

Edinburgh Research Explorer

State-of-the-Art Meeting on Sex and Gender in Transplantation: The Female Perspective

Citation for published version:

Sugianto, RI, Saenger, T, Ahn, C, Chong, A, Goldberg, A, Grabitz, C, Mannon, R, Marson, LP, Memaran, N, Sapir-Pichhadze, R, Tullius, S, von der Born, J, West, L, Foster, BJ, Lerminiaux, L, Wong, G & Melk, A 2023, 'State-of-the-Art Meeting on Sex and Gender in Transplantation: The Female Perspective', Transplantation, vol. 107, no. 9, pp. 1865-1869. https://doi.org/10.1097/TP.0000000000004609

Digital Object Identifier (DOI):

10.1097/TP.000000000000004609

Link:

Link to publication record in Edinburgh Research Explorer

Document Version:

Peer reviewed version

Published In:

Transplantation

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Transplantation

Meeting Report: State of the Art Meeting on Sex and Gender in Organ Transplantation: the Female Perspective --Manuscript Draft--

Manuscript Number:		
Article Type:	Special Article	
Section/Category:	Special Feature	
Corresponding Author:	Anette Melk, MD, PhD Hannover Medical School: Medizinische Hochschule Hannover Hannover, GERMANY	
First Author:	Rizky Indrameikha Sugianto, PhD	
Order of Authors:	Rizky Indrameikha Sugianto, PhD	
	Thorsten Saenger, PhD	
	Curie Ahn, MD	
	Anita S. Chong, PhD	
	Aviva M. Goldberg, MD	
	Carl Grabitz, MD	
	Roslyn B. Mannon, MD	
	Lorna Marson, MD	
	Nima Memaran, MD	
	Ruth Sapir-Pichhadze, MD	
	Stefan G. Tullius, MD, PhD	
	Jeannine von der Born, MD	
	Lori J. West, MD	
	Bethany J. Foster, MD	
	Louise Lerminiaux, MBA	
	Germaine Wong, MD	
	Anette Melk, MD, PhD	
Manuscript Region of Origin:	GERMANY	
Abstract:	Not applicable.	

Meeting Report: State of the Art Meeting on Sex and Gender in Organ Transplantation: the Female Perspective

Rizky Indrameikha Sugianto¹, Thorsten Saenger¹, Curie Ahn², Anita S. Chong³, Aviva M. Goldberg⁴, Carl Grabitz¹, Roslyn B. Mannon⁵, Lorna Marson⁶, Nima Memaran¹, Ruth Sapir-Pichhadze⁷, Stefan G. Tullius⁸, Jeannine von der Born¹, Lori J. West⁹, Bethany J. Foster¹⁰, Louise Lerminiaux¹¹, Germaine Wong¹², Anette Melk¹

- 1 Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany.
- 2 Division of Nephrology, National Medical Center, Seoul, South Korea.
- 3 Department of Surgery, University of Chicago, Chicago, IL.
- 4 Section of Pediatric Nephrology, Department of Pediatrics and Child Health, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada.
- 5 Department of Internal Medicine, Division of Nephrology, University of Nebraska Medical Center, Omaha, NE.
- 6 The Edinburgh Transplant Centre, Royal Infirmary of Edinburgh, Edinburgh, UK.
- 7 Department of Medicine, McGill University, Montreal, Canada.
- 8 Division of Transplant Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.
- 9 Departments of Pediatrics, Surgery, Medical Microbiology/Immunology and Laboratory Medicine/Pathology, University of Alberta, Alberta Transplant Institute, Edmonton, Alberta, Canada. 10 Department of Pediatrics, Montreal Children's Hospital of the McGill University Health Centre,
- Montreal, QC, Canada.
- 11 Patient Advocate Consultant, Wellness Consulting LRL LLC.
- 12 Division of Nephrology, Department of Medicine, School of Public Health, University of Sydney, Sydney, NSW, Australia.

