È iniziata l'era della medicina di genere anche in gastroenterologia?

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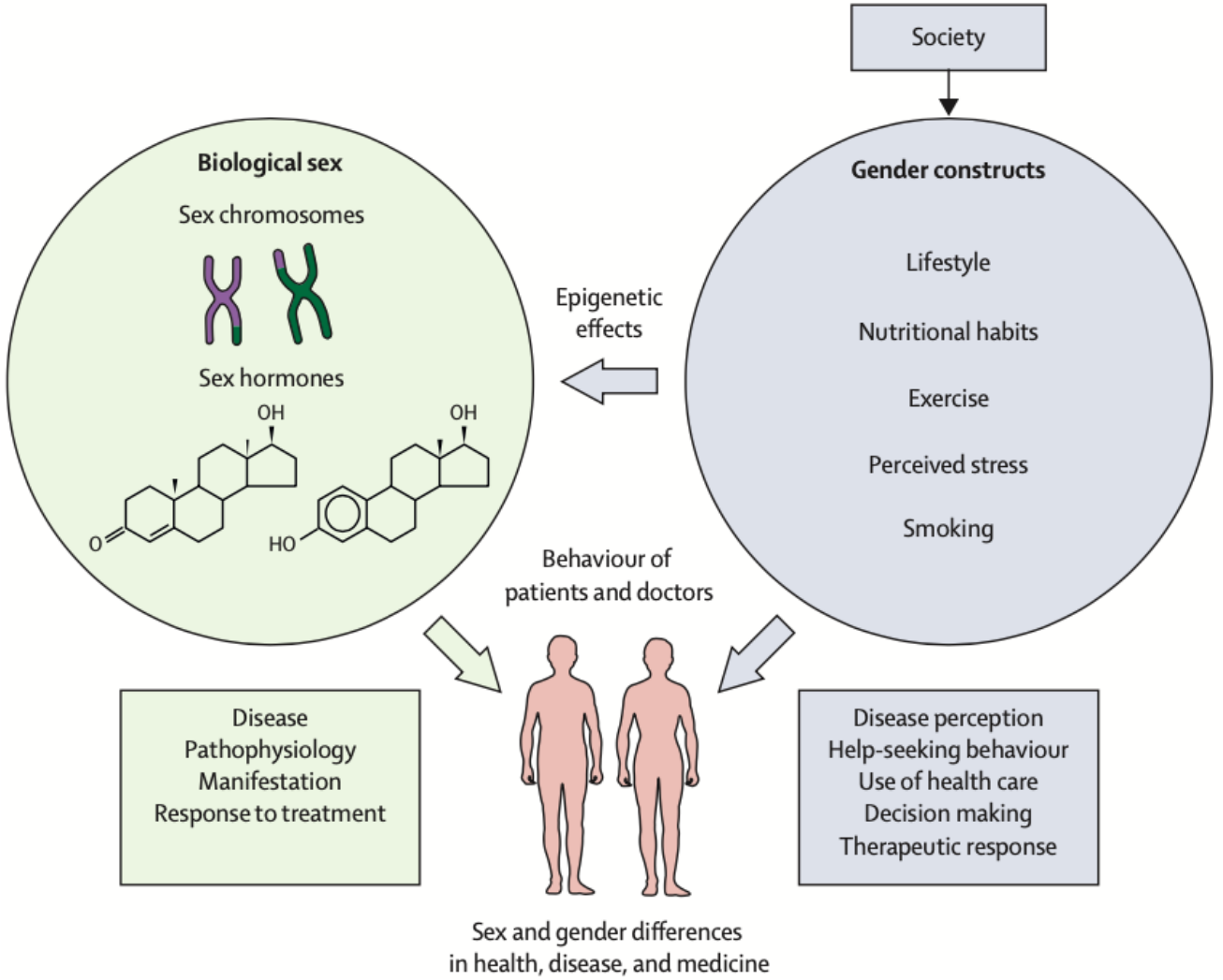
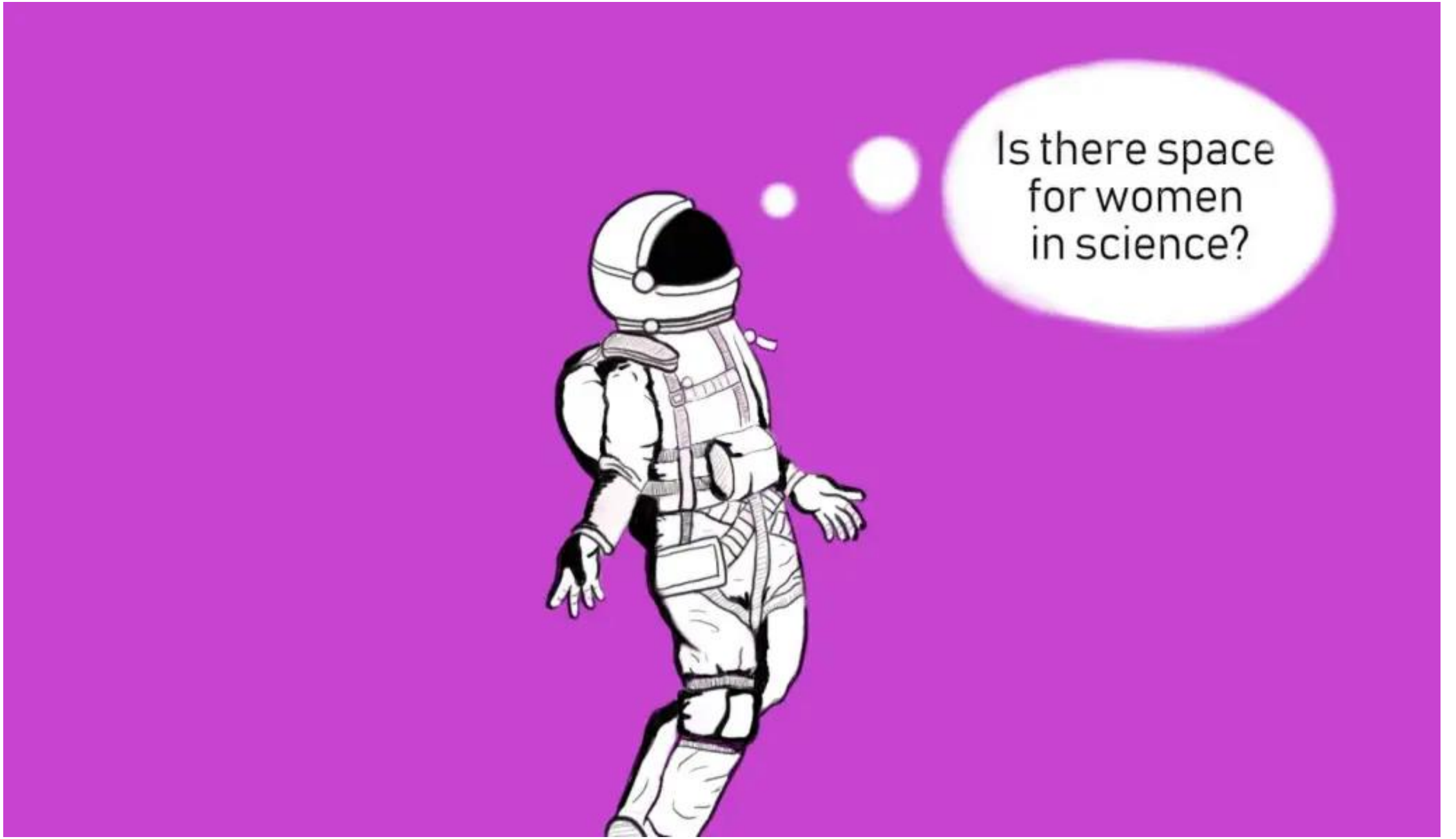
What is gender medicine?

