropriate condition (tick the ones you think are sex-related, gender-related or both or not?) *

	Sex Related	Gender Related	No sex and gender related	I don't know
Age				
Genetics				
Sex Hormones				
Reproductive status				
Marital Status				
Ethnicity				
Personality Traits				
Body Composition				
Religion				
Diet				
Smoking Habit				
Alcohol				
Sexual Orientation				
Environment				
Working Status				
Body size				
Geographic Location				
Disability				
Co-Morbidities				
Socioeconomic Status				

At the best of your knowledge, in randomized control trials to register new drugs which is the average percentage of women enrollment? *
- <10%
- 10-30%
- 31-50%
- 51-70%
- >70%

Have you ever read in clinical guidelines if any recommendation is proposed specifically for men or women? *
- Yes
- No

If Yes, which guideline you refer to? (If no, please leave this section blank)

La tua risposta

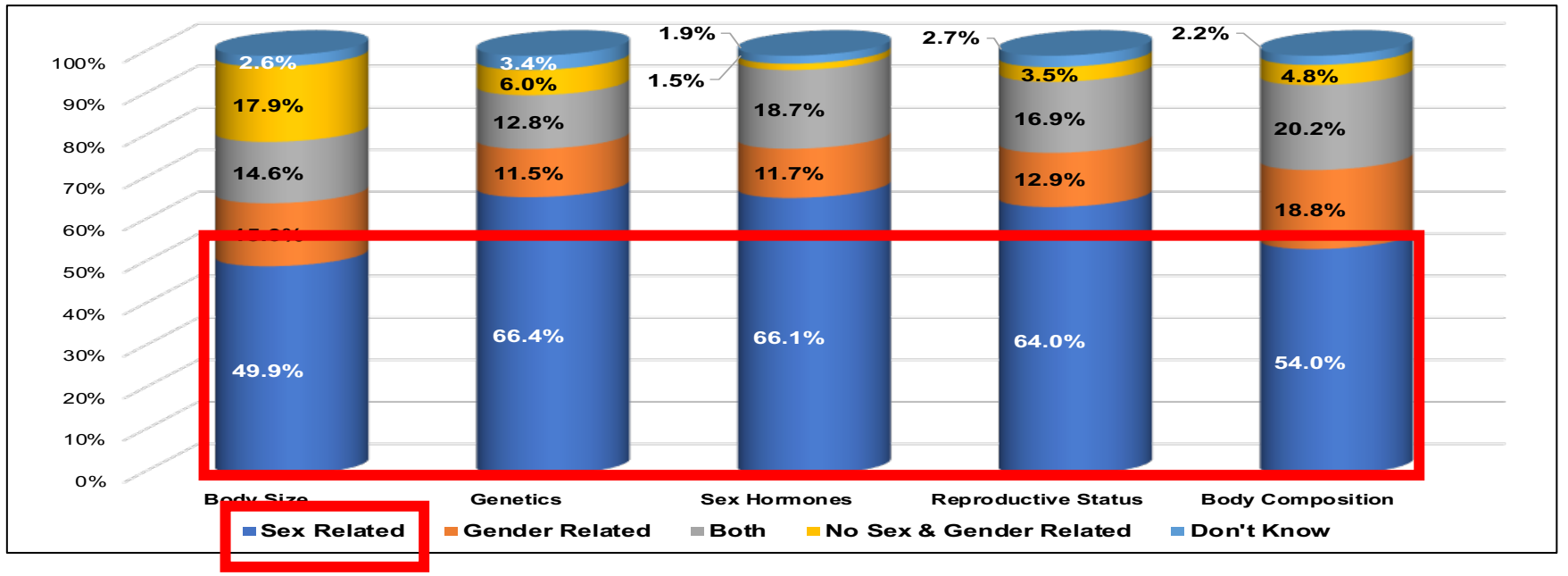
Among the following topics which are the ones you are most interested in knowing if sex and gender differences exist and influence the clinical management? (please max 3 answers) *
- Cardiovascular Diseases
- Vascular disease other than cardiac ones
- Intestinal Bowel Diseases
- Kidney Diseases
- Cerebral Diseases/Cognitive Diseases
- Lung Diseases
- Infectious Diseases
- Immunological Diseases
- Rheumatological Diseases
- Liver Diseases
- Blood Diseases
- Metabolic diseases

