Bias in Medicine?
Gender Bias in Oncology.

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Sex and gender bias in medicine- The example of oncology

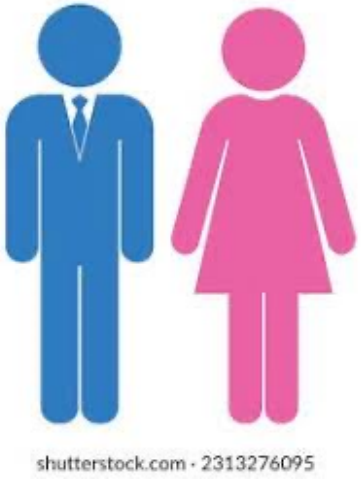
Berna Özdemir, MD PhD

07.03.2024

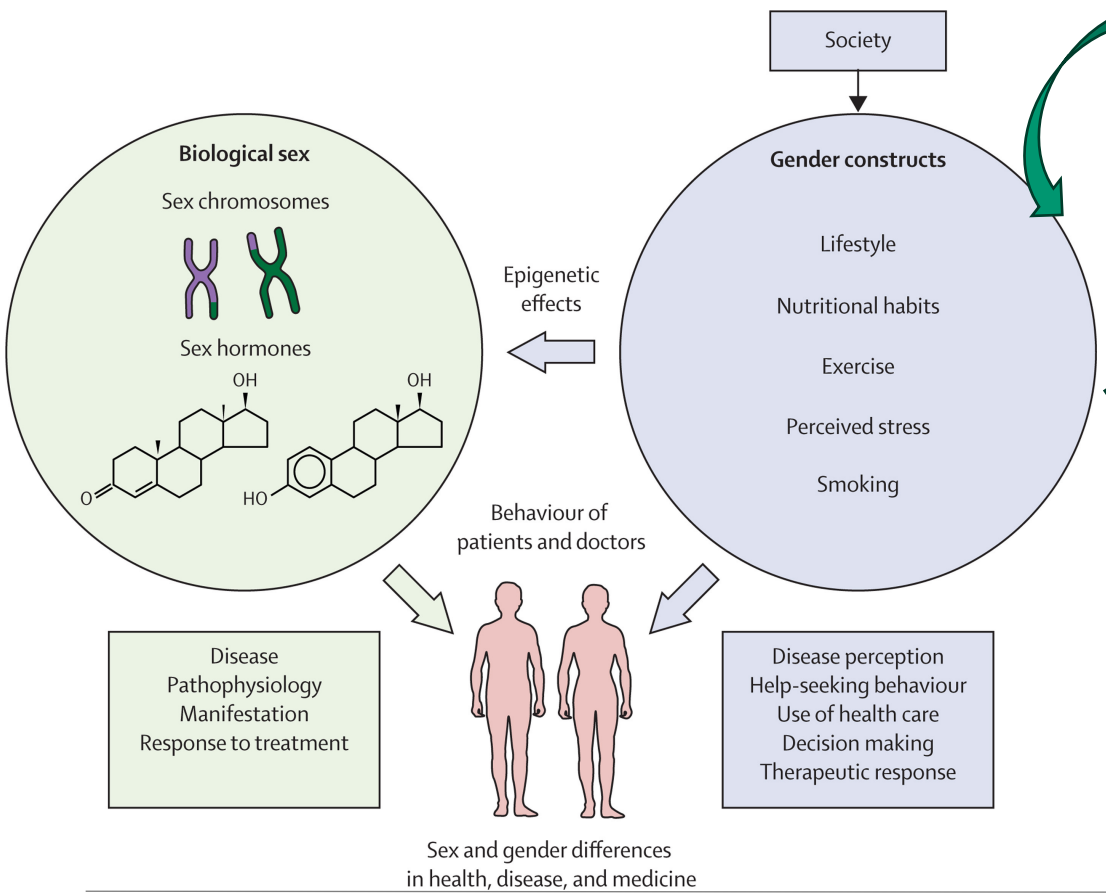
Disclosures

Honoria for lectures/advisory boards to my institution: BMS, MSD, Merck, Ipsen, Roche, Pfizer, Novartis, Janssen, Sanofi

A spectrum of biases in medicine…



Sex and gender bias exist at different levels



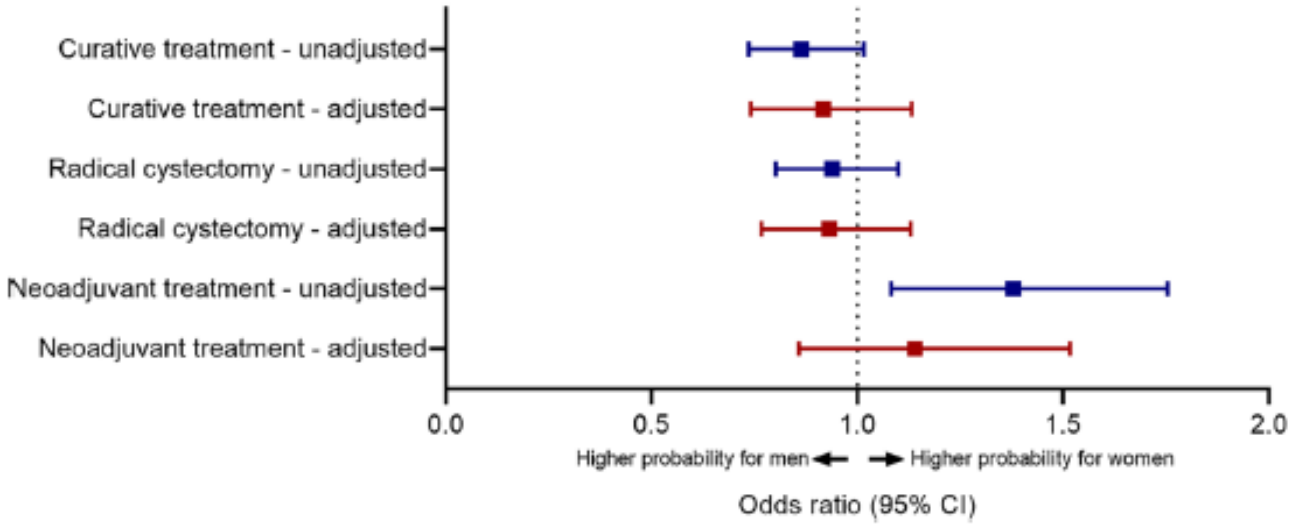
Mauvais-Jarvais F et al. Lancet 2020

Sex of the patient influences treatment allocation

Sex differences in treatment patterns for non-advanced muscle-invasive bladder cancer: a descriptive analysis of 3484 patients of the Netherlands Cancer Registry

Anke Richters[1,2] · Anna M. Leliveld[3] · Catharina A. Goossens-Laan[4] · Katja K. H. Aben[1,2] · Berna C. Özdemir[5]

Fig. 1 Univariable and multivariable analysis of association between sex and treatment among men and women with muscle-invasive bladder cancer. Adjusted odds ratios are adjusted for age, age-adjusted Charlson comorbidity index, performance status, renal function, cT-stage, and histology and hospital type