Address for correspondence:

Anette Melk, MD PhD

Children's Hospital, Hannover Medical School

Carl-Neuberg-Str. 1 30625 Hannover

Melk.Anette@mh-hannover.de

Phone: +49-511-532 5597 Fax: +49-511-532 16 5597

Background and aims

Sex- and gender-based inequities in organ transplantation represent a critically relevant, yet under-appreciated aspect that impacts upon patient and graft outcomes. Biologic factors (sex), as well as psychological-, social-, and economic factors (gender) all contribute to these disparities. While such disparities are observed consistently worldwide, access to care and differences in allograft and patient outcomes by sex and gender differ between countries, emphasizing the necessity to engage the global community. Moreover, as in many other professional areas, gender disparities exist among professionals in transplantation science and medicine. To address the need for global recognition of the interplay between sex and gender in transplantation, and to define unmet needs, Anette Melk (Hannover Medical School), Bethany Foster (McGill University), Germaine Wong (University of Sydney), and Louise Lerminiaux (patient representative) initiated the international hybrid symposium "Sex and Gender in Transplantation: The Female Perspective", which took place October 5th-7th 2022, in Hannover, Germany. The interdisciplinary symposium connected clinicians, researchers, and patients from around the globe. Instead of taking the traditional male perspective, efforts were made to ensure a female perspective and approach to both the content and organization of the symposium. The symposium had three aims. Firstly, we aimed to identify areas pertaining to sex and gender where more research is needed, with an emphasis on creating evidence to inform guidelines and policies. Second, we integrated patients' perspectives and experience in the execution of patient-centred research. Finally, the symposium focused on achieving equity in access to careers in transplantation, defining metrics of success and strategies to accelerate progress in this area.

About the meeting

The symposium was an interactive hybrid event (on site and virtual), enabling broad participation, with special efforts to invite (early career) investigators from multiple continents and disciplines, ensuring multifaceted contributions and perspectives. Two-hundred-thirty-four participants from 40 countries registered; 78 individuals (20 countries) made active contributions with 67 individuals (14 countries) attending in person. **Figure 1** provides further details on the meeting's participants. Participation of a science journalist throughout the meeting, who also served as a facilitator of a panel discussion, was a novel and effective means to create an overall comfortable atmosphere, allowing any question to be asked – critical with such a diverse group of attendees – and ensuring that the discussion was accessible to all attendees.

The meeting included lectures (available through https://diversity-intransplantation.org/symposium-2022/), interactive panel discussions, and oral and poster presentations. To ensure diverse representation and inclusion, the following novel measures were taken: (1) independent panel discussions for both the Eastern and Western hemispheres, enabling participants to join at a reasonable time of day; (2) active involvement of patients at all stages of the meeting from the planning phase through to the post-meeting discussion ensured that topics of importance to patients were highlighted; (3) early-career and established investigators were matched, creating mentor-mentee partnerships as a strategy to sustainably boost research in the field, in addition to providing individual career advice to early-career investigators; (4) practical sessions with guidance on physical exercise and relaxation techniques were implemented and addressed sex-/gender-specific requirements; (5) real time translators, available throughout the symposium, enabled speakers and participants to be more fully engaged and interactive.

Key issues and future directions

Sex and gender impact multiple aspects of transplantation in critical and relevant ways. The interacting influences of sex and gender are illustrated in **Figure 2**. The symposium covered each of the areas below in detail. Recommendations for future research, compiled by attendees, are highlighted in **Table 1**.

Donation and access

Women donate organs more often than men but are less likely to receive a transplant. This phenomenon is strongly related to societal/cultural norms that place women in caregiving or helping roles, both in their families and in the larger society. Women with certain medical conditions (e.g., type-2-diabetes¹, obesity²), ethnicities (non-Hispanic white, black women³), or advanced age are disadvantaged in access to transplantation⁴. Although women are less likely to be waitlisted than men, older women show better transplantation outcomes than older men. This may be driven in part by waitlist selection bias, with healthier women being more likely to be listed⁴. Further studies must address sex and gender differences in the decision-making processes of donors, patients, and physicians involving organ donation and wait-listing, with careful consideration for cultural and religious factors.

Graft and patient survival

Graft survival differs by sex. In kidney⁵ and liver⁶ transplantation, among recipients of male donors, young females showed a higher risk of graft failure than young males⁷. In heart transplantation, female recipients of all ages had higher graft failure risks than males in the setting of a male donor⁸. Female recipients demonstrate greater variability in tacrolimus trough levels than males⁹, raising the possibility that drug metabolism may vary through the menstrual cycle and thus impact the adequacy of controlling alloreactivity. This highlights an urgent need for pharmacokinetic and pharmacodynamic studies to understand sex differences that may affect graft outcomes.