EFIM
www.efim.org

Marra AM, Biskup E, Raparelli V. Eur J Intern Med 2018 Feb 5


SEX
Biological attributes of humans and animals, including physical features, chromosomes, gene expression, hormones and anatomy.
d the possibilities?
Canada

<60%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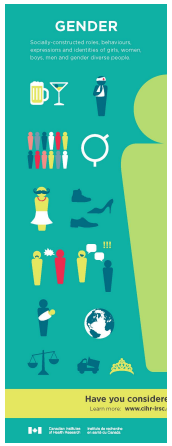
1.5%
18.7%
11.7%
66.1%
2.7%
3.5%
16.9%
12.9%
64.0%
2.2%
4.8%
20.2%
18.8%
54.0%
Body Size
Genetics
Sex Hormones
Reproductive Status
Body Composition
Sex Related
Gender Related
Both
No Sex & Gender Related
Don't Know


GENDER
Socially-constructed roles, behaviours, expressions and identities of girls, women, boys, men and gender diverse people.
Have you consider
Learn more: www.cihr-irsc
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

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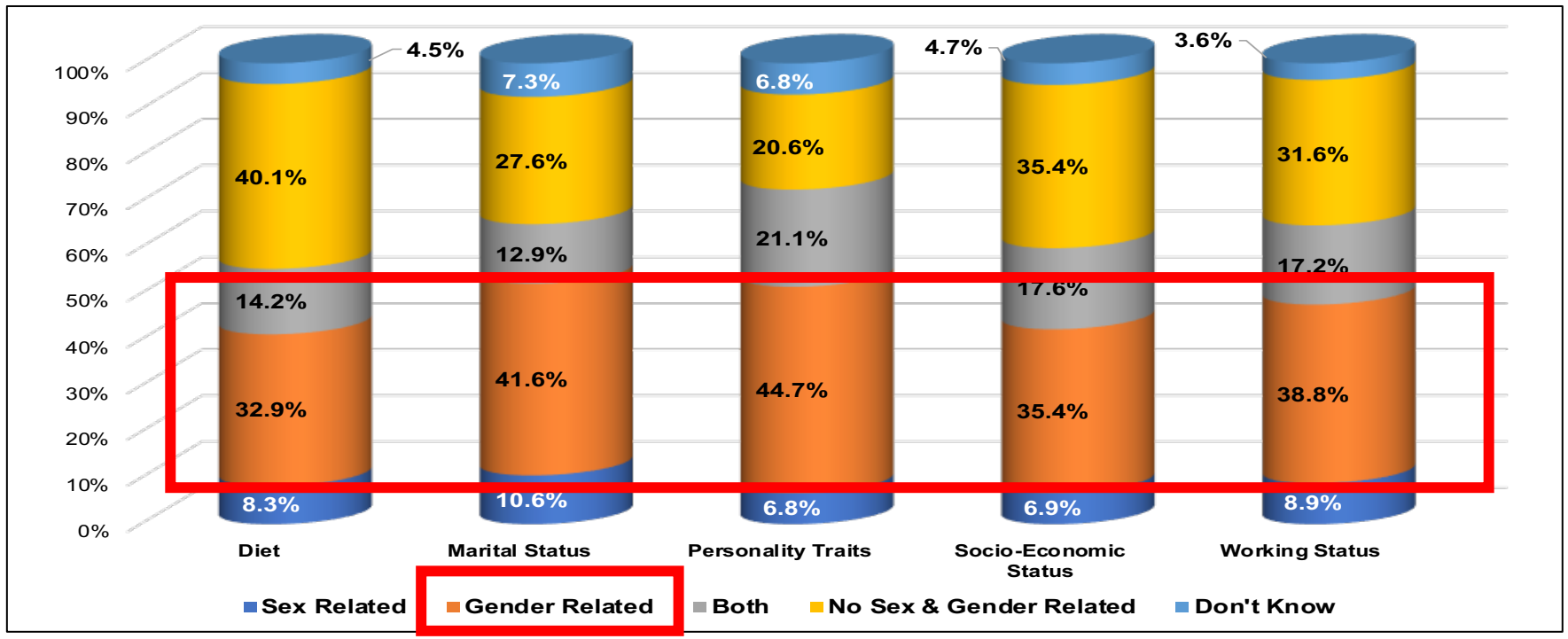
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38.8%
8.9%
Diet
Marital Status
Personality Traits
Socio-Economic Status
Working Status
Sex Related
Gender Related
Both
No Sex & Gender Related
Don't Know