Richters et al. World J Urol 2022

Gender bias in investigation of sex and gender issues

nature human behaviour
LETTERS
https://doi.org/10.1038/s41562-017-0235-x

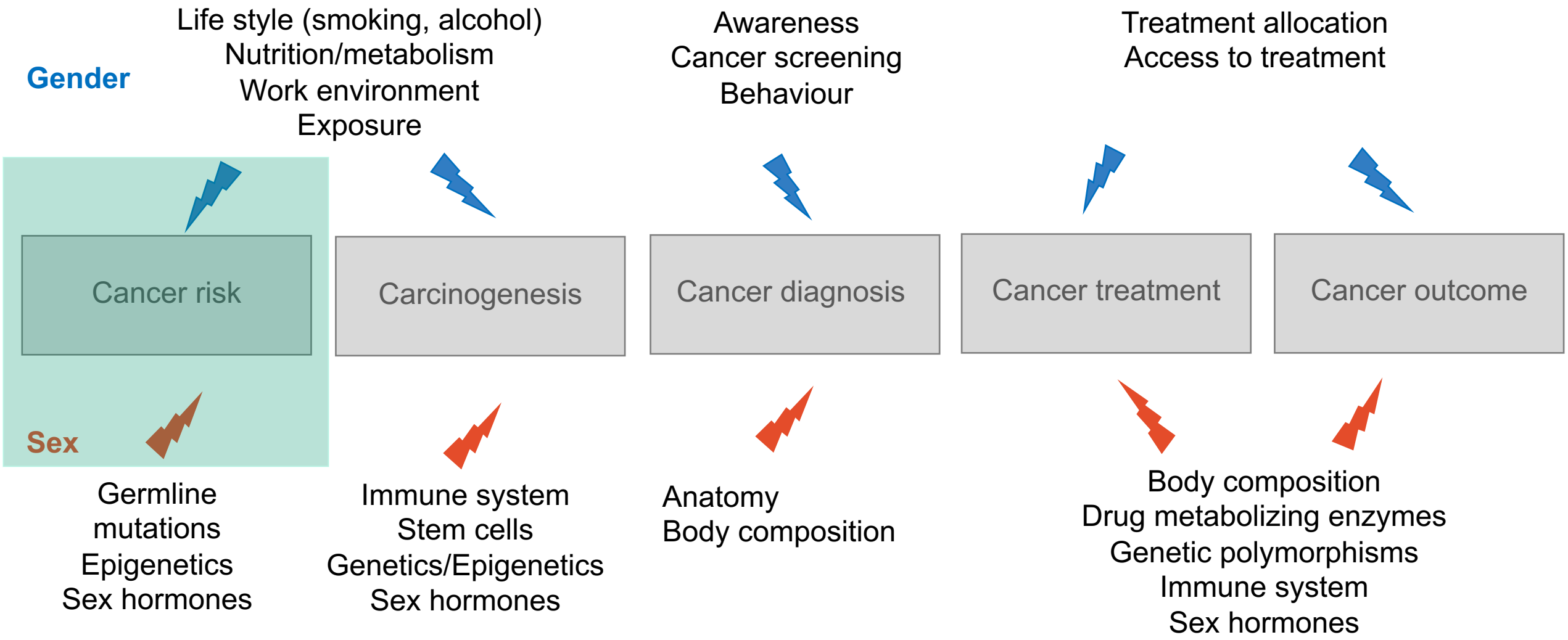
One and a half million medical papers reveal a link between author gender and attention to gender and sex analysis

Mathias Wullum Nielsen[1*], Jens Peter Andersen[2], Londa Schiebinger[3] and Jesper W. Schneider[2]

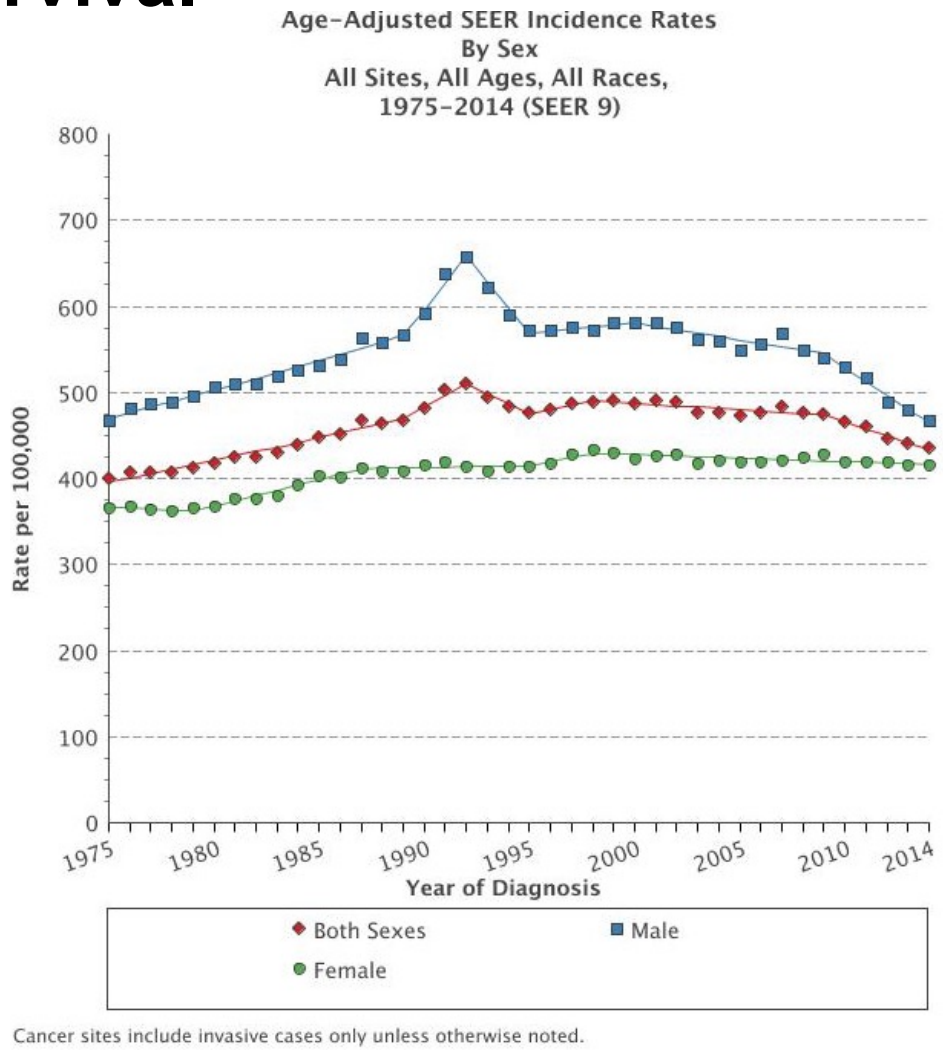
Table 1 | Binary logistic regression model predicting GSA

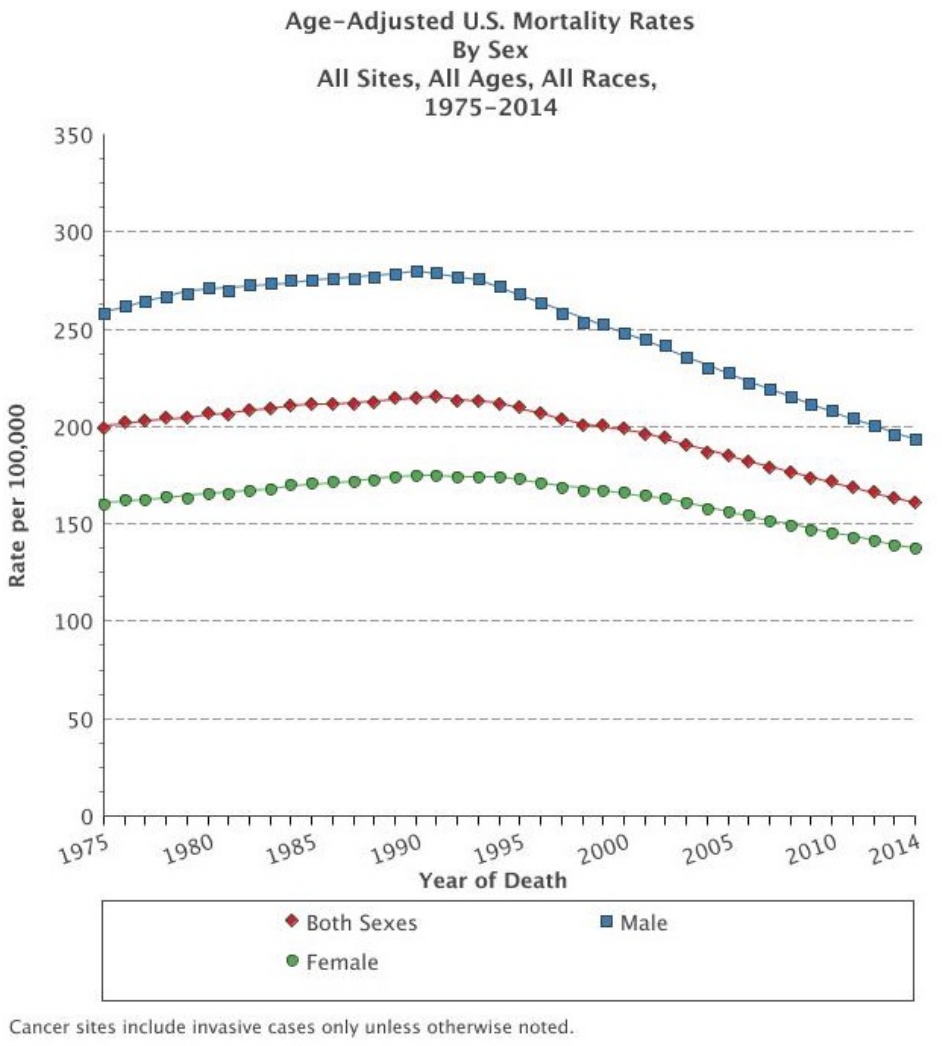
	Model 1 (first author)			Model 2 (last author)			Model 3 (full group)		
Parameter	**Odds ratio**	**s.d.**	**95% CI**	**Odds ratio**	**s.d.**	**95% CI**	**Odds ratio**	**s.d.**	**95% CI**
f_first	1.66	0.07	1.53–1.79						
f_first country	2.75	0.80	1.50–4.62						
f_first MeSH	6.13	1.67	3.55–10.00						
f_first SC	2.11	0.47	1.36–3.19						
f_last				1.56	0.06	1.44–1.68			
f_last country				4.03	1.31	2.02–7.13			
f_last MeSH				4.76	1.55	2.48–8.49			
f_last SC				4.32	1.09	2.60–6.84			
fw							3.14	0.22	2.74–3.59
fw country							2.19	0.85	0.99–4.26
fw MeSH							4.86	1.58	2.55–8.58
fw SC							1.98	0.52	1.16–3.18
Arab States	2.31	0.46	1.55–3.34	2.41	0.48	1.62–3.48	2.26	0.45	1.50–3.26
East Asia	1.79	0.22	1.40–2.26	1.96	0.25	1.54–2.49	1.90	0.25	1.47–2.44
Latin America	1.19	0.19	0.85–1.60	1.31	0.20	0.95–1.76	1.20	0.19	0.86–1.62
Oceania	1.25	0.18	0.93–1.66	1.49	0.22	1.11–1.97	1.33	0.20	1.00–1.75
South and West Asia	1.27	0.21	0.91–1.73	1.33	0.23	0.96–1.83	1.29	0.22	0.99–1.77
South-Central and Eastern Europe	1.36	0.20	1.00–1.80	1.50	0.21	1.10–1.97	1.35	0.20	0.92–1.77
Sub-Saharan Africa	3.03	0.58	2.01–4.28	3.26	0.62	2.19–4.61	3.17	0.60	2.13–4.48
North America	2.08	0.22	1.69–2.56	2.37	0.25	1.93–2.90	2.12	0.22	1.72–2.60
Western Europe	2.00	0.22	1.62–2.46	2.53	0.28	2.05–3.12	2.16	0.23	1.75–2.65
n=1,513,638									