In pediatric kidney transplant recipients when compared to boys, girls demonstrate a higher burden of cardiovascular abnormalities. Post-pubertal girls develop higher blood pressure when exposed to cyclosporine A trough levels ≥120 µg/L¹0, girls with obesity demonstrate higher prevalence of left-ventricular hypertrophy¹¹ (an association also seen in healthy girls¹²), and girls are more susceptible to faster progression of arterial stiffness¹³. These findings suggest that girls with end stage kidney disease lose more potential life-years than boys. In adult kidney transplant recipients, males show higher absolute cardiovascular death rates than females, but the excess risk of cardiovascular mortality (risk above that in the age- and sex-matched general population) is substantially higher in females than males¹⁴. Females experience an increase in left ventricular mass index (LVMI) by 1-year after transplantation, while males show a decreasing LVMI¹⁵. Despite growing evidence that females are more susceptible to cardiovascular damage than males, there are no sex-specific treatment or prevention strategies for transplant recipients.

<u>Differences arising from biologic factors</u>

Biological sex differences are determined by gonadal hormones and sex chromosomes. In addition, over 90% of genes show sex-specific expression, illustrating that sex differences are present at molecular as well as organismal levels¹⁶. Sex differences in lifespan are well recognized, indicating the role of sex in the accumulation of senescent cells resulting in sex-specific aging rates. Sex-specific gene expression and sex hormones influence immune reactivity – with relevance to graft outcomes. Estrogens tend to enhance the inflammatory

immune response, possibly resulting in higher rejection rates; interestingly, females of post-menopausal age^{7,16,17} have lower graft failure rates than males. Despite a lower rate of primary graft dysfunction (possibly related to enhanced repair mechanisms), a sustained pro-inflammatory response is seen in female lung transplant recipients¹⁸. Pre-clinical mouse models suggest that the development of ABO blood group natural antibodies is significantly affected by sex and age, suggesting a potential role for sex hormones^{19,20}. Mouse models allow the contribution of genes encoded in the sex chromosomes to be dissected from the impact of sex hormones and their receptors²¹. Furthermore, the sensitizing effects of pregnancy on humoral immunity contrasted with T cell tolerance to the allogeneic fetus was discussed, with implications for multiparous women who face reduced access to transplantation²². This discussion highlighted that sex differences in immune reactivity and cell regeneration will need to be delineated across the lifespan. More studies are needed to better understand sex differences and its interaction with age regarding immune reactivity and regenerative potential.

Patient-oriented research and clinical care

Mental health, which may affect women and girls differently from men and boys, is often overlooked in transplant care. Matters such as "how long do I get to live", survival guilt, or feeling unworthy of receiving such a precious gift are considerable mental burdens; relationship dynamics that result in higher divorce rates, financial difficulties, body image, and myths add extra strain. Sexual health and the impacts of sexually-transmitted infections such as human papilloma virus must also be considered in long-term care. Female recipients are particularly burdened when facing reproductive decisions²³. Discussions focused on the need for family planning with a shift away from counseling against pregnancy towards supporting a well-informed choice. Access to reproductive care is critical^{24,25}. Awareness among transplant professionals towards holistic long-term care is necessary, as well as more targeted research in areas of most importance to women transplant recipients.

Intersectionality

Intersectionality refers to a way in which a person's identity can expose them to vulnerability and overlapping forms of discrimination and marginalization. As an example, women with kidney failure from lower socioeconomic backgrounds and from some ethnic backgrounds are less likely to be referred for transplantation, and if listed, they are less likely to receive a transplant. Intersectionality has recently been recognized as relevant in transplantation. An intersectionality framework offers a comprehensive approach to better understand complex interactions amongst a variety of disadvantaging mechanisms²⁶. This framework untangles different layers of inequity that are associated with one's identity, including but not limited to sex, age, gender, religion, ethnicity, disability, sexual orientation, class, and socioeconomic status that result in a cumulative adverse impact. This approach goes beyond the mere description of inequities in transplantation, also helping to uncover root causes.