Gender Medicine is the study of the influence of biological (defined by sex) and socio-economic and cultural (defined by gender) differences on the state of health, disease, prognosis and response to treatment of each person.

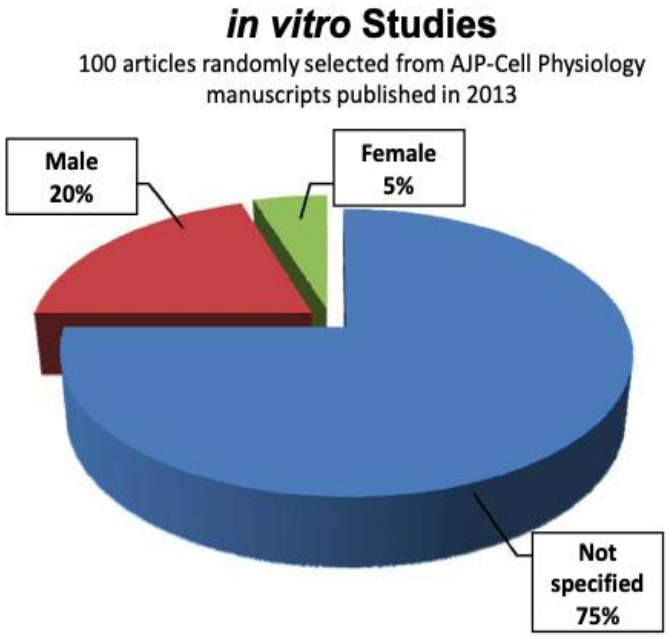
The World Health Organization (WHO) defines SEX the different biological and physiological males and females characteristics and GENDER the socially constructed characteristics of women and men, such as norms, roles, behaviours and relationships (It varies from society to society)

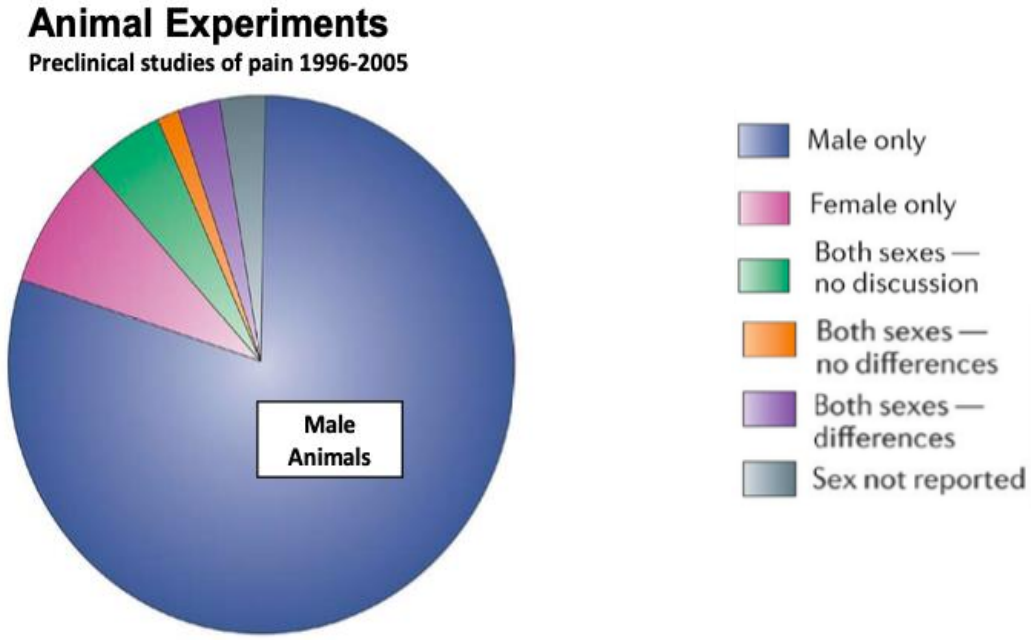


Gender is hierarchical and produces inequalities that intersect with other social and economic inequalities!!!


Is there space for women in science?

The Knowledge Gap: Androcentric approach of medicine





76% (non specified)	80% (male)	67% (men)	51% (female population)
Cellular studies	Animal models	Clinica Studies	Global population

Shak et al, Am J Physiol-Cell Physiology. 2014
Mogil, Nature Reviews Neuroscience. 2012
Buch et al. , Journal of Mol. Med., 2019

1991, The starting point: Yentl syndrome

THE NEW ENGLAND JOURNAL OF MEDICINE July 25, 1991

The New England Journal of Medicine

BERNADINE HEALY, M.D.