EFIM
IMAGINE
Internal Medicine and Assessment of Gender differences In Europe

COMMENT & RESPONSE

Sex, Gender, and Precision Medicine

To the Editor We enthusiastically agree with the conclusion of Bartz et al[1] that sex and gender should play a central role in everyday personalized medical care. However, in our experiences as early-career physicians and scientists, we observe critical barriers to actualizing this ideal. Sex- and gender-informed approaches to care are founded on community standards appropriately representing biological sex and the complex sociocultural construct of gender. Although more research is available to provide sex-specific evidence, significant shortcomings remain in effectively implementing sex-informed care.[2] Regarding gender, a community standard could help drive basic and clinical science education for learners, clinical and translational or health services research, and, ultimately, the delivery of evidence-based gender-sensitive medical care.[3] But, to our knowledge, such a standard does not yet exist.

Some young internists, such as us, are dedicated to the study of sex- and gender-sensitive medicine. Through work done by the European Federation of Internal Medicine's Internal Medicine and Assessment of Gender Differences in Europe (IMAGINE) Working Group,[4] we are aware that in general internal medicine, there may be a less broad portfolio of sex- and gender-specific medical knowledge and skill than other medical specialties. Additionally, context matters, because in some languages, sex and gender are translated identically (eg, *geschlecht* in German). We believe that undergraduate, graduate, and continuing medical education need enhancements to account for diverse patient populations with respect to sex and gender.

Because of the lack of standard methods by which to measure gender, research and health care delivery may be significantly hampered when focused on sex- and gender-diverse individuals. Fortunately, international funding agencies in Europe, Canada, and the US are increasingly issuing grant calls aimed at incentivizing sex- and gender-informed research. Without these data, we face a bottleneck in advancing basic, translational, and clinical scientific knowledge about the intersectionality of sex and gender with other aspects of human health. There is an abundance of literature that identifies shortcomings of clinical guidelines as they apply to minority demographic patients due to exclusion criteria or selective recruitment; this also applies to sex- and gender-diverse individuals,[2,5] who, if not represented in the data, do not benefit from the latest scientific research.

Learning to practice medicine with attention to individual diversity is an essential competency of the medical profession. As we envision our long careers ahead, we imagine being able to deliver to patients—of all sexes and genders—personalized, high-quality care as developing scientific knowledge guides increasingly sex- and gender-informed approaches to care.

Ewelina Biskup, MD
Valeria Raparelli, MD, PhD
Tiffany I. Leung, MD, MPH

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Correction: This article was corrected on June 17, 2020, to add a potential conflict of interest disclosure.

Conflict of Interest Disclosures: Dr Biskup reports being a volunteer member of the executive board of the Women's Brain Project, an international nonprofit organization advocating for and carrying out research on gender differences in brain and mental health diseases. No other disclosures were reported.

