Biocultural approaches to transgender and gender diverse experience and health: Integrating biomarkers and advancing gender/sex research

L. Zachary DuBois | James K. Gibb | Robert-Paul Juster | Sally I. Powers

1Department of Anthropology, University of Oregon, Eugene, Oregon
2Department of Anthropology, University of Toronto, Ontario, Canada
3Psychiatry and Addiction, University of Montreal, Quebec, Canada
4Psychological and Brain Sciences, University of Massachusetts Amherst, Amherst, Massachusetts

Abstract
Transgender and gender diverse (TGD) people are increasingly visible in U.S. communities and in national media. With this increased visibility, access to gender affirming healthcare is also on the rise, particularly for urban youth. Political backlash and entrenchment in a gender binary, however, continue to marginalize TGD people, increasing risk for health disparities. The 2016 National Institute of Health recognition of sexual and gender minority people as a health disparities population increases available funding for much-needed research. In this article, we speak to the need for a biocultural human biology of gender/sex diversity by delineating factors that influence physiological functioning, mental health, and physical health of TGD people. We propose that many of these factors can best be investigated with minimally invasively collected biomarker samples (MICBS) and discuss how to integrate MICBS into research inclusive of TGD people. Research use of MICBS among TGD people remains limited, and wider use could enable essential biological and health data to be collected from a population often excluded from research. We provide a broad overview of terminology and current literature, point to key research questions, and address potential challenges researchers might face when aiming to integrate MICBS in research inclusive of transgender and gender diverse people. We argue that, when used effectively, MICBS can enhance human biologists' ability to empirically measure physiology and health-related outcomes and enable more accurate identification of pathways linking human experience, embodiment, and health.

1 | Toward a Human Biology of Gender/Sex & Sexual Diversity

Gender and sex are central concepts in anthropology. Binary sex and gender categories of male/female and man/woman also structure research in human biology. Taken together, sex and gender organize and guide research questions, study design and interpretations of data. Anthropology has clearly contributed to understanding the diverse ways that gender is lived across cultures and the breadth of variation in biological sex (eg, see Ainsworth, 2015; Blackless et al., 2000; Davies, 2007, 2010; Fausto-Sterling, 2000; Herdt, 1994; Nanda, 1999). Yet despite decades of growth in biocultural approaches, it remains uncertain how best to engage this diversity and the interactions among gender and sex (Fausto-Sterling, 2012; Hoke & Schell, 2020; Leatherman &
In this article, we suggest ways to broaden biocultural research when working with transgender and gender diverse (TGD) people through the integration of minimally invasively collected biomarker samples (MICBS). To facilitate research in this area, we provide a broad overview of terminology and the current literature, point to some key questions, and address potential challenges researchers might face when aiming to integrate MICBS in research inclusive of TGD and sexual minority (SM) people. We argue that effective use of MICBS can enhance human biologists’ ability to measure physiology and health-related outcomes while also enabling more accurate identification of pathways linking human experience, embodiment, and health within these populations.

When it comes to acknowledging the diversity of gender/sex and sexual orientation that exists, terminology can be confusing and even intimidating. Identity terms are highly politicized, deeply personal, and ever evolving through cultural change, exchange, and enhanced visibility. Broadly speaking, the term “gender” refers to more fluid and culturally contextualized expressions of experience and identity. On the other hand, “sex” refers to biological characteristics (e.g., reproductive organs, hormones, and genes) that is often assumed to be more static and foundational. The separation of these terms initially emerged from a feminist aim to disentangle “gender” from reductionist and essentializing biologies of “sex.” Yet, the very definitions of these terms and their interaction with one another is constantly contested and in flux. Terms including “cisgender” (people who identify with their assigned birth sex) and “transgender” (people who do not identify with their assigned birth sex) help to honor diverse identities and undermine assumptions about fixed relationships between identity, lived experience, and the body.

In this article, we will use the terms transgender/trans and gender diverse (TGD) to capture a myriad of identities. As a population, TGD people reflect a range of identities, gender expressions, and sexual orientations within and between regions and countries worldwide (Reisner et al., 2016). Nonetheless, umbrella terms may not entirely capture the breadth of lived experiences and identities of people globally. Gender-identities and experiences that are not aligned with binary conceptions of gender/sex include, for example, the Hijra in India, Waria in Indonesia, Travesti in Brazil, and Two Spirit among Indigenous people in North America (Boellstorff, 2004; Davies, 2010; Kulik, 1998; Nanda, 1999). Following scholars that are advancing research beyond historical constructions of gender and sex binaries, we will use the combined term “gender/sex” (Fausto-Sterling, 2019; van Anders, 2015; van Anders et al., 2017). This combined term highlights gender/sex as lived in an integrated embodied fashion (Krieger, 2005; Worthman & Costello, 2009) but may not be universally appropriate. It should be noted that for some people, combining gender/sex in this way can be problematic or suggest integration of gender identity and the body in ways that may not be affirming of their experience.