THE YENTL SYNDROME

YENTL, the 19th-century heroine of Isaac Bashevis Singer's short story,[1] had to disguise herself as a man to attend school and study the Talmud. Being "just like a man" has historically been a price women have had to pay for equality. Being different from men has meant being second-class and less than equal for most of recorded time and throughout most of the world. It may therefore be sad, but not surprising, that women have all too often been treated less than equally in social relations, political endeavors, business, education, research, and health care.

Yentl, the 19th-century heroine of Singer's short story, had to disguise herself as a man to attend school and study the Talmud.

This Editorial of *New England Journal of Medicine* highlighted the discrimination of women in cardiology: women who were hospitalized for coronary heart diseases underwent fewer major diagnostic and therapeutic procedures than men

N Engl J Med 1991; 325:274-276

Cardiovascular diseases

Epidemiology

- CHD is the leading killer of women > 65 ys
- The in-hospital mortality of an IMAis higher in F than in M up to 70 years of age and survival after 6 months is lower in F
- Hypertension, smoking, and diabetes are associated with higher hazard ratios for myocardial infarction in women than in men

Clinical aspects

- F are less likely than men to have typical angina and are more likely to have atypical or non-anginal pain
- Coronary angiography in women may show no evidence of atherosclerotic coronary artery disease because of the frequent involvement of microvascular circulation

Response to treatment

- Compared with M, F suffering from ischaemic heart disease are less likely to receive evidence-based treatment and when suffering from acute myocardial infarction, they are less likely to receive reperfusion
- Greater drug toxicity in women
- The increased bioavailability and decreased clearance of some drugs in women
- Aspirin resistance is more common in F than M

Franck Mauvais-Jarvis et Al Lancet 2020; 396: 565–82

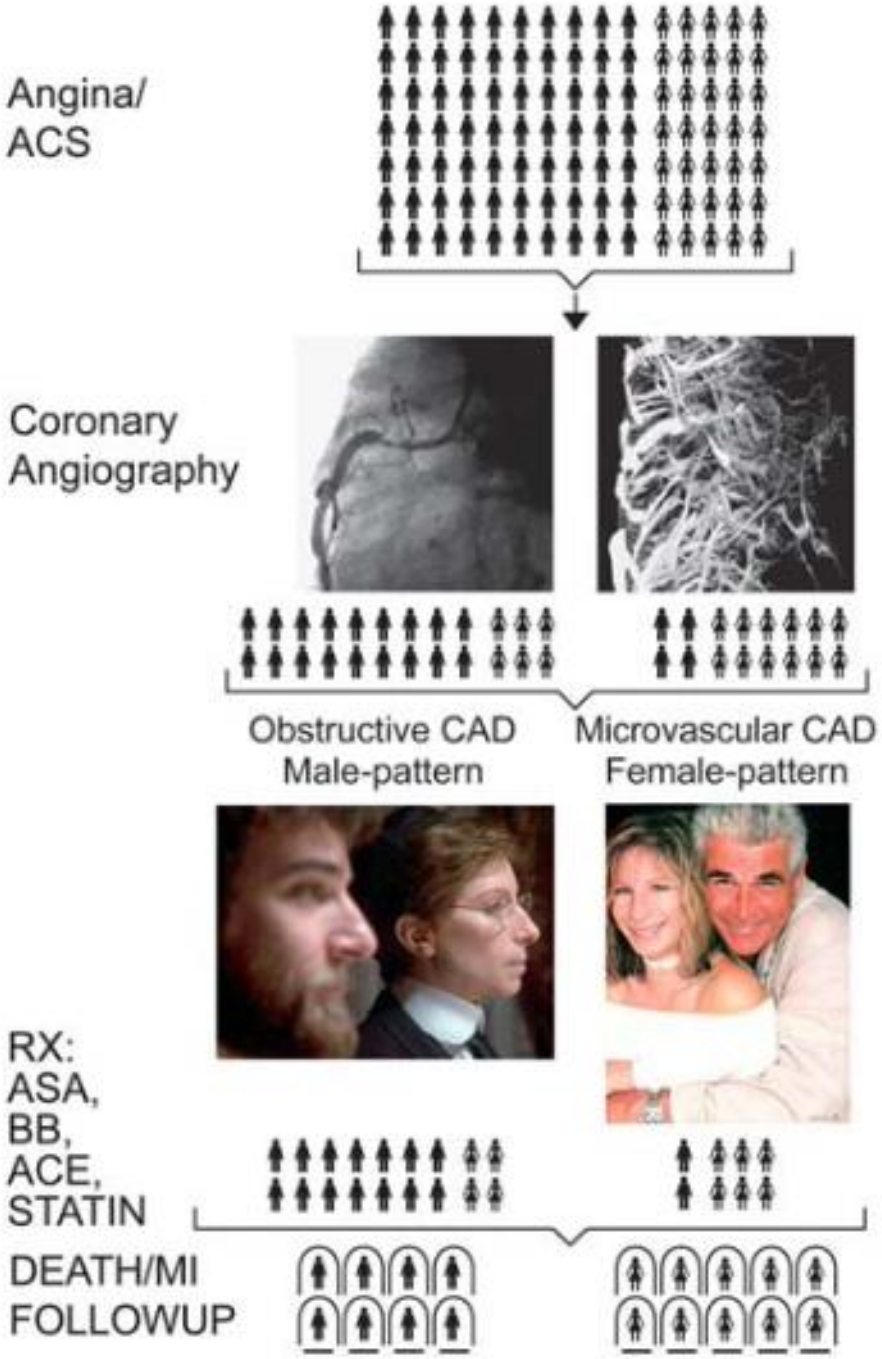
nature

www.nature.com/nature

Vol 465 | Issue no. 7299 | 10 June 2010

Putting gender on the agenda

Biomedical research continues to use many more male subjects than females in both animal studies and human clinical trials. The unintended effect is to short-change women's health care.



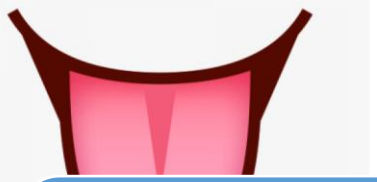
The Yentl syndrome is alive and well!

