

COMMENTARY: VALUING THE VULNERABLE – THE IMPORTANT ROLE OF TRANSGENDER COMMUNITIES IN BIOMEDICAL RESEARCH

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Every cell has a genetic sex that is determined at the time of fertilization. However, the natal sex of cells may not match the hormonal environment in which they reside in transgender individuals. This discordance provides a unique opportunity to study the short- and long-term effects across a range of cellular functions, health conditions, physiologic processes and psychosocial outcomes to the benefit of transgender and cisgender communities. While there is a growing body of knowledge as the literature on sex differences in virtually every organ system accumulates, there remains a paucity of data on the effect of cross hormonal therapy on cellular function in transgender individuals. Beyond cellular function, the effect of cross hormonal therapy on neuroanatomy, the interpretation of neuropsychological assessments or even the effect of daily stressors of stigma and discrimination on long-term neurocognitive function remain unclear.

In 2011 the Institute of Medicine indicated that transgender adults were an understudied population and in critical need of more biomedical and population health research, yet the experience of stigma, discrimination, microaggressions, limited access to culturally competent care continue to make this an unfulfilled mandate. In addition to using a life course perspective, it is essential to identify research gaps and formulate a responsive research agenda while maintaining scientific rigor and respectful involvement of the population under study. None of this, however, will enhance the participation of transgender communities in biomedical research until the transgender and biomedical research communities can engage in open, respectful and bidirectional dialogue.

From respectful, sensitive and appropriate health care to culturally competent research engagement from study inception to data dissemination, transgender communities can make an important and valuable contribution to biomedical research. Inclusion of their voices at all levels, including investigators

BIOLOGIC SEX OF TRANSGENDER INDIVIDUALS

Biologic sex is determined at birth and is conferred on every cell in the body.¹ From monocytes and macrophages to cardiac myocytes, all cells possess a biologic sex. For transgender individuals however, the biologic sex of their cells may not match their hormonal environment. This discordance between the biologic sex of the cell and its hormonal environment provides a unique - and arguably - important opportunity for both the transgender and biomedical research communities

from transgender communities, are essential to advance this much overdue scientific agenda. Transgender, cisgender and the biomedical research communities will all benefit from a more inclusive and expansive research agenda. *Ethn Dis.* 2020;30(2):247-250; doi:10.18865/ed.30.2.247

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to advance not only the science, but also the understanding of the biologic impact of these differences across a range of health conditions and therapies for which there are limited data.

PAUCITY OF DATA ON DIFFERENCES BETWEEN CISGENDER AND TRANSGENDER

With the rapidly accumulating knowledge resulting from the exploration of sex as a biological variable, the paucity of data available on the differences between cisgender and transgender cells, especially when in different hormonal environments, and the consequences of such differences is noteworthy.² There are data that clearly demonstrate sex and age differences in cardiac aging for example, with evidence to suggest that the number of ventricular myocytes declines with age through apoptosis in men, but not in women.³ While this finding may help explain why men are more likely than women to experience heart failure with reduced ejection fraction, data on what happens to aging male myocytes in an estrogen rich environment over the lifespan, compared with cisgender males, are limited. Do these myocytes still undergo apoptosis, and, if so, is

this due to programming based on their biologic sex, or do these myocytes behave more like female myocytes or somewhere in between the two biologic sex effects? Similarly, studies of cardiovascular aging in transgender men and women are limited and the studies that have been reported often have very small numbers. Differences in endothelial function, mitochondrial activity and additional factors are important to understand, not only

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for the health of both cisgender and transgender persons, but because some disease treatment options offered to cisgender males (as an example) include estrogen, and those data could help inform our understanding of the risks and benefits to the patient. Data on these differences are slowly accumulating, but are still limited, emphasizing the need for additional research.⁴⁻⁶