Neither sex nor gender are inherently categorical or binary (Štrkalj & Pather, 2020). While many research questions in human biology warrant group level analyses regarding gender/sex, it is recommended to be transparent and mindful of what informs each study’s categorization of gender/sex and to include working definitions (for recommendations, see Puckett, Brown, Dunn, Mustanski, & Newcomb, 2020). Where possible, we suggest considering the dimensions that inform the gender/sex categories used and to assess aspects of gender and sex separately as well as in interaction with one another (Garofalo & Garvin, 2020; Krieger, 2003). Recent sociopolitical events have raised the issue of human rights for TGD people to the forefront of the social, political, and cultural milieu. A few recent examples include U.S. policies aiming to rigidly define “biological sex,” policies that are “sex-based” promoting transgender-based discrimination in homeless shelters, reversal of protections against medical discrimination of TGD patients, and a U.S. supreme court ruling protecting TGD people from employment discrimination (see Fadulu & Flanagan, 2019). Each of these examples highlight the need for clarity in how human biologists approach research inclusive of gender or sex data and highlight our capacity to contribute to understandings of gender and sex diversity.

Foundational scholarship has shown range and variability in many characteristics traditionally used to define “anatomical sex.” This work reveals a plurality that cannot be neatly bound within binary gender/sex categories (Blackless et al., 2000; Fausto-Sterling, 2000). Recent work shows remarkable plasticity in characteristics of “hormonal sex,” such as variation in testosterone levels in response to relational (Gettler, McDade, Feranil, & Kuzawa, 2011; Kuzawa, Gettler, Huang, & McDade, 2010; van Anders, Hamilton, & Watson, 2007) and socioecological factors (Bribiescas, 1996; Bribiescas & Hill, 2010; Ellison et al., 2002). In addition, fluctuations and psychosocial responsibility of hormones show the limitations of categorical binaries when relating biology to presumed “gendered” behaviors (van Anders, 2013). Scholars have proposed conceptualizations of a “mosaic” rather than binary brain (Joel, 2012; Joel et al., 2015) and “sexual polymorphism” rather than sexual dimorphism (Astorino, 2019). These examples showcase how human biology contributes to our understanding of the interconnecting biosocial nature of
gender/sex while also expanding knowledge and dialogue about human biological variation.

Advancing gender/sex research that is inclusive of TGD people nonetheless presents challenges related to invisibility, access, and lack of data. Broadly speaking, the current population of TGD adults ranges from approximately 25-90 million people worldwide, with estimates of almost 1 million in the United States (Meerwijk & Sevelius, 2017; Winter et al., 2016). Most prevalence data likely underrepresent the number of people who identify outside of the gender/sex binary. The U.S. census, for example, does not currently include data on gender identity (Meerwijk & Sevelius, 2017). This invisibility extends to anthropology and other social and health sciences where data collection methods often only document assigned sex at birth (male/female). This omission undermines the recognition and inclusion of TGD people. Despite this systematic marginalization, TGD people—especially in North America—are increasingly visible in political and public life. Some say we have even reached a “trans tipping point” (Steinmetz, 2014) in socio-cultural advances. Nonetheless, TGD people face significant political backlash, further entrenchment in a rigid gender binary, and high levels of violence, stigma, and discrimination targeting in particular trans women of color (Grant, Motter, & Tanis, 2011; Puckett, Maroney, Wadsworth, Mustanski, & Newcomb, 2019; White Hughto, Reisner, & Pachankis, 2015). These adversities in turn contribute to health disparities among TGD people as compared to the general population (Downing & Przedworski, 2018; Reisner et al., 2016; Su et al., 2016; Winter et al., 2016).