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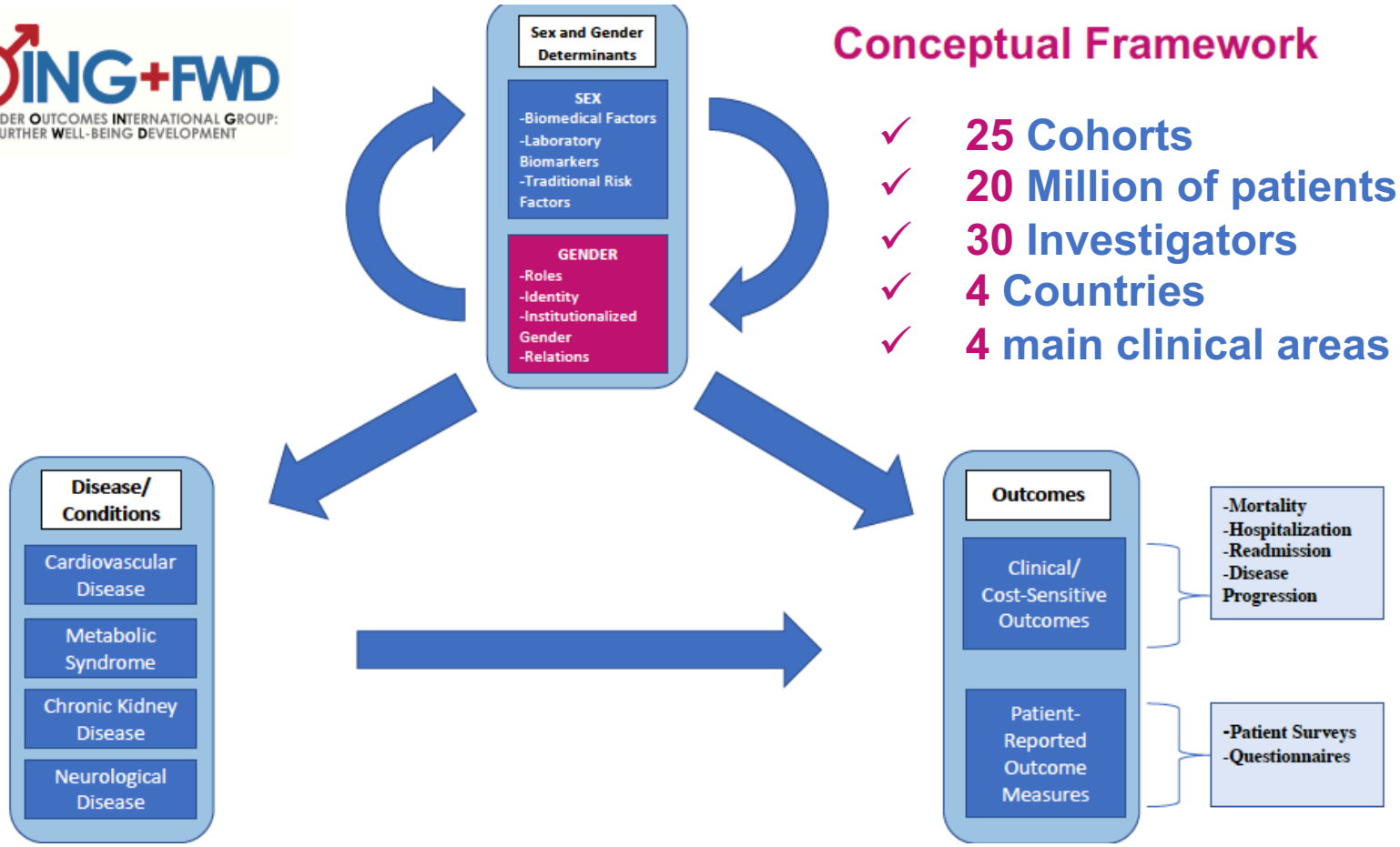
MEASURES GAP?

JAMA Internal Medicine Published online June 8, 2020

HOW TO IMPLEMENT SEX AND GENDER IN PRECISION MEDICINE

The GOING-FWD (Gender Outcomes INternational Group: to Further Well-being Development) Project

GOING+FWD
GENDER OUTCOMES INTERNATIONAL GROUP: TO FURTHER WELL-BEING DEVELOPMENT



Conceptual Framework

- ✓ 25 Cohorts
- ✓ 20 Million of patients
- ✓ 30 Investigators
- ✓ 4 Countries
- ✓ 4 main clinical areas

MULTIDISCIPLINARY TEAM

MD (Cardiology, Neuroscience, Endocrinology, Nephrology, etc), PhD, Nurses, Post-Docs, Epidemiologist, Biostats, Computer Scientists, Social Scientists, Gender Champions