Influence of sex and gender on cancer risk and outcome



Male sex is associated with greater cancer risk and poorer survival





https://seer.cancer.gov/faststats/selections.php?#Output

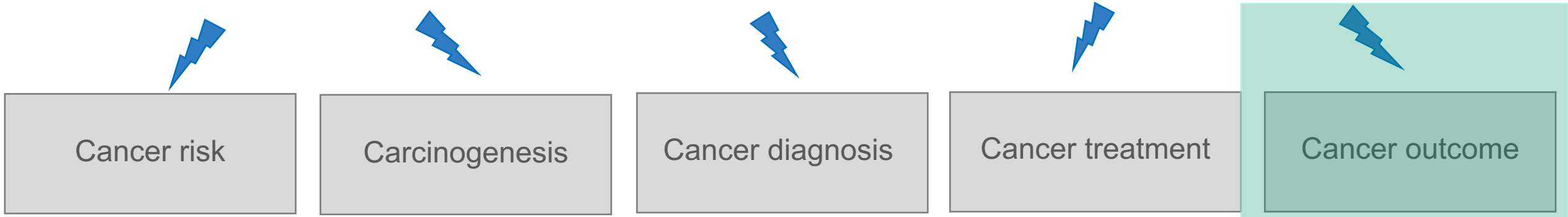
Influence of sex and gender on cancer risk and outcome

Gender

Life style (smoking, alcohol)
Nutrition/metabolism
Work environment
Exposure

Awareness
Cancer screening
Behaviour

Treatment allocation
Access to treatment



Sex

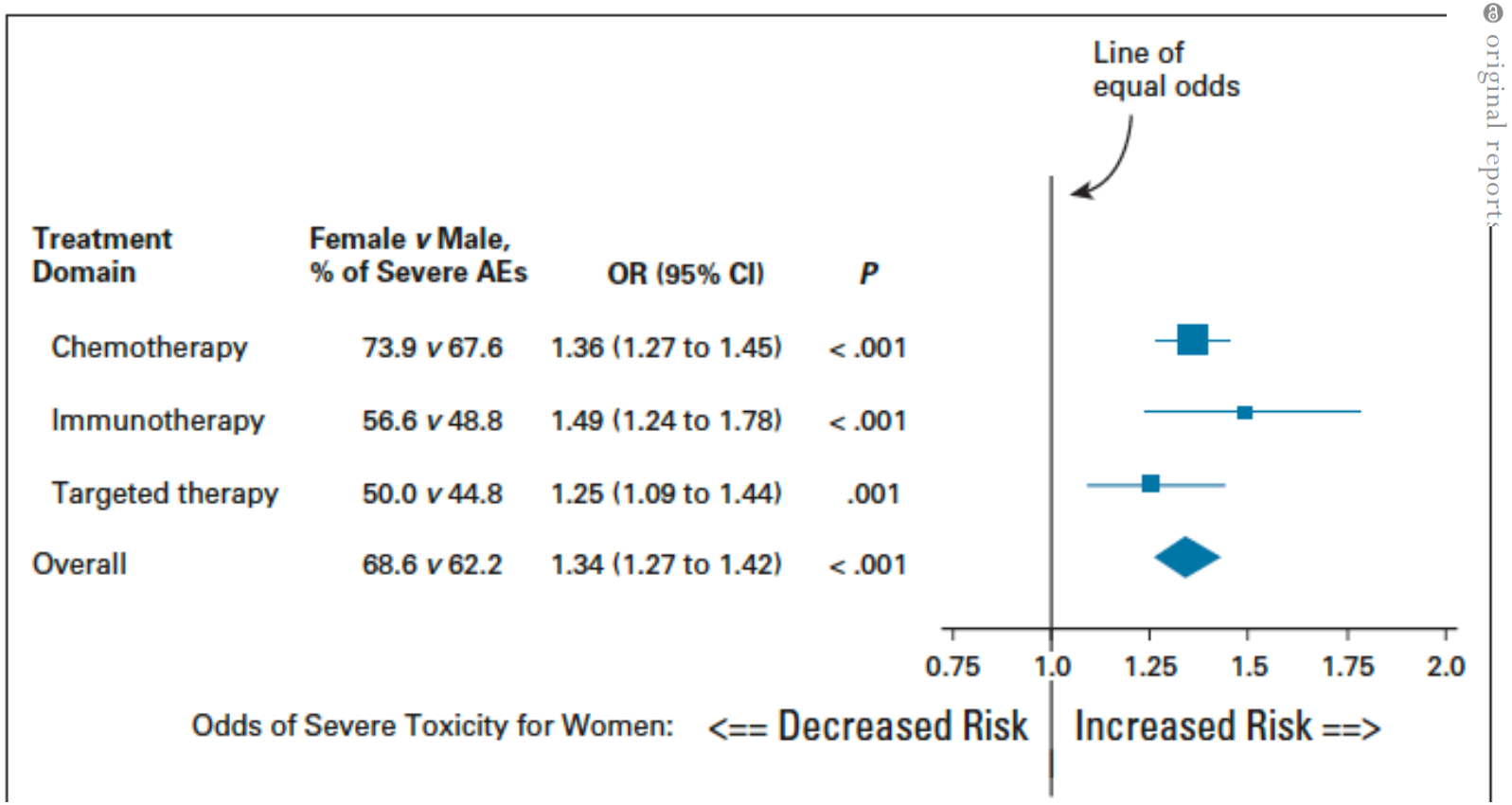
Germline
mutations
Epigenetics
Sex hormones

Immune system
Stem cells
Genetics/Epigenetics
Sex hormones

Anatomy
Body composition

Body composition
Drug metabolizing enzymes
Genetic polymorphisms
Immune system
Sex hormones

Sex differences in treatment toxicity- females at higher risk!



original reports

Sex Differences in Risk of Severe Adverse Events in Patients Receiving Immunotherapy, Targeted Therapy, or Chemotherapy in Cancer Clinical Trials

Joseph M. Unger, PhD[1]; Riha Vaidya, PhD[1]; Kathy S. Albain, MD[2]; Michael LeBlanc, PhD[1]; Lori M. Minasian, MD[3]; Carolyn C. Gotay, PhD[4]; N. Lynn Henry, MD, PhD[5]; Michael J. Fisch, MD[6]; Shing M. Lee, PhD[7]; Charles D. Blanke, MD[8]; and Dawn L. Hershman, MD, MS[7]

>23,000 patients

SWOG Phase 2 and 3 clinical trials conducted between 1980 and 2019, excluding sex-specific cancers