Our aim in this article is to address some of the challenges inherent to advancing our understanding of human biology with refined considerations of gender/sex and sexual diversity. Until recently, research inclusive of TGD people has been relatively under-funded and under-recognized as a priority area. Effective advocacy and visibility have expanded awareness and resources for work in this area. For instance, in 2016, the National Institute of Health formally designated sexual and gender minority people as a health disparities population (NIMHD, 2016). We believe that the expertise of bioculturally oriented human biologists and biological anthropologists is essential for continuing to advance understanding of human bodily and experiential variation beyond the gender/sex binary.

2 | INTEGRATING MICBS INTO TARGET AREAS IN GENDER/SEX RESEARCH

Human biology research that focuses on gender/sex and sexual diversity is poised for advancement. Here, we provide an overview of research inclusive of TGD people to suggest how MICBS have and can continue to enhance research contributing to these specific communities and elaborate our understanding of gender/sex diversity. Broadly speaking, including MICBS in research can enhance inclusion of lived experiences of gender, identity and sexual diversity. For example, measurement of MICBS such as via saliva and dried blood spots (DBS) allows an assessment of health and the identification of pathways through which experiences can become embodied (Worthman & Costello, 2009).

MICBS provide measures of physiological processes, function, and/or therapeutic outcomes (McDade, Burhop, & Dohnal, 2007). They provide a key tool to examine interactions of biology, cultural experience, and context. Indeed, biological anthropologists have shown the importance of “making the invisible visible” and provide research examples of how to draw on MICBS to do so (Sievert & Brown, 2016). A substantial body of biocultural research can guide future MICBS-inclusive research focused on understanding health disparities of TGD people. This extant research includes studies among ethnic and racialized minority people to understand how negative experiences (e.g., discrimination, lifestyle incongruity) become embodied. For example, these adversities contribute to impaired growth (Crooks, 1999; Nyberg et al., 2012), elevated blood pressure and hypertension (Bindon, Knight, Dressler, & Crews, 1997; Dressler, Oths, & Gravlee, 2005; Gravlee, 2009; McClure et al., 2010), increased evening cortisol (Thayer & Kuzawa, 2015), and impaired immune function (Copeland et al., 2014).

Importantly, the use of MICBS can also enhance research participation and enable us to address questions of direct interest to TGD people. Health-related questions continue to remain a priority within this community and the use of MICBS enable data collection outside of clinical settings. This can significantly reduce participant burden and discomfort (see Table 1) as compared to more invasive methods (e.g, venous blood draw) (McDade, Williams, & Snodgrass, 2007; Worthman & Costello, 2009). This is key because stigma and discrimination contribute to poor treatment of TGD people, including in interactions with medical providers. For many TGD people, these interactions can be painful, even traumatic, making “clinical”-like interactions something to dread if not avoid entirely (Padilla, Rodriguez-Madera, Varas-Diaz, & Ramos-Piburns, 2016; Poteat, German, & Kerrigan, 2013; Puckett, Cleary, Rossman, Mustanski, & Newcomb, 2018; Rotondi et al., 2013; Safer et al., 2016; White Hughto, Murchison, Clark, Pachankis, & Reisner, 2016). Failure to respond sensitively to these barriers and issues of mistrust can further limit the degree to which TGD people participate in research (Owen-Smith et al., 2016).
Current research inclusive of TGD people emerges primarily from biomedicine, psychology, epidemiology, and public health. However, we are aware of only a handful of studies that include MICBS. Moreover, outside of HIV-focused work, cross-cultural research on the health of TGD people remains scant as the majority of existing studies draw their samples from Western, Educated, Industrialized, Rich, and Democratic (WEIRD) populations (Henrich, Heine, & Norenzayan, 2010; Clancy & Davis, 2019). Prior to 2016, most studies with physiological data inclusive of TGD people were conducted in clinical contexts, involved invasive sampling, and focused primarily on measuring the safety and efficacy of gender affirming hormonal therapies and/or surgeries (ie, medical transition) or HIV/AIDS.

Below we will identify seven key conceptual areas that showcase existing MICBS studies inclusive of TGD people and highlight important directions for future research related to: (a) minority stress and resilience, (b) transition and gender affirming care, (c) social relationships, (d) HIV/AIDS and global health, (e) structural violence and biology of everyday life, (f) health disparities, and (g) life course approaches and health. Genetic and epigenetic markers provide additional ways forward, but they have yet to be included in TGD research. Our focus here remains on physiological markers and we point to target questions for future research in this area in Table 2.