STAY TUNED

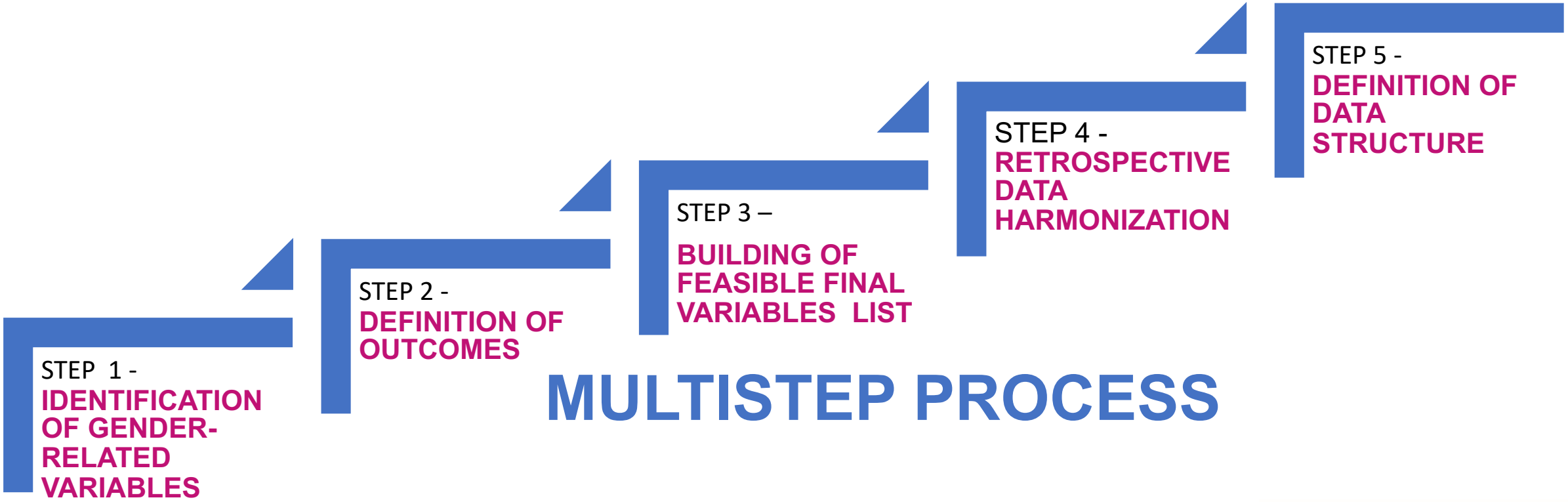
https://www.mcgill.ca/going-fwd4gender/

UNIVERSIDAD DE MURCIA · MEDICAL UNIVERSITY OF VIENNA · McGill · UNIVERSITY OF ALBERTA · Karolinska Institutet · GENDER·NET Plus Promoting gender equality in H2020 and the ERA

HOW TO IMPLEMENT SEX AND GENDER IN PRECISION MEDICINE

The GOING-FWD Methodology for RETROSPECTIVE DATA

We developed a standard methodology that can be applied in pre-existing cohort studies for the *integration of gender-related factors in assessing their impact on health outcomes*



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GENDER OUTCOMES INTERNATIONAL GROUP: TO FURTHER WELL-BEING DEVELOPMENT

STEP 1- IDENTIFICATION OF GENDER-RELATED VARIABLES

Work Package 1
Aim: Identification GENDER-RELATED VARIABLES
- C. Norris & team (CAN)

WISH LIST 1

Roles
Primary earner status
Employment Status
Occupation
Paid Work hours per week
Unpaid work hours per week(eg care giver hours)
Full/part time work
Child caregiver responsibilities The individual or others
Adult caregiver responsibilities
Number of hours per week spent on housework
Status of household's primary responsibility
Number of children
Relations
Marital/Relationship Status
Family or local network (social capital)
Social support
Social support (any recognized social support instrument)
Availability of Caretaker (for self)
Institutionalized variables
Educational Level
SES/Income
Monthly finances
Income (personal, household)
Number of persons living in household
Retirement eligibilities
Perceived Social Standing Questionnaire *McArthur Scale
GII (Gender inequality index) Questionnaire *
Maternity Paternity related variables