RESEARCH NEEDED ON PATHOPHYSIOLOGY FOR CHRONIC CONDITIONS IN TRANSGENDER PERSONS

Cardiovascular disease and aging are among many areas with limited data among transgender individuals. Neuropsychological assessments and

guidelines for the conduct and interpretation of these assessments among transgender persons are also limited.⁷ Mental health stressors and disorders differ significantly between cisgender and transgender individuals.⁸ Mustanski and colleagues have found that among lesbian, gay, bisexual and transgender (LGBT) youth with steadily high or increasing levels of victimization from adolescence to early adulthood were at higher risk for depression and posttraumatic stress disorder.⁹ These experiences of victimization and discrimination have been collectively labeled as minority stressors, and have been associated with harm to health and well-being. More specifically, these chronic stressors contribute to LGBT health disparities, and increase the risk for cognitive decline.⁸ How these stressors interact, if at all, with the neuroanatomy of transgender persons, remains unclear. There are conflicting findings about the neuroanatomy of transgender persons and whether it more closely resembles the neuroanatomy of their natal sex or their gender identity.¹⁰ It is well-known that sexual dimorphism is widespread in the brain; men possess larger putamen, amygdala and hippocampal volumes than women.¹¹ A recent structural magnetic resonance imaging study of transgender persons on cross sex hormone therapy further demonstrated this brain sexual dimorphism. A total of ninety-two study participants were examined: 18 transwomen and 17 transmen, 30 cisgender males and 27 cisgender females. Transwomen and cisgender males showed little difference in the amygdala and putamen; however, transwomen did differ from cisgender males in brain volume in other areas. The extent

to which cross hormones created these changes, as well as how fluid they are remains unknown.¹¹ The relationship of these changes to cognitive decline has been mainly unexplored to date.

Medicare beneficiary data on transgender, compared with data from cisgender beneficiaries, confirms disparities in several conditions from asthma to hepatitis to HIV, schizophrenia and substance use disorders.¹² Yet little is known about any unique underlying antecedents or pathophysiology for these conditions in transgender persons. There are a range of health conditions of concern for transgender persons: hypertension, cardiovascular disease, venous thromboembolic events, osteoporosis, diabetes, neuropsychiatric disorders and more.¹³ For most of these conditions, the data from studies are limited by small numbers, case series and case reports. A literature review of primary transgender health care research from January 1, 2001 to June 30, 2015 was performed to identify research gaps and opportunities. Although 1304 eligible records were identified, only 41 discussed transgender primary or preventive care. The majority of the studies addressed HIV rates or risk behaviors, while fewer articles covered pelvic examinations, tobacco use, insurance coverage, and cholesterol screenings. No studies addressed mammography or chest/breast tissue examinations, colorectal screenings, or flu shots.¹⁴ Research on HIV treatments, HIV prevention and sexual health disorders in contrast are more comprehensive; however, the needs of transgender communities clearly extend far beyond the reproductive and sexual. Recently, primary care guidelines have emerged for transgender

patients including those who are aging.^{15,16} However, primary care management needs to be evidence-based and this foundation is limited at present.

In a 2011 report, the Institute of Medicine (IOM) indicated that transgender adults were an understudied population and in critical need of more biomedical and population health research.¹⁷ This report followed the 1999 IOM report on lesbian health. In 2010, the National Institutes of Health requested that the IOM convene a committee to review the state of the knowledge about the health of lesbian, gay, bisexual and transgender people. This also included identifying research gaps and formulating a responsive research agenda. This extensive report identified important considerations when conducting research among these populations; recommendations included: utilizing a life course perspective; and, incorporating culturally competent study designs while maintaining scientific rigor and respectful involvement of the population under study from research design to data collection and dissemination.¹⁷ In addition, the report noted it was essential that research in these populations also recognize the many subpopulations, including racial and ethnic minority individuals who are also a sexual minority and thus experience stigma and discrimination on multiple levels. Finally, the report also noted the paucity of research in many areas, especially for young and elder transgender persons, as well as the disparities in mental health disorders (anxiety, depression, mood disorders) and the long-term consequences of hormone use.¹⁷

Yet, despite a growing transgender community, research on these differ-

ences between cisgender and transgender persons on a macrostructural, as well as cellular, metabolic, immunologic and physiologic level (not to mention the additional role of hormones) remains limited. In the meantime, important scientific questions remain unanswered, evidence to support primary care management guidelines is unavailable, and mistrust of the biomedical research enterprise continues.

COLLABORATION BETWEEN TRANSGENDER AND BIOMEDICAL RESEARCH COMMUNITIES

The transgender and the biomedical research communities must partner to not only address the scientific questions that arise, but also to expand the scientific knowledge of the many cellular, hormonal, metabolic, and pharmacologic interactions for the benefit of both cis-gender and transgender communities. Stigma, mistrust, limited health care access, ignorance, and institutional bias have stunted growth in these areas for far too long – and simply cannot be allowed to continue unchecked for yet another eight years.