Equity and diversity in professional development

Professionals in the field of medicine are becoming more diverse. However, despite these encouraging developments there are still major challenges. More than a third of respondents to a survey initiated by the International Liver Transplantation Society state that they have experienced discrimination, with gender discrimination being the most frequent²⁷. Almost half of women professionals report not having received mentoring during their career²⁷. Despite equal gender distribution of medical school graduates, the "leaky pipeline" (i.e., women are less likely to advance to higher positions) exists worldwide. Disparities are even more

pronounced in low- and middle-income countries. It is therefore one of the mandates of international organizations such as *Women in Transplantation* to work to reduce inequities globally (https://www.tts-wit.org/)²⁸.

Ethical considerations

Traditional ethical principles like autonomy, justice, beneficence, and non-maleficence are classically referenced in organ donation policies and transplantation ethics. However, there is room for other approaches like feminist bioethics²⁹, which addresses ethical issues impacting marginalized groups, including but not limited to women. As an extension to "mainstream" transplantation ethics, a feminist bioethics viewpoint offers novel solutions to neglected or persisting ethical issues through a deeper understanding of the relationships between donors and recipients.

Conclusion and Outlook

This meeting highlighted gaps in existing data and outlined future research directions. Existing research lacks consistency and transparency in methodology and reporting, and high-quality data are often missing. Additional investigation, including patient-centred research, is needed to advocate for policy changes to ensure equitable access to transplantation, and to improve outcomes for women and men around the world. Aspects regarding patients' mental health, intersectionality, and pre- and post-transplantation patient education should be incorporated in clinical training. Concerted efforts are needed to establish a collaborative research consortium with the goal of collecting, collating, and sharing high-quality global data. Prompt knowledge transfer must be assured for education and training. A rapid pipeline implementing new findings into patient care is indispensable.

Acknowledgments

This symposium was made possible through exclusive and generous funding by the *Volkswagen Stiftung*. Additional early-career travel grants were supported by *MHH plus Förderstiftung*. Three awards for posters and presentations were provided by Women in Transplantation. RBM is supported in part by the Dennis Ross Research Fund in Nephrology of the Nebraska Foundation. RIS is supported by the fellowship grant from Women in Transplantation (One Lambda Inc.).

References

- 1. Ahearn P, Johansen KL, Tan JC, McCulloch CE, Grimes BA, Ku E. Sex Disparity in Deceased-Donor Kidney Transplant Access by Cause of Kidney Disease. *Clin J Am Soc Nephrol.* 2021;16(2): 241-250.
- 2. Ladhani M, Craig JC, Wong G. Obesity and gender-biased access to deceased donor kidney transplantation. *Nephrol Dial Transplant*. 2020;35(1): 184-189.
- 3. Smothers L, Patzer RE, Pastan SO, DuBay D, Harding JL. Gender Disparities in Kidney Transplantation Referral Vary by Age and Race: A Multiregional Cohort Study in the Southeast United States. *Kidney Int Rep.* 2022;7(6): 1248-1257.
- 4. Melk A, Schmidt BMW, Geyer S, Epping J. Sex disparities in dialysis initiation, access to waitlist, transplantation and transplant outcome in German patients with renal disease-A population based analysis. *PLoS One.* 2020;15(11): e0241556.
- 5. Vinson AJ, Zhang X, Dahhou M, et al. Age-Dependent Sex Differences in Graft Loss After Kidney Transplantation. *Transplantation*. 2021.
- 6. De Simone AI, Zhang X, Dahhou M, et al. Differences in Liver Graft Survival by Recipient Sex. *Transplant Direct.* 2020;6(12): e629.
- 7. Lepeytre F, Dahhou M, Zhang X, et al. Association of Sex with Risk of Kidney Graft Failure Differs by Age. *J Am Soc Nephrol.* 2017;28(10): 3014-3023.
- 8. Foster BJ, Zhang X, De Simone A, et al. Differences in Heart Graft Survival by Recipient Sex. *Transplant Direct*. 2021;7(10): e749.
- 9. Vaisbourd Y, Dahhou M, Zhang X, et al. Differences in medication adherence by sex and organ type among adolescent and young adult solid organ transplant recipients. *Pediatr Transplant*. 2022: e14446.
- 10. Sugianto RI, Schmidt BMW, Memaran N, et al. Sex and age as determinants for high blood pressure in pediatric renal transplant recipients: A longitudinal analysis of the CERTAIN Registry. *Ped Nephrol.* 2019; accepted for publication.
- 11. Brady TM, Roem J, Cox C, et al. Adiposity, Sex, and Cardiovascular Disease Risk in Children With CKD: A Longitudinal Study of Youth Enrolled in the Chronic Kidney Disease in Children (CKiD) Study. *Am J Kidney Dis.* 2020;76(2): 166-173.
- 12. von der Born J, Baberowski S, Memaran N, et al. Impact of Sex and Obesity on Echocardiographic Parameters in Children and Adolescents. *Pediatr Cardiol.* 2022.
- 13. Sugianto RI, Memaran N, Schmidt BMW, et al. Findings from 4C-T Study demonstrate an increased cardiovascular burden in girls with end stage kidney disease and kidney transplantation. *Kidney Int.* 2021.
- 14. Wyld MLR, De La Mata NL, Masson P, O'Lone E, Kelly PJ, Webster AC. Cardiac Mortality in Kidney Transplant Patients: A Population-based Cohort Study 1988-2013 in Australia and New Zealand. *Transplantation*. 2021;105(2): 413-422.
- 15. Stocklassa T, Borchert-Morlins B, Memaran N, et al. Sex Differences in Subclinical Cardiovascular Organ Damage After Renal Transplantation: A Single-Center Cohort Study. *J Womens Health (Larchmt)*. 2020.
- 16. Lau A, West L, Tullius SG. The Impact of Sex on Alloimmunity. *Trends Immunol.* 2018;39(5): 407-418.
- 17. Maenosono R, Nian Y, Iske J, et al. Recipient sex and estradiol levels affect transplant outcomes in an age-specific fashion. *Am J Transplant*. 2021.
- 18. Chacon-Alberty L, Ye S, Daoud D, et al. Analysis of sex-based differences in clinical and molecular responses to ischemia reperfusion after lung transplantation. *Respir Res.* 2021;22(1): 318.
- 19. Adam I., Motyka B., Tao K., Cowan P., J. WL. Natural vs. induced ABO antibodies in a murine model: Role of sex and T cells. Paper presented at: American Transplant Congress2022; Boston.
- 20. Anjum B, Adam I, Fersovich J, et al. FEMALE COMPLEXITY: HIGH 'NATURAL' ABO ANTI-A ANTIBODIES AND IGG CLASS SWITCH IN FEMALE VS MALE MICE. Paper presented at: Transplantation2020.
- 21. Arnold AP. X chromosome agents of sexual differentiation. *Nat Rev Endocrinol.* 2022;18(9): 574-583.