Treatment selection and the outcomes acute coronary syndrome (ACS) and angina by sex

European Heart Journal (2011) 32, 1313–1315


Female mice liberated for inclusion in neuroscience and biomedical research
Sex Differences in Outcome Measures After Stroke
Offline: Gender and global health—an inexcusable global failure
Osteoporosis Significantly Underdiagnosed, Undertreated in Men
THE PAIN GAP
Geschlecht in der Medizin: ein Thema mit vielen Facetten
Are Women Less Likely to Receive High-Intensity Statins After MI?
Pharmacologic Research in Pregnant Women — Time to Get It Right
Inequality in medicine
More Women Dying Of Heart Disease, Yet Men Still Get More Treatment
nature medicine
Accounting for sex in the genome
Myocardial Infarction in Young Women
An Unrecognized and Unexplained Epidemic
Adverse Drug Reactions to Guideline-Recommended Heart Failure Drugs in Women
Women With Heart Failure
Unheard, Untreated, and Unstudied*
Eating Disorders in Men: Underdiagnosed, Undertreated, and Misunderstood
Deutscher Herzbericht
Das schwache Herz der Frauen
Women With Acute MI Less Likely to Survive or Receive Guideline-Recommended Care
The influence of sex and gender on immunity, infection and vaccination
Sex Difference in STEMI Survival Persists into Modern Stenting Era
Biology and bias: do we have the will to improve cardiovascular disease outcomes for women?
Minor Stroke, TIA Diagnosis More Often Missed in Women
Outcomes in liver transplantation: Does sex matter?
doi:10.1093/eurheartj/ehz146
Clinical trial enrolment favours men
Gender Gap Still Wide Open as US Data Show Men Have Consistently Better PCI Outcomes
Women Twice as Likely to Develop Depression After Stroke
Women's Alzheimer's going undiagnosed because of better memory for words, study indicates
FDA Takes Action on Ambien; Concedes Women at Greater Risk
THE YENTL SYNDROME
Bernadine Healy, M.D.
Sex Differences in Cardiovascular Disease and Cognitive Impairment: Another Health Disparity for Women?
Sex Differences in Efficacy and Toxicity of Systemic Treatments: An Undervalued Issue in the Era of Precision Oncology
FDA analysis: Women underrepresented in HF, CAD, ACS trials
The Feminine Face of Ischemic Heart Disease
Challenges and Opportunities*

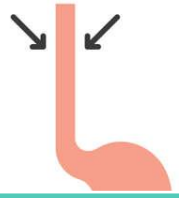
Digesting Sex and Gender: Gastroenterology



TONGUE

More women than men can be classified as “super tasters,” tasting both bitter and sweet foods more intensely

More women can detect certain tastes at lower concentrations than men

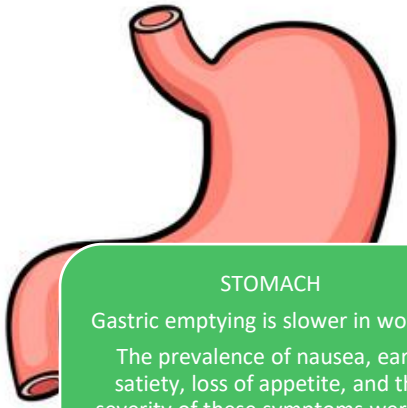


ESOPHAGUS

Womes are more likely to have GERD symptoms without esophagitis while symptomatic men are more likely to have Barrett’s esophagus

Men are far more likely than women (ratio of 6–8:1) to develop esophageal adenocarcinoma (in Barrett’s esophagus)

Men are also far more likely to have esophageal squamous cell carcinoma, as a result of greater prevalence of tobacco use and heavier drinking



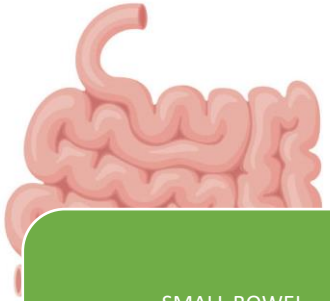
STOMACH

Gastric emptying is slower in women

The prevalence of nausea, early satiety, loss of appetite, and the severity of these symptoms were all significantly greater in women, especially obese women

Gastric cancer is twice as prevalent in men (H Pylori infection more severe)

Men were twice as likely to have peptic ulcer disease as women



SMALL BOWEL

Delayed small bowel transit is also more common in women

Rates of duodenal and small bowel malignant neoplasms are higher in men than in women, including small bowel adeno- carcinomas, neuroendocrine tumors, sarcomas, and lymphomas

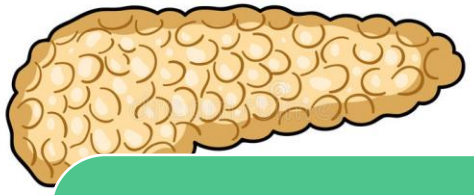
McGregor, et Al (2016). *Sex and Gender in Acute Care Medicine|Digesting Sex and Gender: Gastroenterology, 136–146*

Digesting Sex and Gender: Gastroenterology

GALL BLADDER AND BILIARY TRACT

Womes higher incidence of gallstones max during the reproductive years cholelithiasis

Men with cholelithiasis have more complications of gallstone disease than women with stones



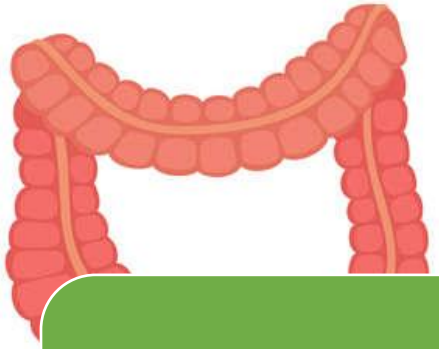
PANCREAS

More men than women develop alcoholic acute pancreatitis

Gallstone pancreatitis affects more women than men

Chronic pancreatitis also has a male predilection (alcholic pancreatitis)

Men are 30% more likely to develop pancreatic cancer than women



COLON AND RECTUM

Women's delayed colonic transit may con- tribute to chronic constipation seen more com- monly in women than in men