Unger JM et al. JCO 2022

Sex differences in treatment efficacy

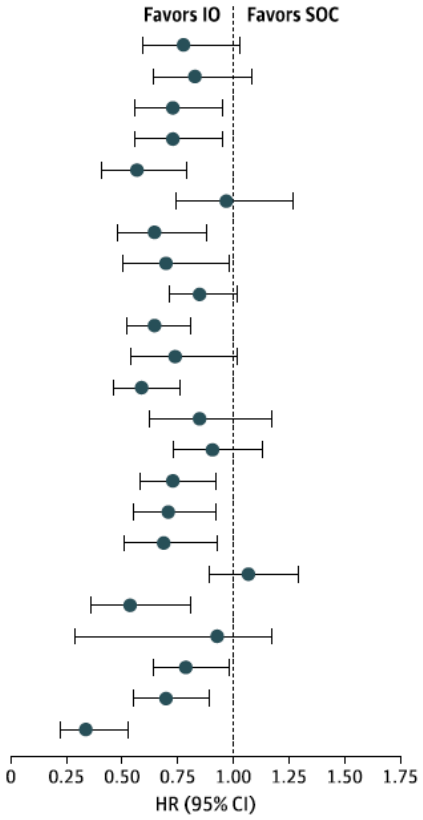
JAMA Oncology | Original Investigation

Association of Patient Sex With Efficacy of Immune Checkpoint Inhibitors and Overall Survival in Advanced Cancers
A Systematic Review and Meta-analysis

Christopher J. D. Wallis, MD, PhD; Mohit Butaney, MD; Raj Satkunasivam, MD, MS; Stephen J. Freedland, MD; Sandip P. Patel, MD; Omid Hamid, MD; Sumanta K. Pal, MD; Zachary Klaassen, MD

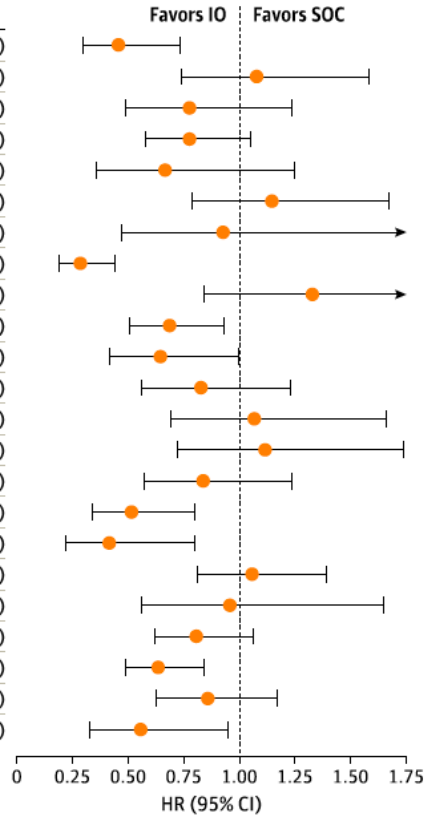
A Overall survival for men

Source	HR (95% CI)
Antonia et al,[34] 2018[a]	0.78 (0.59-1.03)
Barlesi et al,[36] 2018[a]	0.83 (0.64-1.08)
Bellmunt et al,[15] 2017	0.73 (0.56-0.94)
Borghaei et al,[16] 2015	0.73 (0.56-0.96)
Brahmer et al,[17] 2015	0.57 (0.41-0.78)
Carbone et al,[18] 2017	0.97 (0.74-1.26)
Ferris et al,[19] 2016	0.65 (0.48-0.88)
Gandhi et al,[20] 2018[a]	0.70 (0.50-0.99)
Govindan et al,[21] 2017	0.85 (0.71-1.02)
Herbst et al,[22] 2016	0.65 (0.52-0.81)
Horn et al,[37] 2018[a]	0.74 (0.54-1.02)
Kang et al,[23] 2017	0.59 (0.46-0.75)
Larkin et al,[24] 2018	0.85 (0.62-1.17)
Maio et al,[25] 2017	0.91 (0.73-1.13)
Motzer et al,[26] 2015	0.73 (0.58-0.92)
Motzer et al,[27] 2018[a]	0.71 (0.55-0.92)
Paz-Ares et al,[35] 2018[a]	0.69 (0.51-0.94)
Reck et al,[28] 2016	1.07 (0.89-1.28)
Reck et al,[29] 2016	0.54 (0.36-0.80)
Ribas et al,[30] 2013	0.93 (0.74-1.17)
Rittmeyer et al,[31] 2017[a]	0.79 (0.64-0.97)
Robert et al,[32] 2011	0.70 (0.55-0.90)
Robert et al,[33] 2015	0.34 (0.22-0.54)



B Overall survival for women

HR (95% CI)
0.46 (0.30-0.73)
1.08 (0.74-1.59)
0.78 (0.49-1.24)
0.78 (0.58-1.04)
0.67 (0.36-1.25)
1.15 (0.79-1.66)
0.93 (0.47-1.85)
0.29 (0.19-0.44)
1.33 (0.84-2.11)
0.69 (0.51-0.94)
0.65 (0.42-1.00)
0.83 (0.56-1.23)
1.07 (0.69-1.65)
1.12 (0.72-1.75)
0.84 (0.57-1.24)
0.52 (0.34-0.78)
0.42 (0.22-0.81)
1.06 (0.81-1.37)
0.96 (0.56-1.64)
0.81 (0.62-1.06)
0.64 (0.49-0.85)
0.86 (0.63-1.17)
0.56 (0.33-0.95)



Wallis CJD et al. JAMA Oncol 2019

Female sex is associated with poor response to immune checkpoint inhibitors

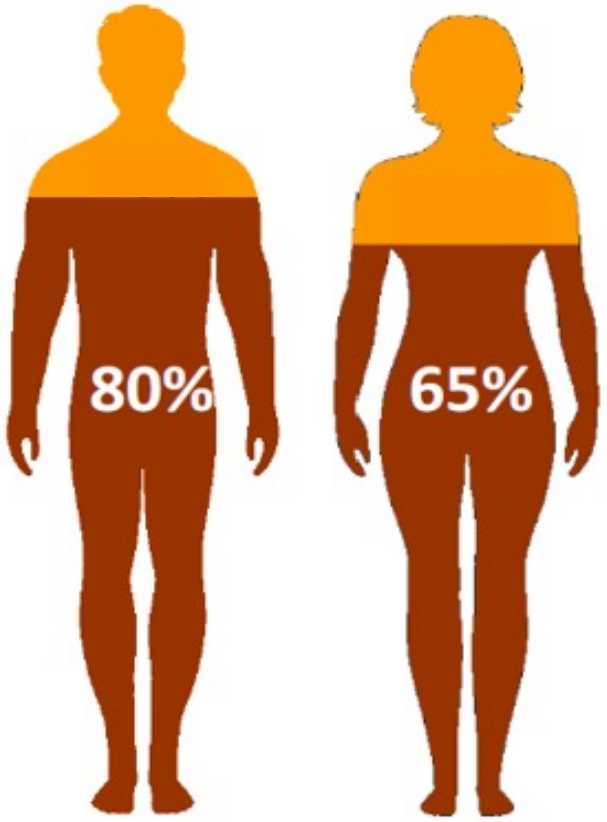
Cox regression analysis and clinical scoring model for response to anti-PD-1 therapy

Variable	Odds ratio (95% CI)	P-value	Scoring
Female	0.51 (0.27, 0.94)	0.03	1
Age <65 years	0.55 (0.30, 0.98)	0.04	1
Previous ipilimumab treatment	0.38 (0.20, 0.69)	<0.001	2
Elevated LDH[a]	0.48 (0.25, 0.90)	0.02	1
Liver metastasis	0.34 (0.17, 0.66)	<0.001	2