- 22. Suah AN, Tran DV, Khiew SH, et al. Pregnancy-induced humoral sensitization overrides T cell tolerance to fetus-matched allografts in mice. *J Clin Invest*. 2021;131(1).
- 23. Jesudason S, Piccoli GB. Pregnancy outcomes after kidney transplantation: the challenges of success. *Kidney Int.* 2022;102(4): 697-699.
- 24. Morgan JC, Foster BJ, Vinson AJ, et al. Navigating the Dobbs versus Jackson America for Patients with CKD and Kidney Transplants. *J Am Soc Nephrol*. 2023;34(2): 201-204.
- 25. Sawinski D, Hendren E, Cunningham A, Niederhaus SV, Gill JS. The Importance of Maintaining Reproductive Choices for Kidney Transplant Recipients. *J Am Soc Nephrol.* 2023;34(2): 198-200.
- 26. Crenshaw KW. Mapping the Margins: Intersectionality, Identity Politics, and Violence Against Women of Color. In: Fineman MA, Mykitiuk R, eds. *The Public Nature of Private Violence*. New York: Routledge; 1994:93-120.
- 27. Aguilera V, Andacoglu O, Francoz C, et al. Gender and Racial Disparity Among Liver Transplantation Professionals: Report of a Global Survey. *Transpl Int.* 2022;35: 10506.
- 28. Mannon RB, Reed EF, Melk A, et al. A multi-faceted approach to sex and gender equity in solid organ transplantation: The Women in Transplantation Initiative of The Transplantation Society. *Front Immunol.* 2022;13: 1006855.
- 29. Rogers WA. GENDER INEQUITIES IN ORGAN DONATION AND TRANSPLANTATION A feminist bioethics analysis. In: Rogers WA, Scully JL, Carter SM, Entwistle VA, Mills C, eds. *THE ROUTLEDGE HANDBOOK OF FEMINIST BIOETHICS*. Vol 30. New York: Routledge; 2023:421-435.