Identity
Stress
14-Item Perceived stress scale (PSS) *
Stress level at work (any measure of stress)
Stress level at home (any measure of stress)
Stress management
Personality traits
Emotional intelligence Questionnaire *
Any validated measures of personality (NEO classic 5 personality traits
BEMS (instrument) measurement of gender identity
Depression/Anxiety
Patient Health Questionnaire-9 *
HAD Scale - Hospital Anxiety and Depression Scale*
Anxiety/Depression any scale
Childhood trauma (reported history)
Discrimination
Day-to-day experiences
Perceived bias
Stigmatization
Violence (hx or present)
Intimate partner domestic
Ethnic violence
Sexual orientation
Immigration Status
Behavioral/Lifestyle Risk Factors
European Health Determinants Module
Current smoking
Smoking history
Cigarettes per day
Physical activity
Physical activity (self-reported: PPAQ)
Physical activity (accelerometer)
Food diary - Diet quality index
Alcohol consumption
Substance use (Use of drugs)
Nutrition
Overall diet quality index
Physical activity barriers (fatigue, lack of motivation, etc.)
Nutrition barriers (enpensiveness, lack of motivation, etc.)
Physical activity facilitators (social support, self-motivation, etc.)
Nutrition facilitators (social support, self-motivation, etc.)

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WISH LIST 2

STEP 2 - DEFINITION OF OUTCOMES

Work Package 2
Aim: Identification of Cost-Sensitive and PROMs
- K. Humphries & Team (CAN)
- A. Kautzy-Willer & Team (AUT)

- ✓ Each of the cohort data dictionaries were screened for outcomes of interest outlined in the GOING FWD proposal

- ✓ Clinical Outcomes and Patient-Reported Outcome Measures (specific for disease)

Diabetes

Chronic Kidney Disease

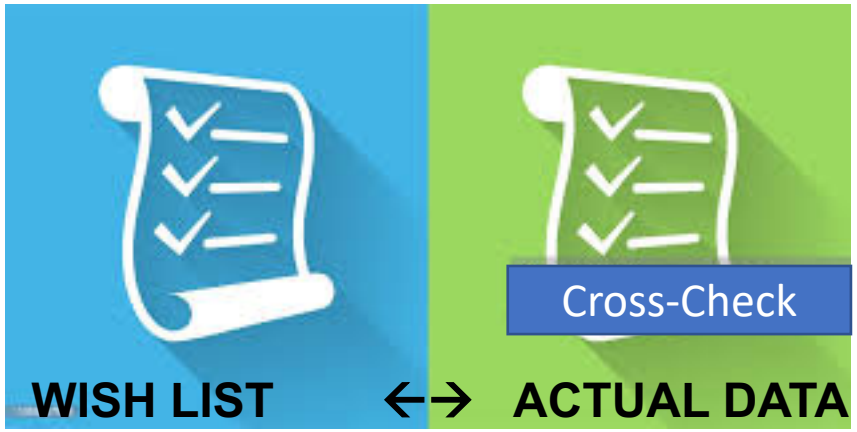
Coronary Artery Disease

Patient Reported Outcome Measures (PROMs)
Measures impact of an illness or health condition from the **patient's perspective**
Examples: quality of life, symptom severity, functional status, health status
Used to monitor the progress of a health condition or whether a treatment has been effective by comparing results over time
Measured from the patient's perspective, usually via questionnaires
Used together to assess quality of care and services from patient's viewpoint

STEP 3 - BUILDING OF FEASIBLE FINAL VARIABLE LIST

- ✓ A **cross-validation** (double blinded) between variables (i.e. gender-related factors and outcomes) available per database (data dictionary) was performed.

- ✓ In case of disagreement or discordant definitions of variables, a **more inclusive approach** was pursued for both gender-related variables and outcomes.



STEP 4 - RETROSPECTIVE DATA HARMONIZATION

HARMONIZATION - Process of bringing together data of varying formats in order to generate **one cohesive data set**

Finally, a list of harmonized variables will be created using the Maelstrom Research guidelines for rigorous retrospective data harmonization and merging when possible.

mælstrom

International Journal of Epidemiology, 2017, 103–115
doi: 10.1093/ije/dyw075
Advance Access Publication Date: 5 June 2016
Original article

Methodology

Maelstrom Research guidelines for rigorous retrospective data harmonization

Isabel Fortier,[1]* Parminder Raina,[2] Edwin R Van den Heuvel,[3] Lauren E Griffith,[2] Camille Craig,[1] Matilda Saliba,[1] Dany Doiron,[1] Ronald P Stolk,[4] Bartha M Knoppers,[5] Vincent Ferretti,[6] Peter Granda[7] and Paul Burton[8]