Nosrati A, et al. Br J Cancer 2017

Biological differences explain some of the sex and gender bias

Body composition
Sex hormones
Sex chromosomes



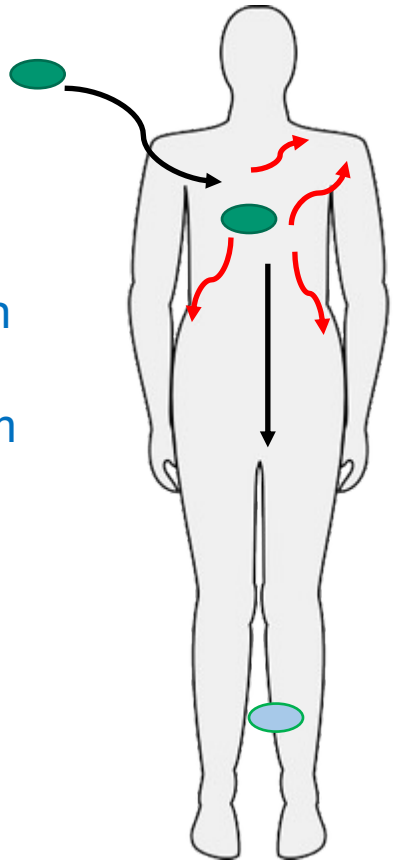
Pharmacokinetics

Absorption

Distribution

Metabolism

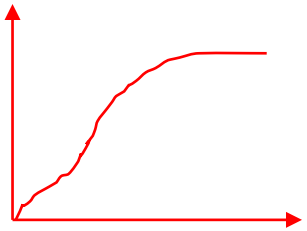
Excretion



Pharmacodynamics

Drug effect

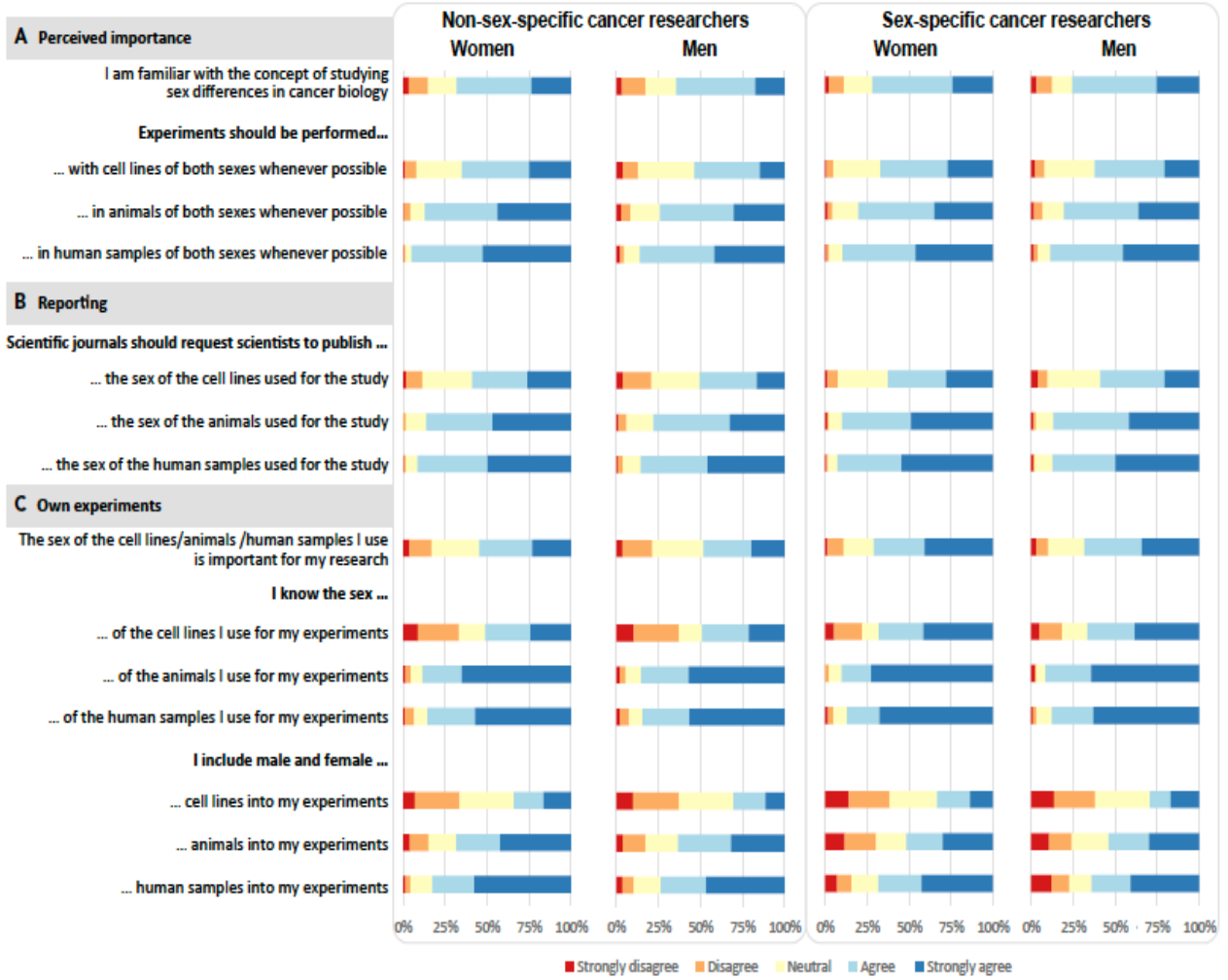
Dose—response relationship



Özdemir BC et al. JCO 2018

..but there is a big data gap!

Cell lines?
Male bias!

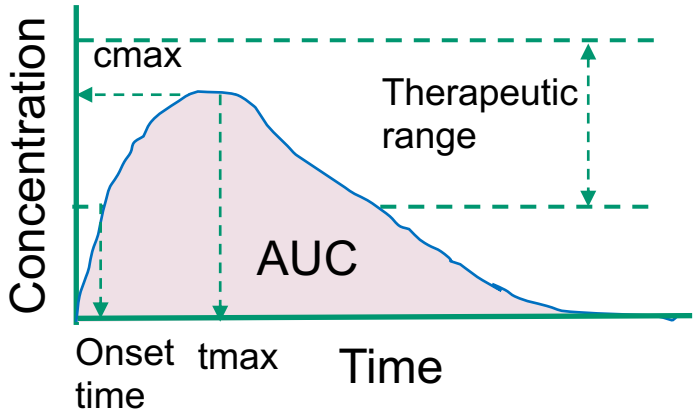


1243 cancer researchers surveyed on importance of sex of cell lines, animals and human samples for cancer research

Familiar with the study of sex differences	70%		
Reporting of sex	58%	85%	89%
Knowledge on sex	54%	90%	87%
Inclusion of sex	64%	79%	88%

Özdemir BC et al. iScience 2023

..but there is a big data gap!



Reference: M, 70 kg, White

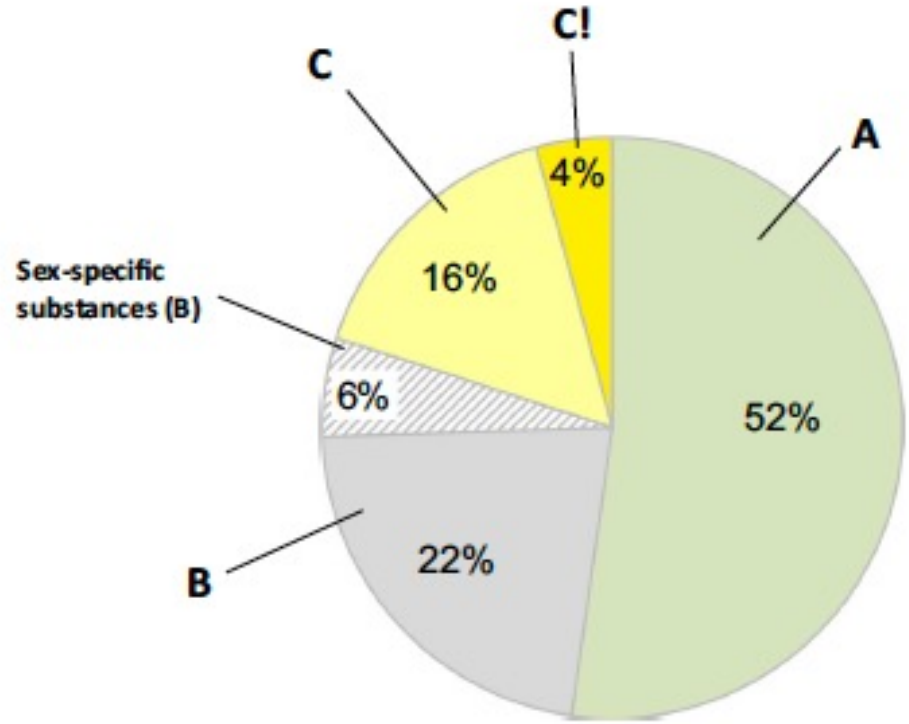
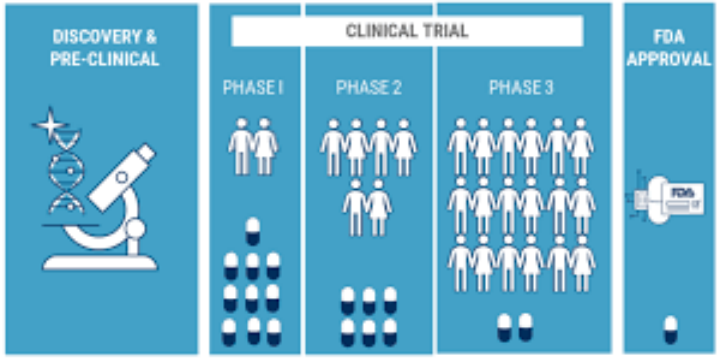


Fig. 1 Distribution of drug substances ($n = 400$) according to classification categories; No clinically relevant sex differences (**A**), Data on sex differences are lacking or where the data interpretation is complicated (**B**), Clinically relevant sex differences in some patient populations (**C**), Clinically relevant sex differences (**C!**)

Lind et al Biol Sex Diff 2023

..but there is a big data gap!