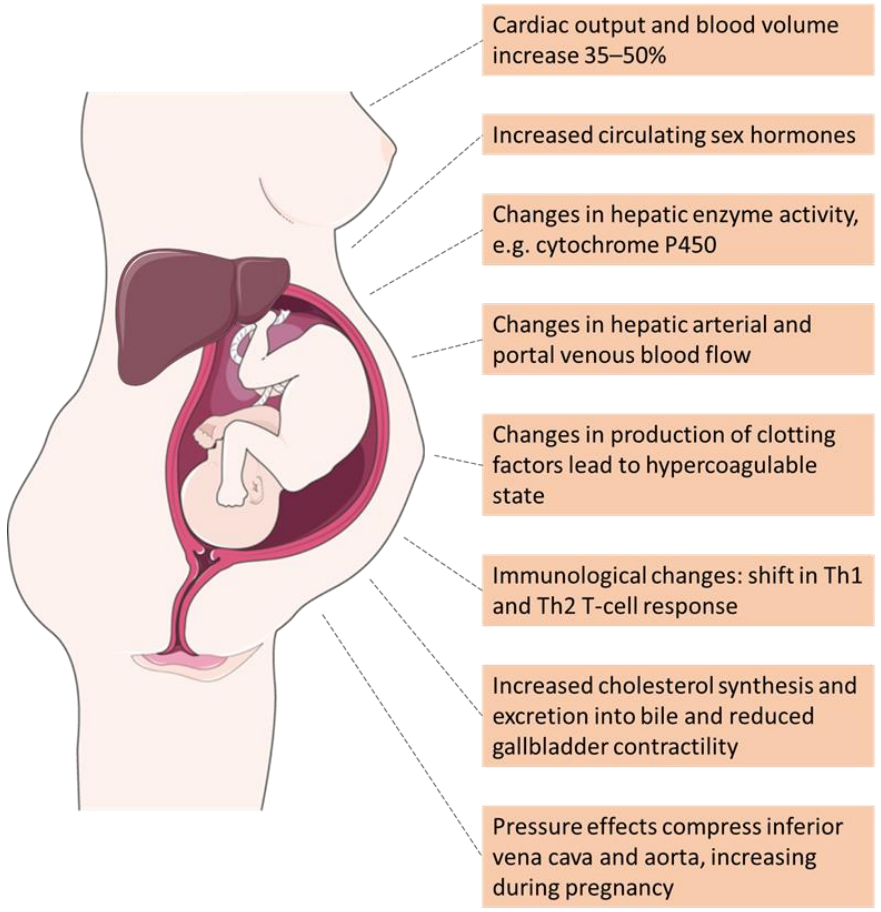
McGregor, et Al (2016). *Sex and Gender in Acute Care Medicine|Digesting Sex and Gender: Gastroenterology, 136–146*

Liver disease: does Sex Matter?

Disease	Relative Incidence Female:Male	Outcome in Women
Increased Incidence		
Autoimmune hepatitis	F/M ratio 3.6:1	Better long-term survival and outcome in M than F
Benign liver lesions		
Cavernous hemangioma	5-6:1	
Focal nodular hyperplasia	6-8:1	
Adenoma	>8-9:1	
Hepatic cyst	4:1	
Biliary cystadenoma	25:1	
Drug-induced liver injury	2:1	No survival difference
Primary biliary cirrhosis	F/M ratio 10:1	M less symptomatic than F; Concomitant autoimmune diseases more common in F (sicca syndrome, sclerodermia, raynaud phenomenon), whereas HCC complication are significantly greater in M
Decreased Incidence		
Alcohol-related liver disease	RR 3, 7 in M and 7, 3 in F	More severe Hepatic damage faster in F than M
Hepatocellular carcinoma	1:3-4	Women have improved survival from hepatocellular carcinoma
Primary sclerosing cholangitis	1:2.3	No survival difference
Similar Incidence or Conflicting Data		
Hepatitis B virus infection	Men more commonly had viral hepatitis	Less severe Men have an increased rate of decompensated cirrhosis
Hepatitis C virus infection	Men more commonly had viral hepatitis	Less severe Men have an increased rate of decompensated cirrhosis
Metabolic liver disease		Hemochromatosis less severe in women
Nonalcoholic fatty liver disease	Prevalence of MS in men and postmenopausal women	Women more likely to have diabetes and metabolic syndrome

May 2017;92(5):810-825

Pregnancy and Liver Disease



Hypertensive disorders (preeclampsia/eclampsia and the HELLP syndrome).

- Haemolysis, thrombocytopenia, and elevated liver enzymes
- Complications are DIC and acute renal failure
- Combination of immunologic maladaptation, chronic placental ischemia, an increased maternal inflammatory response to trophoblasts, and increases in inflammatory cytokines

Acute fatty liver of pregnancy (AFLP)

- Presentation involves a non-specific prodrome, nausea/vomiting, malaise, and jaundice, it can ensue, characterised by hepatic encephalopathy, coagulopathy, and hypoglycaemia
- AFLP is caused by inherited deficiencies of enzymes that are involved in the mito-chondrial metabolism of fetal fatty acids

Intrahepatic cholestasis of pregnancy (ICP)