Until more data are available there are steps that primary care providers and transgender individuals can take to maximize opportunities for better health outcomes and engagement with health care systems.¹⁸ Transgender patients must understand that the number of health care providers with transgender care expertise remains limited. The good news is that surveys of primary care providers demonstrate the majority are willing and ready to provide care for transgender patients.¹⁹ Finding

a primary care provider to work with, who understands and is respectful of transgender patients, including the preferred pronouns, is an important first step. Self-advocacy and awareness of the characteristics of gender affirming care will help identify practices that are transgender-friendly.¹⁹ Given that the life histories of many transgender persons include stigma, discrimination and even violence, having access to trauma-informed care is also essential.²⁰

For providers, there are guidelines to assist in the care of the transgender patient. Arguably as important, if not more so, is an openness and willingness to care for transgender patients with

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respect, care, diligence and understanding. Providers must also become familiar with the basics of gender affirming care including use of preferred pronouns, name and carrying this affirmation across the psychological (resisting transphobia), medical (hormonal therapies, surgeries) and legal (legal name change) components of transgender care.²⁰ Registration and intake forms that collect sex at birth and gender identity are important aspects of gender affirming care.²⁰ Finally, a multidisciplinary care team may provide the most integrated approach to gender affirming service delivery for this population.²⁰ As

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transgender persons can have a variety of organs in a configuration that may be unfamiliar (breasts and a prostate or ovaries but no uterus or breasts), care focused on an organ-based approach may be preferable to relying on natal sex. This is especially true as transgender patients age and need cancer screening.

CONCLUSION

Ultimately, the path to a more robust and productive transgender research agenda will neither be easy, smooth nor fast. The lived experience of transgender individuals is a gaping wound, repeatedly opened by micro- and macroaggressions driven by fear, ignorance, stigma and discrimination.²¹ Lack of access to care and limited numbers of medical providers knowledgeable about transgender care only aggravate this wound, driving those who most need care further away from health care and research.²²

Open bidirectional dialogue with transgender communities, providing respectful, sensitive and culturally appropriate health care, culturally competent research engagement from study inception to data dissemination, and, including investigators that resemble the affected community will help. Yet these efforts will fall exceedingly short until we recognize the value of transgender communities for what is at their core – their humanity. When biomedical research and health care systems can recognize this shared human bond with mutual respect for the commonalities and differences they seek to explore, the road to scientific discovery and engagement will be opened. Let the healing journey begin.

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REFERENCES

1. O'Hanlan KA, Gordon JC, Sullivan MW. Biological origins of sexual orientation and gender identity: impact on health. *Gynecol Oncol*. 2018;149(1):33-42. <https://doi.org/10.1016/j.ygyno.2017.11.014> PMID:29605047
2. Clayton JA. Applying the new SABV (sex as a biological variable) policy to research and clinical care. *Physiol Behav*. 2018;187:2-5. <https://doi.org/10.1016/j.physbeh.2017.08.012> PMID:28823546
3. Merz AA, Cheng S. Sex differences in cardiovascular ageing. *Heart*. 2016;102(11):825-831. <https://doi.org/10.1136/heartjnl-2015-308769> PMID:26917537
4. Shatzel JJ, Connelly KJ, DeLoughery TG. Thrombotic issues in transgender medicine: A review. *Am J Hematol*. 2017;92(2):204-208. <https://doi.org/10.1002/ajh.24593> PMID:27779767
5. Defreyne J, Van de Bruaene LDL, Rietzschel E, Van Schuylenbergh J, T'Sjoen GGR. effects of gender-affirming hormones on lipid, metabolic, and cardiac surrogate blood markers in transgender persons. *Clin Chem*. 2019;65(1):119-134. <https://doi.org/10.1137/clinchem.2018.288241> PMID:30602477
6. Stanhewicz AE, Wenner MM, Stachenfeld NS. Sex differences in endothelial function important to vascular health and overall cardiovascular disease risk across the lifespan. *Am J Physiol Heart Circ Physiol*. 2018;315(6):H1569-H1588. <https://doi.org/10.1152/ajpheart.00396.2018> PMID:30216121
7. Trittschuh EH, Parmenter BA, Clausell ER, Mariano MJ, Reger MA. Conducting neuropsychological assessment with transgender individuals. *Clin Neuropsychol*. 2018;32(8):1393-1410. <https://doi.org/10.1080/13854046.2018.1440632> PMID:29463167
8. Correrro AN, Neilson KA. A review of minority stress as a risk factor for cognitive decline in lesbian, gay, bisexual and transgender (LGBT) elders. *J Gay Lesbian Ment Health*. 2019. <https://doi.org/10.1080/19359705.2019.1644570>
9. Mustanski B, Andrews R, Puckett JA. The effects of cumulative victimization on mental health among lesbian, gay, bisexual, and transgender adolescents and young adults. *Am J Public Health*. 2016;106(3):527-533. <https://doi.org/10.2105/AJPH.2015.302976> PMID:26794175
10. Mueller SC, Landré L, Wierckx K, T'Sjoen G. A structural magnetic resonance imaging study in transgender persons on cross-sex hormone therapy. *Neuroendocrinology*. 2017;105(2):123-130. <https://doi.org/10.1159/000448787> PMID:27490457