M: F≈60:40

RESEARCH LETTER

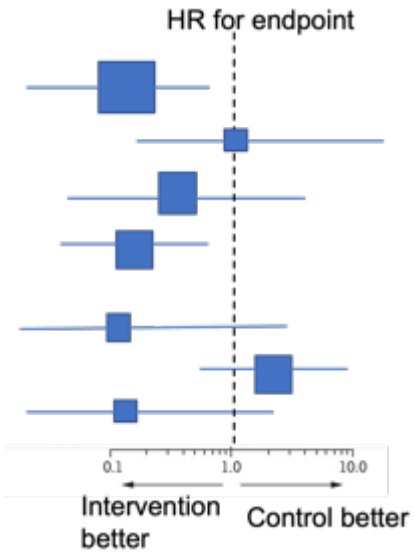
The Inclusion of Women in Global Oncology Drug Trials Over the Past 20 Years

Table. Comparison Between Sex-Specific Enrollment and Clinical Trial Characteristics

Characteristic	Sex, No. (%)		*P* value[a]
	Female	Male	
Total enrolled	73 103 (40)	109 313 (60)	<.001
Trial phase			
1	3034 (48)	3322 (52)	.001
2	18 838 (43)	24 508 (57)	<.001
3	40 139 (38)	66 611 (62)	<.001
Year			
2000-2010	23 350 (40)	34 745 (60)	<.001
2011-2020	49 753 (42)	68 022 (58)	
Tumor type			
Lung	40 829 (41)	57 979 (59)	<.001
Colon	7600 (33)	15 266 (67)	<.001
Thyroid	904 (51)	875 (49)	.50
Melanoma	11 317 (42)	15 529 (58)	<.001
Kidney	6586 (33)	13 127 (67)	<.001
Pancreas	5867 (47)	6537 (53)	<.001
Sites			
US	49 911 (40)	75 755(60)	<.001
Canada	29 603 (39)	45 372 (61)	<.001
China	23 456 (41)	33 645 (56)	<.001
United Kingdom	28 472 (39)	44 478 (61)	<.001
Australia	28 505 (39)	44 332 (61)	<.001
Funding (US)			
Industry	41 391 (41)	60 473 (59)	<.001
NIH	6828 (48)	7285 (52)	

Jenei K et al JAMA Oncol 2021

..but there is a big data gap!



Endpoints by patient sex?

Challenges with sex-specific subgroup analyses in oncology clinical trials for drug approvals between 2015–2020

Results: We identified a total of 73 NMEs approved for cancer treatment between 2015–2020, of which 61 met our eligibility criteria. Of these, 32 studies (52 %) reported a subgroup analysis by sex and were included in our analysis. Phase 2 (41 %) and Phase 3 (53 %) studies represented most studies. No study met ≥ 3 credibility criteria.

Table 1
Credibility of subgroup analysis criterion by Sun et al. 2012 [15] (n = 32).

Criteria			Number of studies (%)
Design	1	**Is the subgroup variable a characteristic measured at baseline?**	32 (100)
	2	Was the subgroup variable a stratification factor at randomisation?	1 (3)
	3	**Was the hypothesis specified a priori?**	21 (66)
	4	Was the subgroup analysis one of a small number of subgroup analyses tested (≤5)?	0 (0)
Analysis	5	**Was the test of interaction significant (interaction p < 0.05)?**	9 (28)
	6	Was the significant interaction effect independent if there were multiple significant interactions?	1 (3)
	7	Was the direction of the subgroup effect correctly pre-specified?	0 (0)
Context	8	Was the subgroup effect consistent with previous studies?	0 (0)
	9	Was the subgroup effect consistent across related outcomes?	0 (0)
	10	Was there indirect evidence to support the apparent subgroups effect?	1 (3)

Bolded criteria deemed "critical" by Sun et al. 2012 [15].

J Jenei K et al. Cancer Pol 2021

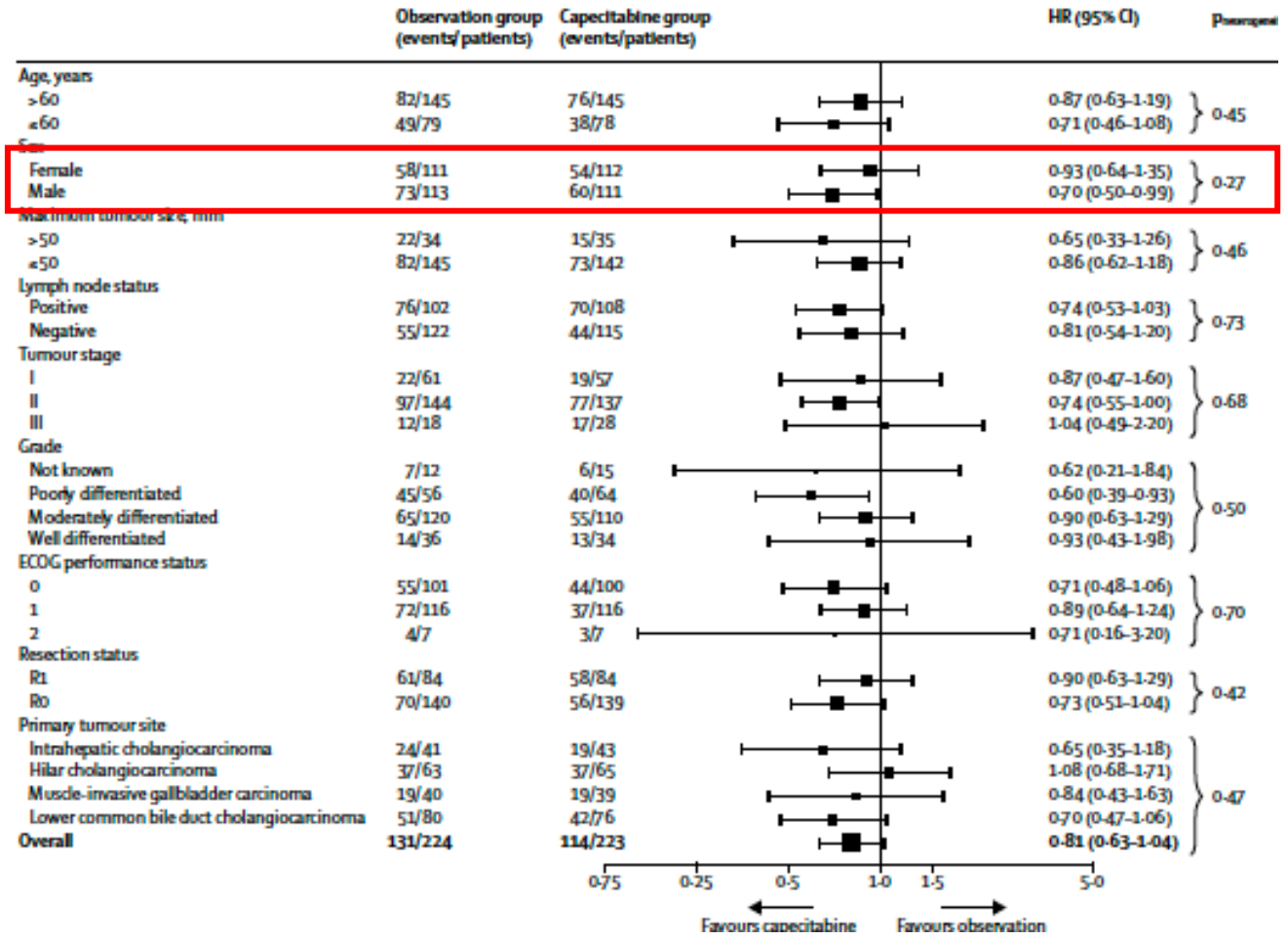
Data gap- The example of the BILCAP trial

Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study

John N Primrose, Richard P Fox, Daniel H Palmer, Hassan Z Malik, Raj Prasad, Darius Mirza, Alan Anthony, Pippa Corrie, Stephen Falk, Meg Finch-Jones, Harpreet Wasan, Paul Ross, Lucy Wall, Jonathan Wadsley, Jeff T R Evans, Deborah Stocken, Raaj Praseedom, Yuk Ting Ma, Brian Davidson, John P Neoptolemos, Tim Iveson, James Raftery, Shihua Zhu, David Cunningham, O James Garden, Clive Stubbs, Juan W Valle, John Bridgewater, on behalf of the BILCAP study group

Lancet Oncol 2019

	Capecitabine group (n=223)	Observation group (n=224)
Sex		
Female	112 (50%)	111 (50%)
Male	111 (50%)	113 (50%)
Age, years	62 (55–68)	64 (55–69)