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Accepted 16 March 2016

Abstract

Background: It is widely accepted and acknowledged that data harmonization is crucial: in its absence, the co-analysis of major tranches of high quality extant data is liable to inefficiency or error. However, despite its widespread practice, no formalized/systematic guidelines exist to ensure high quality retrospective data harmonization.
Methods: To better understand real-world harmonization practices and facilitate development of formal guidelines, three interrelated initiatives were undertaken between 2006 and 2015. They included a phone survey with 34 major international research initiatives, a series of workshops with experts, and case studies applying the proposed guidelines.
Results: A wide range of projects use retrospective harmonization to support their research activities but even when appropriate approaches are used, the terminologies, procedures, technologies and methods adopted vary markedly. The generic guidelines outlined in this article delineate the essentials required and describe an interdependent step-by-step approach to harmonization: 0) define the research question, objectives and protocol; 1) assemble pre-existing knowledge and select studies; 2) define targeted variables and evaluate harmonization potential; 3) process data; 4) estimate quality of the harmonized dataset(s) generated; and 5) disseminate and preserve final harmonization products.
Conclusions: This manuscript provides guidelines aiming to encourage rigorous and effective approaches to harmonization which are comprehensively and transparently documented and straightforward to interpret and implement. This can be seen as a key step

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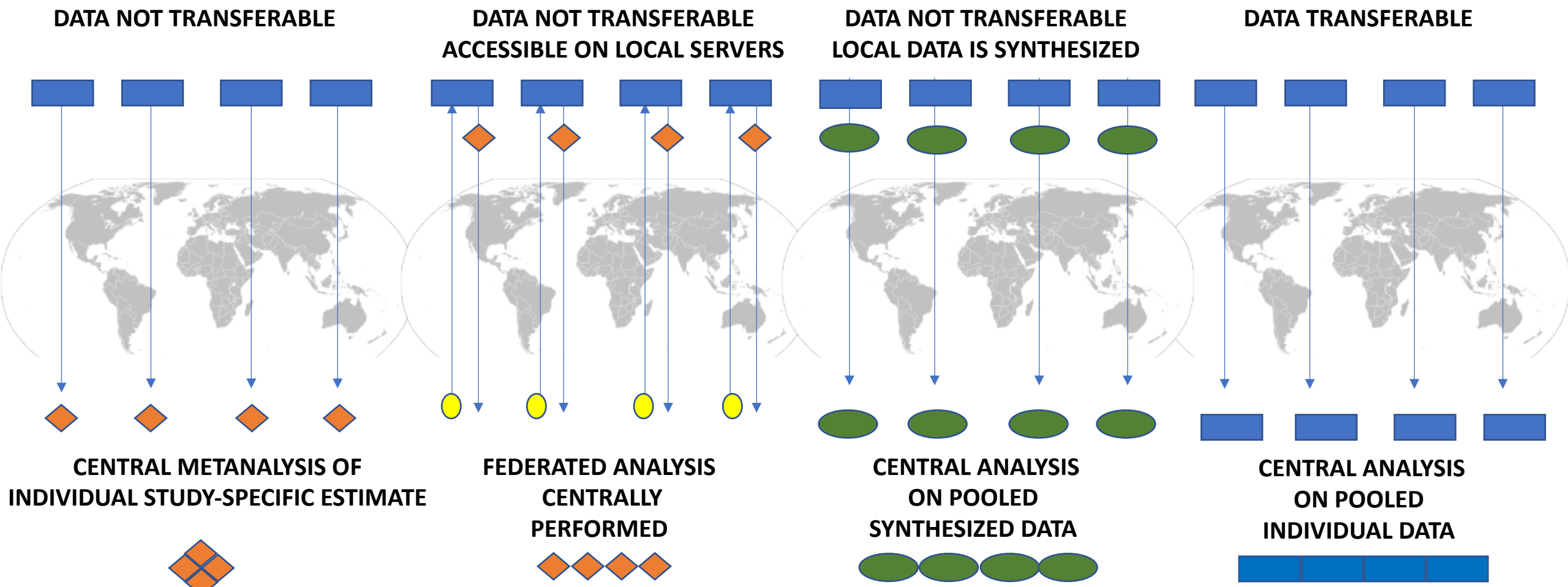
STEP 5 – DEFINITION OF DATA STRUCTURE