Table 1. Future research areas in transplantation medicine as outlined for each dimension of biology (sex), psychosocial and cultural (gender), and the interaction of both.

Cells/Tissues/Organs Basic/clinical research	Organism/individual Clinical/observational/qualitative research	Population Observational/qualitative research
SEX as biologic factor	interaction/combined contribution of SEX and GENDER	GENDER as Psychosocial, cultural, economic factor
Sex differences in cell repair and regeneration.	Identifying differences in graft and patient survival.	Understanding reasons of differences in donation.
Sex differences in inflammatory responses.	Impact of sex mismatch.	Identifying disparities in access to transplant, re-transplant, and post-transplant care in different countries with regard to medical care and cultural aspects.
Characterization of sex- specific immune reactivity at different stages across the lifespan.	Identifying differences in all causeand specific-excess mortality between sexes.	Understanding physicians' decisions regarding transplant eligibility/delisting and if this differs with regard to patients' gender in different countries.
Addressing the interaction of sex and age in experimental models.	Understanding how sex modifies the impact of risk factors and the progression of comorbidities.	Understanding patients' decisions regarding transplantation and whether this differs amongst genders.
Identifying sex-specific biomarkers regarding cardiovascular morbidity.	Immunosuppressive/medication adherence (behavioral modification).	High quality data to identify the proportion of transplant-eligible females and males on waitlists in different countries.
Understanding sex differences in pharmacokinetics and pharmacodynamics.	Identifying sex/gender differences in quality of life/ life participation post-transplant.	Understanding recipients' decisions on family planning.
Impact of pregnancy on access to transplantation and post-transplant outcomes.	Models of care for pregnancy planning.	

Figures

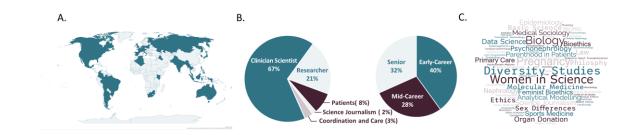


Figure 1. Distribution of participants' field of expertise and country of origin. (A) Map of participants' countries of origin. **(B)** Clinicians, clinician-scientists and scientists in addition to a science journalist and patient representatives actively participated in the meeting. Of those with a research background, two-thirds were early- or mid-career investigators. Patients, early-, mid-level and senior investigators coming from low- or middle-income countries were granted travel grants enabling attendance in person. **(C)** Participants' field of expertise and particular topics discussed during the meeting. Color and font size were assigned randomly.

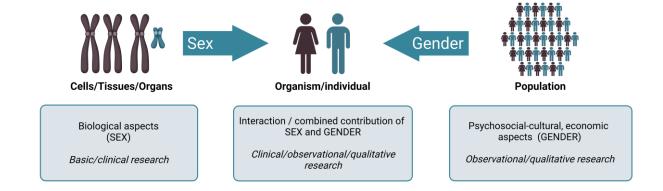
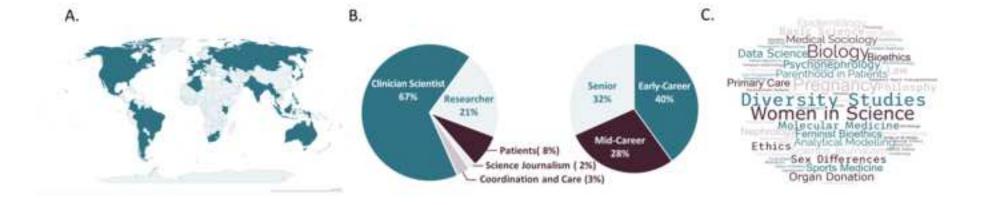


Figure 2. Interaction of sex and gender on transplantation. Biology (sex), psychosocial and cultural (gender) factors interact to influence outcomes. Given the complex interaction of donor and recipient, in addition to the different dimensions of sex and gender, their impact on transplantation outcomes must be addressed using basic science, clinical, observational, and population studies. A deeper understanding of the root causes for existing disparities in transplantation must be addressed through quantitative as well as qualitative research.













Cells/Tissues/Organs

Organism/individual

Population

Biological aspects (SEX)

Basic/clinical research

Interaction / combined contribution of SEX and GENDER

Clinical/observational/qualitative research Psychosocial-cultural, economic aspects (GENDER)

Observational/qualitative research