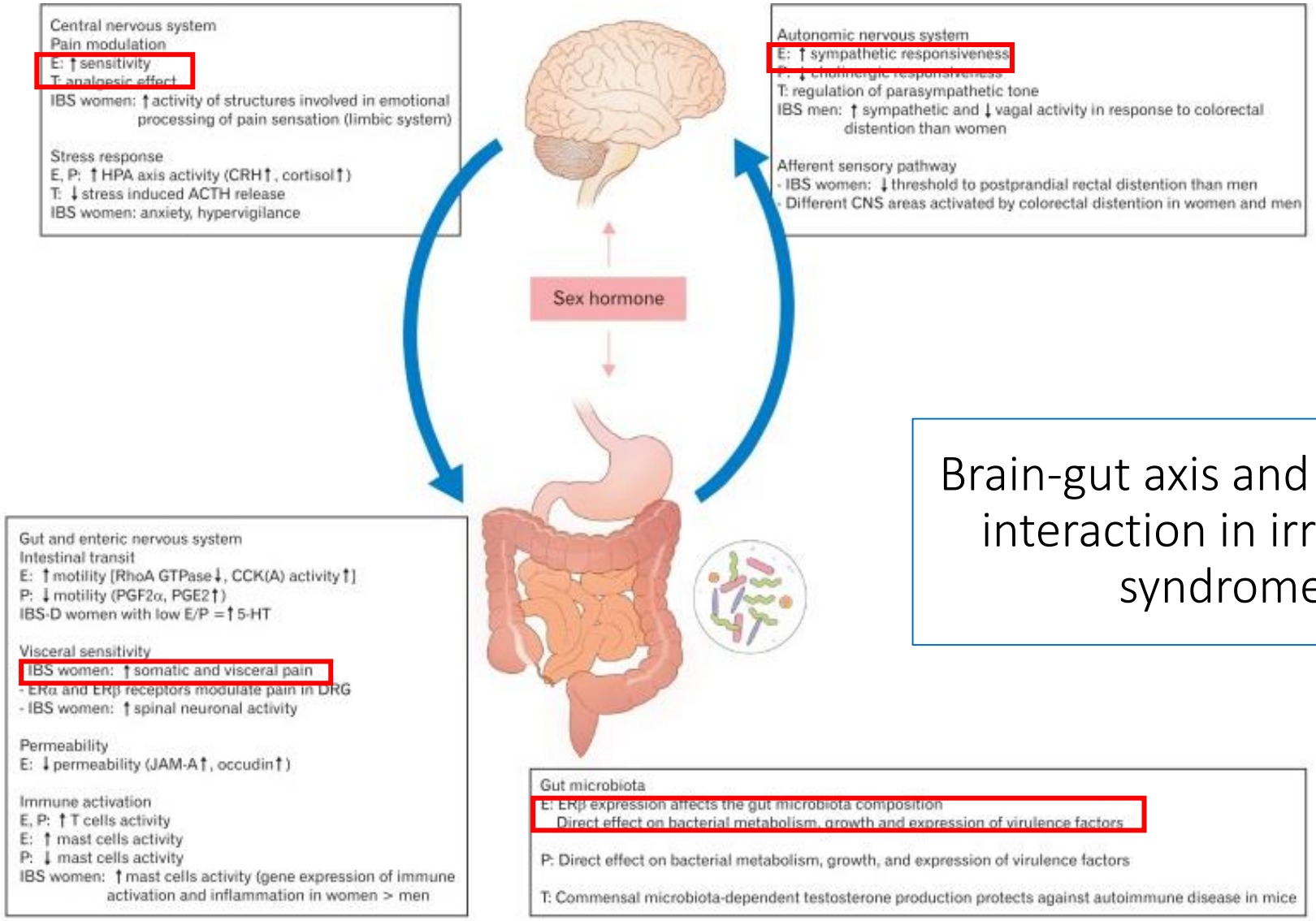
- The classic symptom of ICP is pruritus, but epigastric pain, fatigue, anorexia, and jaundice have also been observed. The typical laboratory finding in ICP is an elevation in bile acid levels. AST and ALT levels range from normal levels to 10 times to 20 times normal.
- Arises secondary to impaired excretion of bile acids

Pregnancy in Patients with Liver Disease

- **Viral hepatitis:** pregnant women are more likely to develop acute hepatitis, hepatic encephalopathy, hepatorenal syndrome, and ALF
- **Autoimmune hepatitis and cholestatic disorders:** Autoimmune hepatitis generally improves during pregnancy, but 20% of patients will experience flares
- **Cirrhosis and portal hypertension:** Portal hypertension worsens during pregnancy, which increases the risk of variceal haemorrhage
- **Gallstones:** The prevalence of gallstones is increased in pregnancy due to enhanced bile lithogenicity and stasis secondary to impaired gallbladder contractility

Top GI Illnesses Where Sex Matters in treatment evolution

IBS: does Sex Matter?



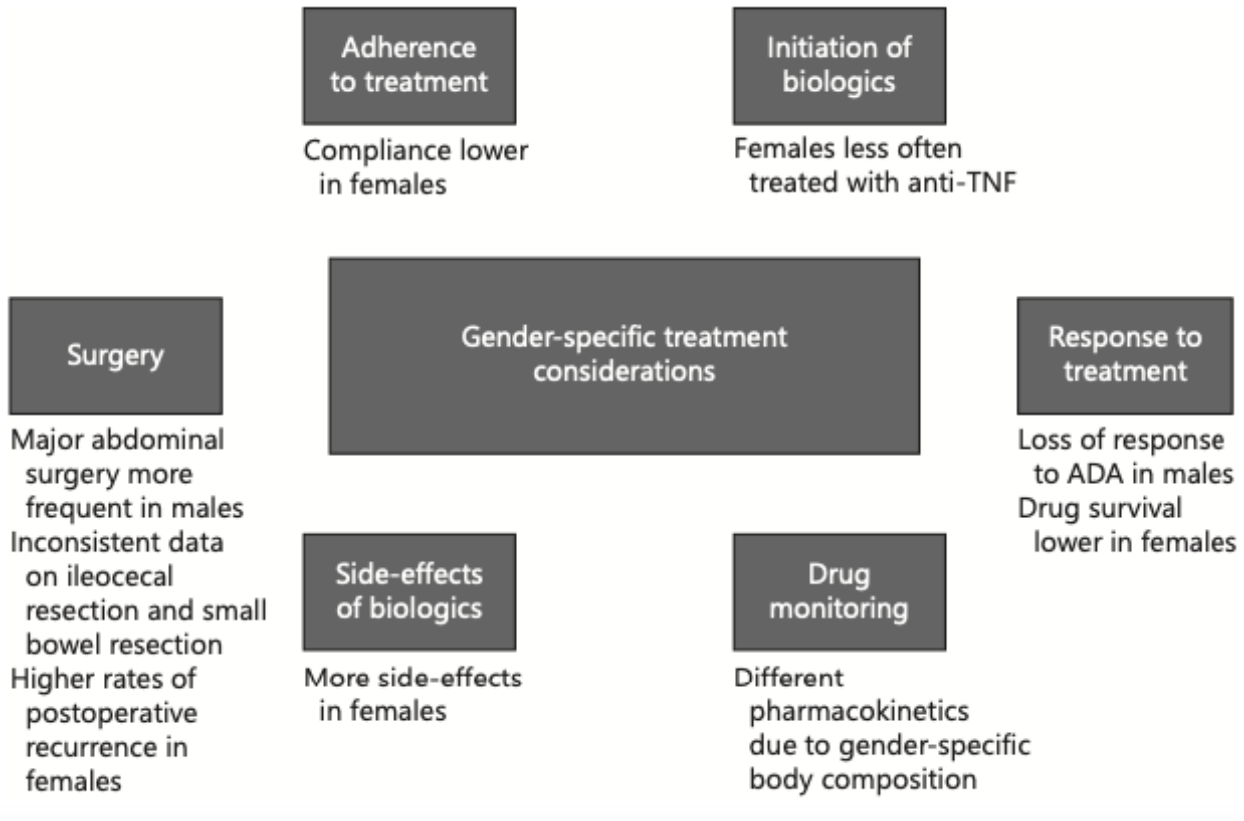
Brain-gut axis and sex hormones interaction in irritable bowel syndrome (IBS)