Depending on the type of database, each partner then provided the data management structure and the analysis plan based on the following options:



HOW TO IMPLEMENT SEX AND GENDER IN PRECISION MEDICINE

Methods for Prospectively Incorporating Gender into Health Sciences Research

1: Research Question Development - Is gender relevant?

- Yes, study involves humans
- No, study involves animals or cells

2: Which gender domains/scales may influence relationship of interest (may be one or many)?

- Gender Identity (identifying as a man, woman or gender-diverse person)
- Gender Roles (behaviours and roles fulfilled)
- Gender relations (interpersonal relationships and gender)
- Institutionalized Gedner (unequal distribution of power, resources or opportunites in society based on gender)

3: Which specific variables may influence the relationship of interest and can be collected (one or many from one or many domains)?

- consider specific gender-related variables relevant to population and/or outcomes studied
- consider whether any specific gender-relted variable may indirectly affect the independent variables of interest
- consider conceptual framework/pathways through which these variables may act

4: Do collected variables need to be reduced?

- many collected (particularly within same domain/scale)
- variables highly correlated

5: Incorporate collected variables into statistical analysis

- gender variables may directly independently affect ourcome of interest (treat as main effect)
- gender variables may modify or mediate outcome of interest (treat as mediating/modifying factors)
  - explore correlations among main independent variables, gender-related variables and outcomes
  - explore interaction terms, particularly among scales and among main independent variable, gender-related variables and outcomes

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MEASURES GAP?

Have you ever considered the possibilities?

J Clin Epidemiol. 2020 Sep 24:S0895-4356(20)31104-5.

How does gender add value to your work as a healthcare provider or scientist in the era of *precision medicine*?

HOW TO CHANGE YOUR PERSPECTIVE TOWARDS SEX, GENDER AND PRECISION MEDICINE

GET INSPIRED BY EXPERTS IN SEX, GENDER, AND LIFE SCIENCES

Gender has added a new dimension to my clinical practice and I think it has **improved the care I deliver**
(Louise Pilote)

We will not truly provide precision medicine until we ***understand the psycho-social/cultural factors that enhance or worsen outcomes***
(Collen n. Norris)

I know I'm living up to my professional role as a cutting-edge 21st century physician and healer when I ask 'have I correctly documented the ***sex/gender of my patient****, reflected on* ***sex differences in pathophysiology*** *or* ***gender biases*** *in testing, and prescribed/deprescribed treatments in a* ***holistic, personalized*** *manner'? for every patient I see*
(Cara Tannenbaum)

Through *the collection and measurement of* ***both sex and gender related factors****,* ***we can move the needle on the most vexing challenges we face in healthcare today***
(Rachel P. Dreyer)

I am always surprised how little we know about *the underlying* ***mechanisms***
(Christian Delles)

HOW TO CHANGE YOUR PERSPECTIVE TOWARDS SEX, GENDER AND PRECISION MEDICINE

GET INSPIRED BY EXPERTS IN SEX, GENDER, AND LIFE SCIENCES

*Analyzing gender gives me the opportunity to **bring the social context of people´s lives into biomedical research**.*
(Sabine Oertelt-Prigione)

*Uncertainty is here to stay and this "new normal" necessitates **implementation of gender dimension to deliver value that is relevant for health of humans***
(Karolina Kublickiene)

*By integrating sex and gender analysis into their work, researchers **can enhance excellence and social responsibility in science and engineering***
(Londa Schiebinger)

*Gender attention not only give value, but it is **indispensable in an MD daily practice,** it is **unethical** to work without considering differences*
(Giovannella Baggio)

*Integrating gender in my clinical practice and in my research helps me better understand and treat my patients and **transforms my knowledge and practice beyond medicine***
(Carole Clair)

«The secret of change is to focus all of your energy, not on fighting the old, but **building on the new**»
Socrate (470-399 BC)