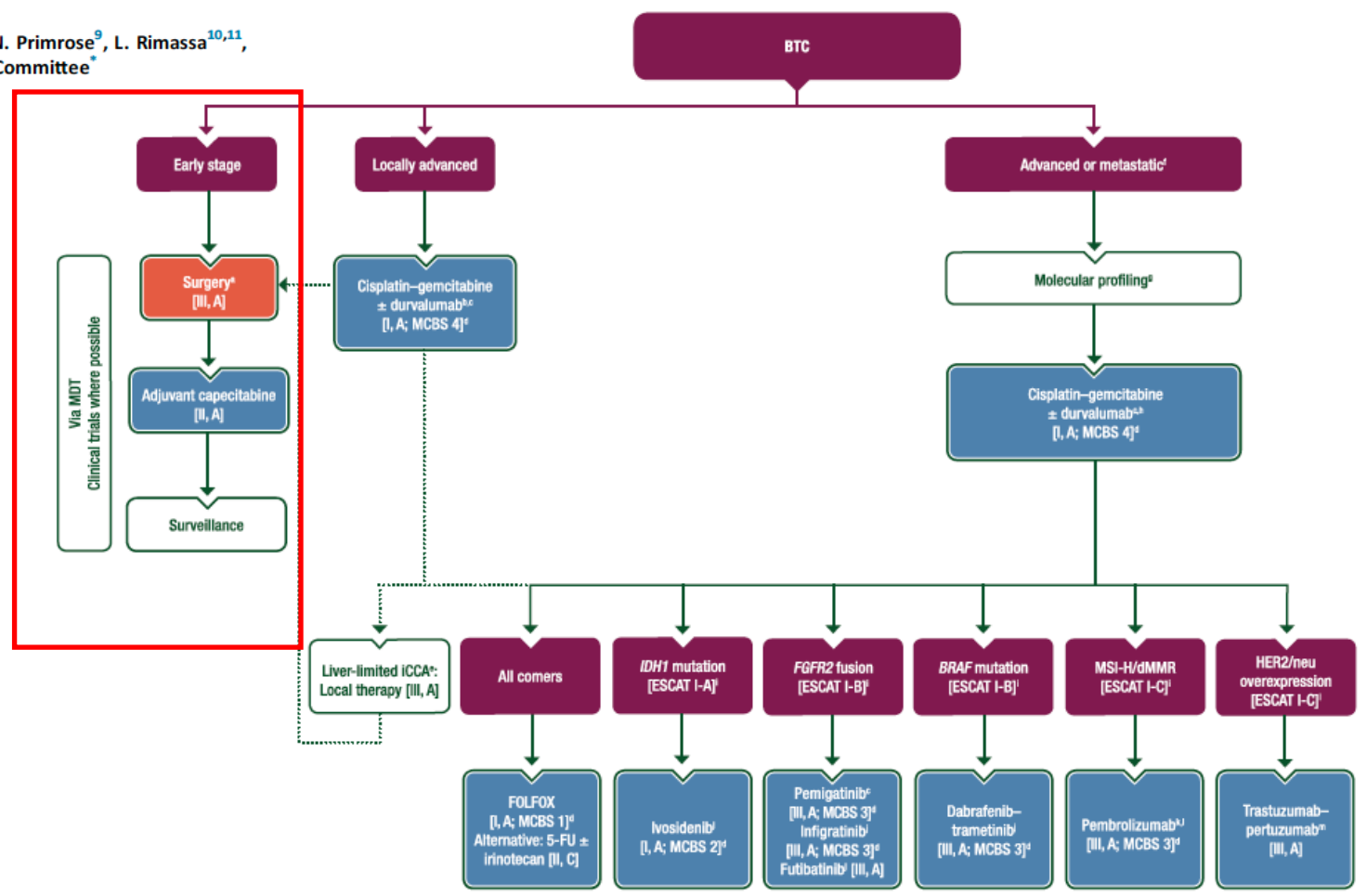
Interpretation Although this study did not meet its primary endpoint of improving overall survival in the intention-to-treat population, the prespecified sensitivity and per-protocol analyses suggest that capecitabine can improve overall survival in patients with resected biliary tract cancer when used as adjuvant chemotherapy following surgery and could be considered as standard of care. Furthermore, the safety profile is manageable, supporting the use of capecitabine in this setting.

The data gap has far reaching consequences..

Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

A. Vogel[1], J. Bridgewater[2], J. Edeline[3,4], R. K. Kelley[5], H. J. Klümpen[6], D. Malka[7,8], J. N. Primrose[9], L. Rimassa[10,11], A. Stenzinger[12], J. W. Valle[13,14] & M. Ducreux[8,15], on behalf of the ESMO Guidelines Committee*

Ann Oncol 2022



Data gap- The example of the ECHELON-1 trial

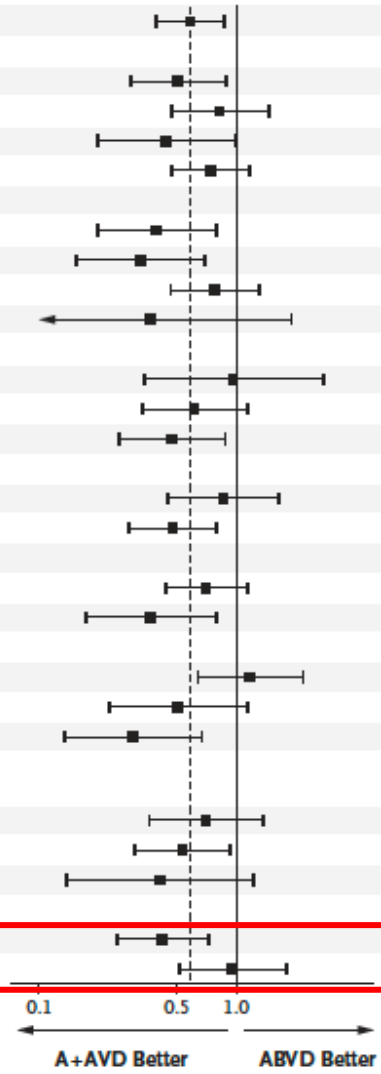
Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma

Stephen M. Ansell, M.D., Ph.D., John Radford, M.D., Joseph M. Connors, M.D., Monika Długosz-Danecka, M.D., Ph.D., Won-Seog Kim, M.D., Andrea Gallamini, M.D., Radhakrishnan Ramchandren, M.D., Jonathan W. Friedberg, M.D., Ranjana Advani, M.D., Martin Hutchings, Ph.D., Andrew M. Evens, D.O., Piotr Smolewski, M.D., Ph.D., Kerry J. Savage, M.D., Nancy L. Bartlett, M.D., Hyeon-Seok Eom, M.D., Ph.D., Jeremy S. Abramson, M.D., Cassie Dong, Ph.D., Frank Campana, M.D., Keenan Fenton, M.A., Markus Puhlmann, M.D., and David J. Straus, M.D., for the ECHELON-1 Study Group*