Kim YS, Kim N. *J Neurogastroenterol Motil*. 2018;24(4):544-558

Therapeutic target	Name	Mechanism of action	Effect of sex or gender
Loos stool (IBS-D)	Alosetron	5-HT$_3$ receptor antagonist	Currently for F with severe IBS-D. Initially improvement in F but not in M; later, effective in both M and F.
	Ondansetron	5-HT$_3$ receptor antagonist	Did not conduct separate analyses by sex.
	Cilansetron	5-HT$_3$ receptor antagonist	Significant improvement in M compared to that in F
	Tegaserod Withdrawn	5-HT$_4$ receptor agonist	Greater efficacy in F. from US market due to cardiovascular side effects.
	Ramosetron	5-HT$_3$ receptor antagonist	Initially limited to M with IBS-D; now a half-dose for F
Hard stool (IBS-C)	Lubiprostone	ClC-2 activator	Approved for F ≥ 18 yr with IBS-C; effective treatment of chronic idiopathic constipation in both M and F
	Linaclotide	Guanylate cyclase receptor agonist	Efficacious in both M and F
Altered gut microbiota	Rifaximin	Decrease in gas-producing bacteria	Did not conduct separate analyses by sex.
Visceral hypersensitivity	Anti depressant	Various	Did not conduct separate analyses by sex.
	Peppermint oil	Smooth muscle relaxe	Limited data
Bloating	FODMAP	Decreases fermentable gas-producing foods	Limited data
	Probiotics	Bacteria	Limited data
	Psychotherapy		Did not conduct separate analyses by sex

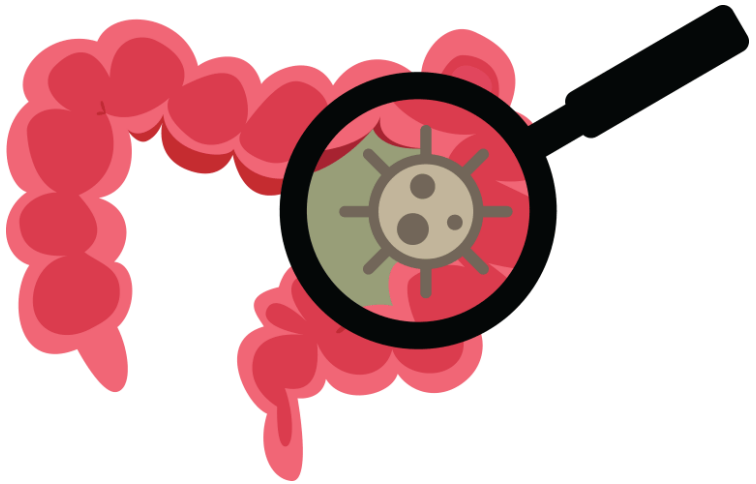
IBD: does Sex Matter?

Dimension	Gender-specific difference
Epidemiology	Higher rates of CD in females in EU and US Higher rates of CD in males in Asia Young females with lower risk for CD, older females with higher risk Older males with higher risk for UC
Environmental factors	Appendectomy and smoking in females Antibiotic use in males
Genetics	Female imprinting in familial IBD Susceptibility gene variants such as IL-23R variant L310P (protects women but not men from getting UC) X-chromosome abnormalities
Disease activity and phenotype	EIM more frequent in females Upper GI involvement in males Ileal disease more frequent in males
Disease complications	Higher risk and mortality for CRC in males Higher mortality of pulmonary complications in females Osteopenia more frequent in males
Treatment	Male gender associated with loss of response to anti-TNF Drug survival higher in males More side-effects to anti-TNF in females Adherence rates lower in females
Psychosocial factors	Depression more frequent in females Self-reported QoL lower in females Fatigue more frequent in females



Digestion 2020;101(suppl 1):98–104

Colon cancer: does Sex Matter?



- F have a lower overall incidence of CRC than M
- F over 50 years have a higher incidence of right-sided CRC, which have the worst outcomes
- Tumours from F with right-sided CRC exhibit a distinct molecular signature compared with those of F with left-sided CRC (not observed in M)
- Microsatellite instability (MSI) and BRAF mutations are observed in right-sided CRC, whereas chromosomal instability and p53 mutations are left-sided CRC
- Estrogen appears to be a protective factor against MSI, as suggested by the increased risk of MSI-high colon cancer in older women and in hormone replacement therapy
- Estrogen regulates activity ion transport functions and proliferative responses in hypoxia
- Women with right-sided CRC may have a specific metabolic and immune phenotype which accounts for differences in prognosis and treatment response.

Benedix F, et Al. Dis Colon Rectum 2010; 53: 57–64
Sun Y, et Al Transl Oncol 2020; 13: 42–56

Will be a gynocentric medicine there?

First steps for integrating sex and gender considerations into basic experimental biomedical research

Sex/Gender Toolbox for Experimental Scientists

Develop your knowledge of S/G issues

- Do a careful **literature review**. Are there known sex differences or gender disparities for the phenonmenon of interest?
- Avoid using the **terms** 'sex' and 'gender' interchangeably in your writing.