### 2.1 Minority stress and resilience

The impact of stress and stigma are key areas for understanding the lives and health of TGD people. Human biologists have shown how broader social, political-economic, and structural factors mediate variation in biological and health outcomes, particularly among marginalized groups (Goodman & Leatherman, 1998; Leatherman & Goodman, 2020). In so doing, stigma and stress frameworks enable understandings of health disparities as they emerge and are exacerbated within a sociocultural context (Brewis & Wutich, 2019; Meyer, 2003; White Hughto et al., 2015). Minority stressors are understood to occur at multiple levels, including structural (eg, societal and institutional-level policies and practices) and interpersonal levels (eg, discrimination and violence), with downstream effects at the individual level (eg, internalized stigma or identity concealment) negatively affecting health and well-being (Hendricks & Testa, 2012; Meyer, 2003; Timmins, Rimes, & Rahman, 2017).

Much research employs minority stress frameworks to understand experience and health among SM people, including TGD people. Ethnographic work is useful to understand experiences of gender/sex diversity in countries with high rates of anti-trans violence, for example, ethnographies of transgender women in Brazil (Kulik, 1998) and the U.S. (Valentine, 2007). Prejudicial policies, social stigma, and experiences of discrimination are particularly salient stressors for TGD people and can be key determinants of both mental and physical health disparities (Hatzenbuehler & McLaughlin, 2014). Nonetheless, despite the adaptation of minority stress frameworks for examining how stress specific to TGD people becomes embodied, these models are in need of testing and expansion to reflect TGD lived experience. Much remains to be done in this target area, including identifying TGD specific stressors, continued integration of MICBS, and further developing appropriate models for characterizing experiences unique to TGD people.

Studies linking psychosocial stress to embodied experience and health is one area in which MICBS have been integrated into field-based research among TGD people (DuBois, 2012a; DuBois, 2012b; DuBois, Powers, Everett, & Juster, 2017; Hodges-Simeon et al., 2020; Madera et al., 2017; McQuillan, Kuhns, Miller, McDade, & Garofalo, 2020). In these studies, stress is defined as the real or perceived threat to an individual that results in biobehavioral responses (McEwen & Seeman, 1999). Stress hormones like cortisol provide reliable assessments of physiological stress responses and can also be measured using minimally invasive sampling techniques (e.g., saliva) to capture day-to-day variation (Ice, Katz-Stein, Himes, & Kane, 2004; Loucks, Juster, & Pruessner, 2008). Cortisol can also be measured in hair and nails to assess the accumulation of stress hormones over several months, rather than diurnal hormone...
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<th>Topic</th>
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| Minority Stress & Resilience              | • How do various types of stressors experienced by TGD people become embodied impacting health and well-being?  
• What are the biobehavioral strategies employed by trans youth to overcome transprejudice, and how are these strategies associated with physiologic indicators of health?  
• What are the physiological correlates, contributors, and consequences of resilience of TGD persons?  
• How might answers to each question in this topic be impacted by additional identities other than gender/sex, such as race and ethnicity? |
| Transition and Gender Affirming Care       | • How do exogenously administered hormones interact with factors including poverty, racism, stress, allostatic load (AL), and diet impacting health?  
• What does a human biology of aging look like for TGD people who medically transition?  
• How does medical transition during various life stages, (e.g., pubertal suppression) impact development and long-term health of TGD people?  
• How might answers to each question in this topic be impacted by additional identities other than gender/sex, such as race and ethnicity? |
| Social Relationships                       | • What circumstances subject TGD people to greater relationship stress with negative consequences for health?  
• Are the benefits or stresses of relationships for TGD people particularly important for health outcomes in one life phase over another?  
• Under what conditions are resilience, physiological responses, and health of TGD people strengthened by relationships?  
• How might answers to each question in this topic be impacted by additional identities other than gender/sex, such as race and ethnicity? |
| HIV/AIDS & Global Health                   | • How might risk and treatment adherence be augmented by stigma-related stress for TGD people?  
• What health issues do low-income HIV-TGD people on pre-exposure prophylaxis (PrEP) face and what are effective interventions?  
• How might answers to each question in this topic be impacted by additional identities other than gender/sex, such as race and ethnicity? |
| Structural Violence and Biologies of Everyday Life | • What are the biological correlates of financial hardship experienced by TGD people?  
• How do TGD people experience food insecurity and houselessness, and what are the biosocial consequences?  
• How do health outcomes change from first entry to follow-up among TGD refugees and migrants?  
• Does migration buffer minority stress and enhance resilience among TGD people?  
• What are the psychosocial and physiologic correlates of gender-based discrimination and environmental exposure (environmental discrimination & injustice)?  
• How might answers to each question in this topic be impacted by additional identities other than gender/sex, such as race and ethnicity? |
| Health Disparities                         | • How do TGD people embody their experiences with food, water, or resource insecurity?  
• How do disparities in access to health care impact the health and well-being of TGD people?  
• How do TGD communities of color embody inequality?  
• What interventions are most impactful for supporting long-term health and well-being of TGD people? |
| Life Course Approaches & Health            | • How do experiences of bullying and/or rejection regarding gender/sex diversity during early life affect stress and disease risk later in life?  
• How do cultural variations in gender experience become embodied and impact health over the life course?  
• How do TGD peoples’ experiences of trauma affect cellular aging and telomere length?  
• How does the timing and experience of “coming out” impact growth and development?  
• How might pubertal suppression and/or gender affirming hormonal treatments for youth interact with socioeconomic, psychosocial, and nutritional factors to shape growth patterns?  
• How might answers to each question in this topic be impacted by additional identities other than gender/sex, such as race and ethnicity? |
changes (Fischer, Schumacher, Skoluda, & Strahler, 2020; Meyer & Novak, 2012). Although studies of acute hormone reactivity to psychosocial stressors have yet to be conducted among TGD people, sexual orientation has been found to modulate cortisol (Juster et al., 2015) and cardiovascular (Juster et al., 2019) stress reactivity. In these studies, compared to heterosexual controls, SM men show lower cortisol and higher heart rate while SM women show higher cortisol and no cardiovascular differences.