11. Ruigrok AN, Salimi-Khorshidi G, Lai MC, et al. A meta-analysis of sex differences in human brain structure. *Neurosci Biobehav Rev*. 2014;39:34-50. <https://doi.org/10.1016/j.neubiorev.2013.12.004> PMID:24374381
12. Dragon CN, Guerino P, Ewald E, Laffan AM. Transgender medicare beneficiaries and chronic conditions: exploring fee-for-service claims data. *LGBT Health*. 2017;4(6):404-411. <https://doi.org/10.1089/lgbt.2016.0208> PMID:29125908
13. Feldman J, Brown GR, Deutsch MB, et al. Priorities for transgender medical and healthcare research. *Curr Opin Endocrinol Diabetes Obes*. 2016;23(2):180-187. <https://doi.org/10.1097/MED.0000000000000231> PMID:26825469
14. Edmiston EK, Donald CA, Sattler AR, Peebles JK, Ehrenfeld JM, Eckstrand KL. Opportunities and gaps in primary care preventative health services for transgender patients: a systemic review. *Transgend Health*. 2016;1(1):216-230. <https://doi.org/10.1089/trgh.2016.0019> PMID:28861536
15. Selix NW, Rowniak S. Provision of patient-centered transgender care. *J Midwifery Womens Health*. 2016;61(6):744-751. <https://doi.org/10.1111/jmwh.12518> PMID:27783887
16. Gamble RM, Taylor SS, Huggins AD, Ehrenfeld JM. Trans-specific Geriatric Health Assessment (TGHA): an inclusive clinical guideline for the geriatric transgender patient in a primary care setting. *Maturitas*. 2020;132:70-75. <https://doi.org/10.1016/j.maturitas.2019.12.005> PMID:31883667
17. Institute of Medicine. *The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding*. Washington, DC: The National Academies Press; 2011.
18. Safer JD, Coleman E, Feldman J, et al. Barriers to healthcare for transgender individuals. *Curr Opin Endocrinol Diabetes Obes*. 2016;23(2):168-171. <https://doi.org/10.1097/MED.0000000000000227> PMID:26910276
19. Shires DA, Stroumsa D, Jaffee KD, Woodford MR. Primary care clinicians' willingness to care for transgender patients. *Ann Fam Med*. 2018;16(6):555-558. <https://doi.org/10.1370/afm.2298> PMID:30420373
20. Reisner SL, Radix A, Deutsch MB. Integrated and Gender-affirming transgender clinical care and research. *J Acquir Immune Defic Syndr*. 2016;72(suppl 3):S235-S242. <https://doi.org/10.1097/QAI.0000000000001088> PMID:27429189
21. Mizock L, Lewis TK. Trauma in transgender populations: risk, resilience, and clinical care. *J Emotional Abuse*. 2008;8(3):335-354. <https://doi.org/10.1080/10926790802262523>
22. Chen JA, Granato H, Shipherd JC, Simpson T, Lehavot K. A qualitative analysis of transgender veterans' lived experiences. *Psychol Sex Orientat Gen Divers*. 2017;4(1):63-74. <https://doi.org/10.1037/sgd0000217>