Discuss S/G where appropriate

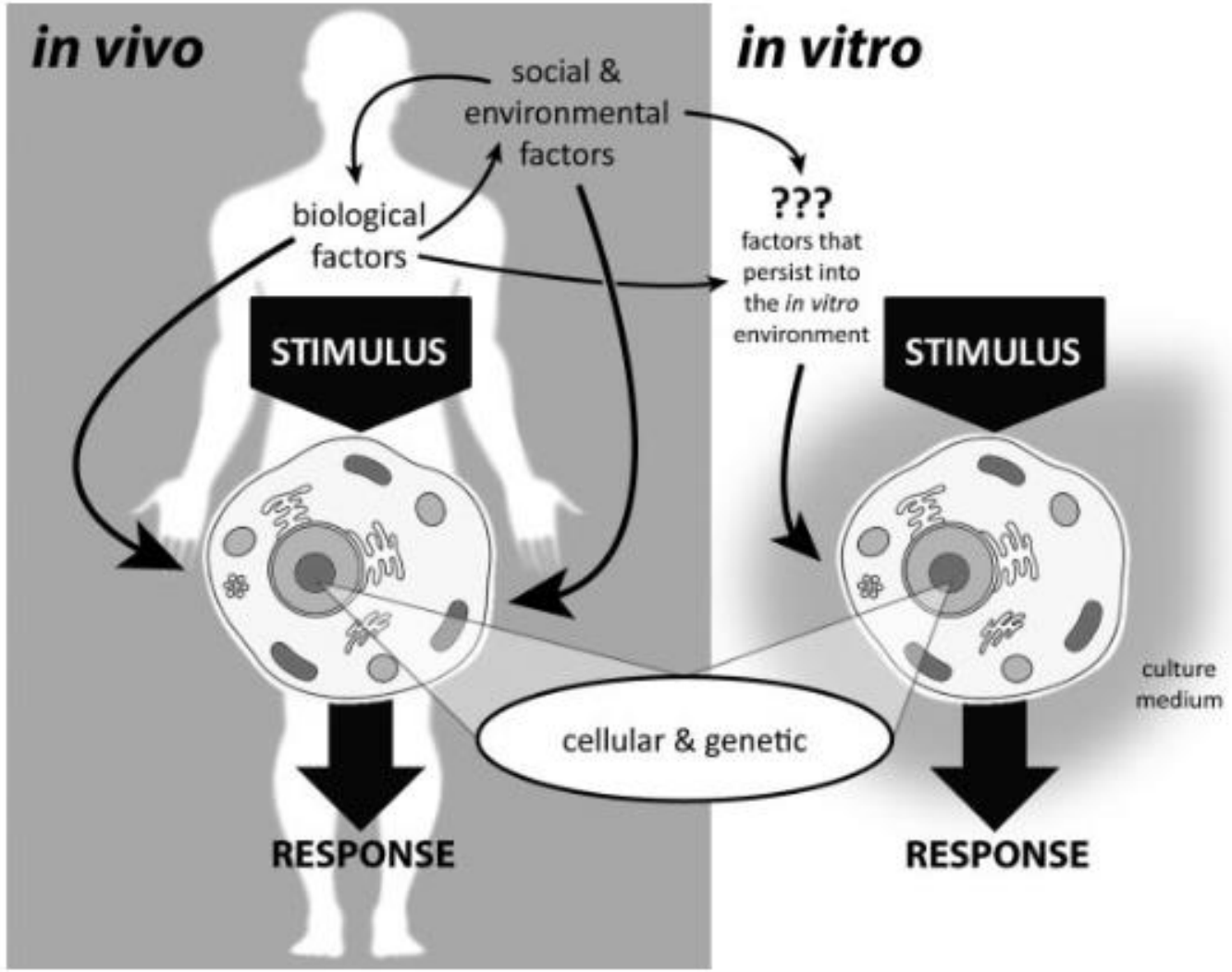
- **Always** report the sex of the cells, tissues, animals, or subjects you are using.
- If using one sex only, **justify** why, and note the **limitations** in your discussion.
- Always discuss the possible s/g **implications** of your findings.

Introduce a small intervention

- Do a small **pilot experiment** to examine the influence of some element of s/g in your model system:
  - Add a **hormone** to one of your cultures.
  - **Include male and female** animals in the key experimental groups.
- **Report what you find**, whether sex differences are observed or not.

Raise the profile of S/G issues

- **As a reviewer**, ensure that applicants/authors identify and justify the sex of the materials used, and make sure that the terms 'sex' and 'gender' are used appropriately.
- **Ask questions** of colleagues and trainees: have they considered whether s/g issues might be relevant to their work?



Ritz SA, et Al FASEB J. 2014;28(1):4–13

New regolation since 2016

- **National Institutes of Health (USA):** including females in vertebrate studies.

- **Canadian Institutes of Health Research**: All research applicants will integrate sex and gender into their research design

- **Gender policy committee of the European Association of Science Editors**: journal editors should ask all authors to report their results separated by sex and gender.

- **The International Committee of Medical Journal Editors** : sex and gender analysis are integrated into its guidelines in December 2016.

- **The Lancet and Sex and Gender Equity in Research:** guidelines published for authors and journal editors for evaluating manuscripts for excellence in sex and gender analysis.
- **UK National Centre for the Replacement, Refinement and Reduction of Animals in Research:** issued calling for basic research to always report the sex of lab animals.

- **Horizon 2020 (EU):** Sex and gender must be integrated into all stages of research and innovation.

Ministero della Salute

Piano per l'applicazione e la diffusione della Medicina di Genere

(in attuazione dell'articolo 3,comma 1, Legge 3/2018)

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.

… in conclusion

- Sex is first and foremost a genetic modifier of disease pathophysiology, clinical presentation, and response to treatment
- We are at the beginning of understanding the importance of gender differences in the treatment of our patients
- Both gender and hormonal differences should be considered and will certainly influence the treatment of male and female patients in the future.
- Most current medical guidelines and protocols are not gender-specific or sex-specific; when evidence-based data are available, sex- based practice recommendations should be established and health-system protocol campaigns should be implemented
- Sex and gender are the foundation of precision medicine, and their inherent differences should inform decision making to promote gender equity in health.

Franck Mauvais-Jarvis et Al Lancet 2020; 396: 565–8

"…..é più importante sapere che tipo di persona abbia una malattia, piuttosto che sapere che tipo di malattia abbia una persona"

Ippocrate (IV Secolo a.C.)