The first MICBS-based study inclusive of TGD people was The Transition Experience Study conducted with a U.S.-based sample of 65 transitioning transgender men. This pioneering study was the first to include MICBS among TGD people to understand how stigma and stress “get under the skin and skull.” The study remains unique in that it involved sampling of multiple biomarkers in addition to in-depth in-person interviews (DuBois, 2012a). MICBS of cortisol, testosterone, C-reactive protein (CRP) and Epstein-Barr virus antibodies were measured from saliva and DBS. In addition, 24-hr ambulatory blood pressure (amBP), bioimpedance, and anthropometric measurements were taken. This field-based study thus established feasibility of collecting these measures with TGD people. Most importantly, this study identified unique stressors related to TGD experience (eg, transitioning identity stress, “coming out” stress, and stress associated with the use of gender-specific public restrooms) that were linked with increased diurnal HPA-axis production (DuBois et al., 2017), CRP, and amBP (DuBois, 2012b).

Since then, other studies with TGD people have measured cortisol levels, finding reductions in morning blood cortisol after gender affirming hormonal treatment (Colizzi, Costa, Pace, & Todarello, 2013) and elevated hair cortisol for 30% of a sample of 10 trans women, as compared to hair cortisol norms from large laboratory samples without reference to racial/ethnic, gender, or age variations (Madera et al., 2017). Another study found an association between rumination and elevated evening salivary cortisol of LGBT people (TGD people were 10% of the sample; Zoccola et al., 2017). Additionally, a study among TGD people living in India found that salivary cortisol was positively associated with perceived stress scores and periodontal disease (Sivaranjani et al., 2019). Further, Hodges-Simeon et al. (2020) documented a clear circadian rhythm between cortisol, secretory immunoglobulin A (sIgA), and (endogenous) testosterone, among cisgender men. However, among transgender men, they found a similar circadian pattern between cortisol and sIgA but not with exogenously administered testosterone. Finally, a prospective clinical cohort study with 56 transgender and gender nonconforming youth demonstrated that greater inflammation derived from DBS correlates with greater gender-based stressors and lower gender-based supports (McQuillan et al., 2020).

Central to stress physiology is the concept of allostaticity, which refers to the adaptive biological process that preserves “stability through change” (Sterling & Eyer, 1988). This concept has informed stress research across multiple disciplines. Accumulated strain or “wear and tear” on multiple physiological systems is referred to as allostatic load (AL; McEwen & Stellar, 1993). The AL model has been applied to the study of SM people (Juster, Ouellet, et al., 2016; Juster, Pruessner, et al., 2016; Juster, Smith, Ouellet, Sindl, & Lupien, 2013), highlighting important sub-group differences (Mays, Juster, Williamson, Seeman, & Cochran, 2018). For example, gay men appear to have lower AL, while bisexual men appear to have the highest AL compared to heterosexual men. These sub-group differences speak to differential pathways to vulnerability as well as resilience among SM people. In addition, members of our group are working to develop indices from multiple MICBS and complete the first assessment of AL among TGD people (DuBois, 2012a).