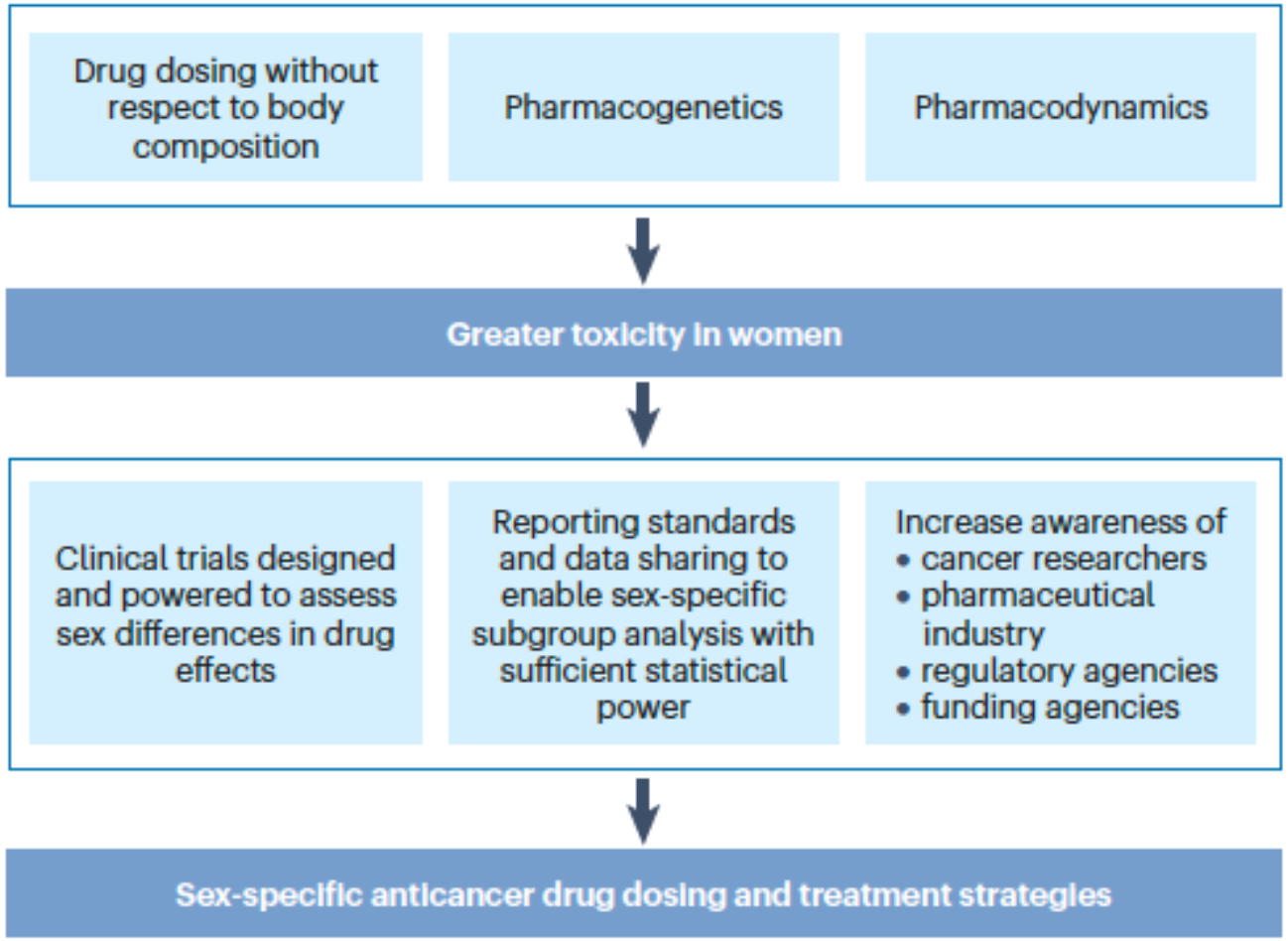
NEJM 2022

Patients who received A+AVD for the treatment of stage III or IV Hodgkin's lymphoma had a survival advantage over those who received ABVD. (Funded by Takeda Development Center Americas and Seagen; ECHELON-1 ClinicalTrials.gov number, NCT01712490; EudraCT number, 2011-005450-60.)

Subgroup	A+AVD	ABVD	Hazard Ratio for Death (95% CI)
	no. of deaths/total no. of patients (%)		
Overall	39/664 (5.9)	64/670 (9.6)	0.59 (0.40–0.88)
Age			
<60 yr	19/580 (3.3)	35/568 (6.2)	0.51 (0.29–0.89)
≥60 yr	20/84 (24)	29/102 (28.4)	0.83 (0.47–1.47)
<45 yr	9/451 (2.0)	18/423 (4.3)	0.44 (0.20–0.99)
≥45 yr	30/213 (14.1)	46/247 (18.6)	0.75 (0.47–1.18)
Geographic region			
Americas	11/261 (4.2)	27/262 (10.3)	0.40 (0.20–0.80)
North America	9/250 (3.6)	26/247 (10.5)	0.33 (0.15–0.70)
Europe	26/333 (7.8)	32/336 (9.5)	0.78 (0.47–1.32)
Asia	2/70 (3)	5/72 (7)	0.37 (0.07–1.91)
No. of IPS risk factors			
0 or 1	7/142 (4.9)	7/141 (5.0)	0.97 (0.34–2.77)
2 or 3	17/355 (4.8)	26/357 (7.3)	0.62 (0.33–1.14)
4–7	15/167 (9.0)	31/172 (18.0)	0.48 (0.26–0.88)
Cancer stage at baseline			
III	17/237 (7.2)	20/246 (8.1)	0.86 (0.45–1.65)
IV	22/425 (5.2)	43/421 (10.2)	0.48 (0.29–0.80)
B symptoms at baseline			
	30/400 (7.5)	39/381 (10.2)	0.71 (0.44–1.14)
	9/264 (3.4)	25/289 (8.7)	0.37 (0.17–0.80)
	22/217 (10.1)	19/228 (8.3)	1.18 (0.64–2.19)
	9/217 (4.1)	17/223 (7.6)	0.51 (0.23–1.14)
	8/194 (4.1)	25/193 (13.0)	0.30 (0.14–0.67)
ECOG performance-status score at baseline			
0	15/376 (4.0)	21/378 (5.6)	0.70 (0.36–1.37)
1	19/260 (7.3)	34/263 (12.9)	0.54 (0.31–0.94)
2	5/28 (18)	9/27 (33)	0.41 (0.14–1.23)
Sex			
Male	19/378 (5.0)	45/398 (11.3)	0.43 (0.25–0.73)
Female	20/286 (7.0)	19/272 (7.0)	0.96 (0.51–1.80)



Structural barriers to address sex and gender bias in oncology



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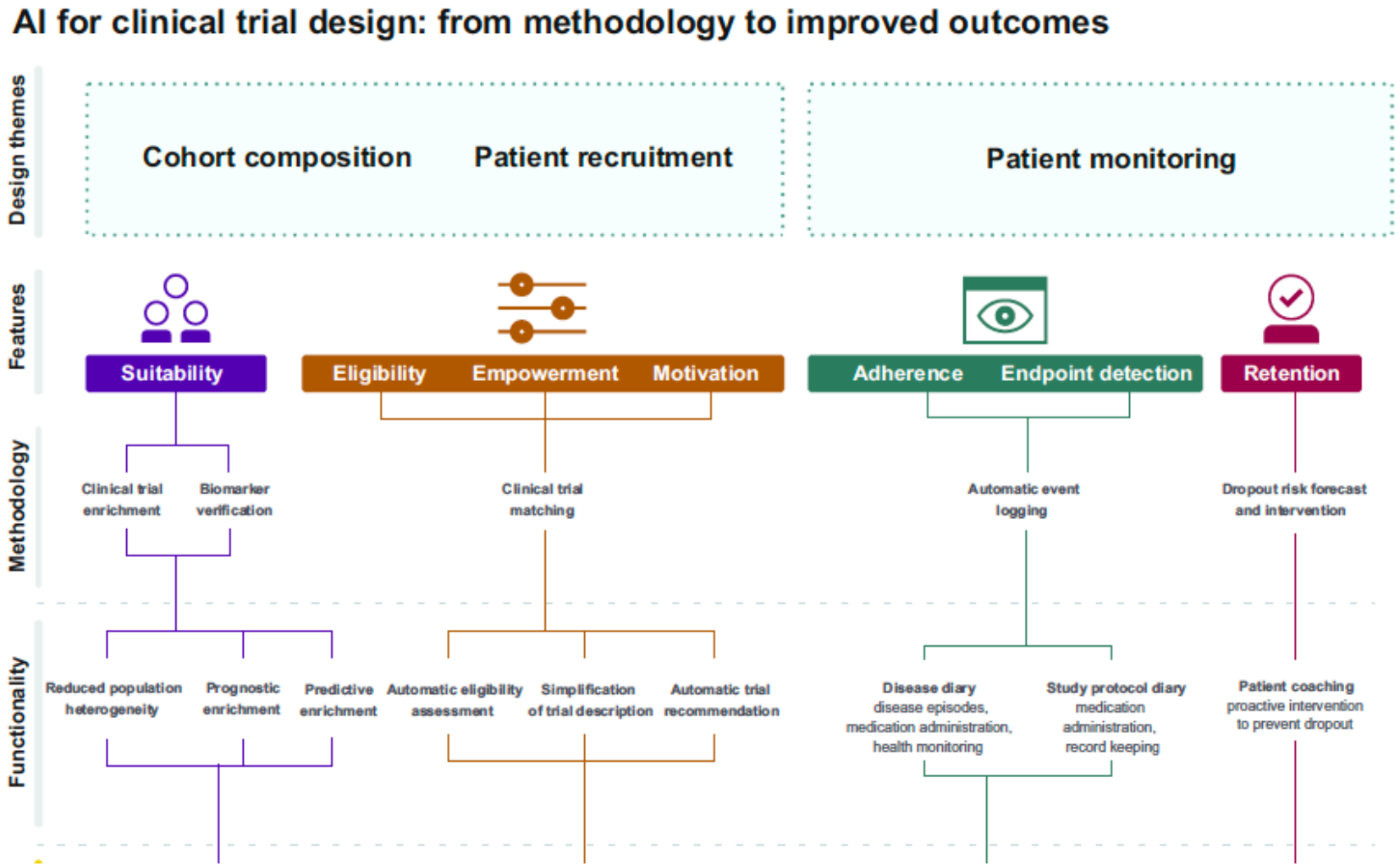
The potential of AI for improving clinical trial design and conduct



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Thank you for your attention!

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