Beyond studying stress, understanding what contributes to resilience for TGD people is an emerging area of research where MICBS could continue to provide further insights. Resilience refers to the ability to utilize available resources to protect against or recover from adversity and sustain health (Panter-Brick & Leckman, 2013). Studies of resilience among TGD people have identified the importance of connections to gender affirming communities, and the capacity to access supportive social and educational resources (Singh, Meng, & Hansen, 2014). This research is currently focused on mental health, drawing primarily on qualitative data (Singh, 2013; Singh, Hays, & Watson, 2011; Singh & McKleroy, 2011). A study by our group found that transgender men experiencing less trans-specific stressors related to transitioning, “coming out” and gender-specific public restrooms showed lower diurnal cortisol than those reporting greater distress. This was associated with a steeper afternoon decline in cortisol that suggests a “biology of resilience” in the face of real and anticipated social stress (DuBois et al., 2017).

Future biocultural research examining resilience among TGD people could focus on identifying effective coping strategies that enable effective physiological recovery and adaptive functioning.

### 2.2 Transition and gender affirming care

When considering what it means to be transgender or gender diverse, it is problematic that many people think
only of medical transition and the physical changes produced through gender affirming care (e.g., hormonal therapies and surgeries). Rather, we propose consideration of both medical and social transition (e.g., name/pronoun changes). Both medical and social transition involve complex biosocial processes that include social interactions, endured stigma, personal liberty, affirmation, and resilience that collectively shape TGD peoples' lives (DuBois, 2012a; DuBois et al., 2017). A few general points to bear in mind regarding transition: (a) not all people who identify as transgender medically transition; (b) not all people who medically transition identify as transgender; (c) there are many barriers that may inhibit a person's ability to access competent gender-affirming care, including lack of insurance coverage (Puckett et al., 2018); (d) a person who identifies as gender diverse or nonbinary (e.g., uses they/them pronouns) may also medically transition (e.g., via estrogen or testosterone therapy as appropriate for their gender expression); (e) local socioecological context shapes variation in transition trajectory, timing, and experience.

Transitional and liminal experiences have long been of interest to anthropologists (Turner, 1967; van Gennup, 2019 (1909)). Indeed, ethnographic research provides key insights to understand TGD people's experience (e.g., Valentine, 2007). However, because of the role of biomedicine in medical transition and the important health needs within this community, the majority of research being conducted in this area continues to center around clinical studies and aims to establish the safety of medical transition (Asscheman et al., 2011). For instance, several studies have assessed efficacy of gender affirming hormonal therapies for reducing distress and improving mental health in TGD people (Colton Meier, Fitzgerald, Pardo, & Babcock, 2011; Gómez-Gil et al., 2012; Nadal, Davidoff, Davis, & Wong, 2014). Currently, clinical studies are normally limited to retrospective cohorts, with short follow-up duration, and small sample sizes (Defreyne, Bruaene, Rietzschel, Schuylenbergh, & T'Sjoen, 2019). Furthermore, these studies utilize clinic-based assessments and include only individuals who are medically transitioning through biomedically supported pathways. Because there are significant barriers to gender affirming care worldwide that limit access (Padilla, Rodríguez-Madera, Ramos Pibernus, Varas-Díaz, & Neilands, 2018; Rotondi et al., 2013), MICBS assessment outside of clinical environments could be integrated with interview, ethnographic, and survey data to understand transition experience in different contexts globally.

Comparative and field-based research needs to be conducted with an explicit focus on the inclusion of trans-identified people of color, gender nonbinary people, and youth. Despite high rates of poverty, unemployment, and violence that disproportionately impact trans women of color (James, Herman, Rankin, & Keisling, 2015), too few studies apply targeted recruitment strategies within TGD communities to understand intersecting marginalized identities (Crenshaw, 1989) and health inequality (Wesp, Malcoe, Elliott, & Poteat, 2019). Target areas for future research could include long-term longitudinal, field-based studies that include MICBS to further understand experience and health in the context of gender affirming medical care and transition. Simultaneously, an enhanced understanding of biocultural factors contributing to variation in embodied experience and health are needed.

Microbiome-based research is one of a few areas that has been inclusive of TGD people, with current research conducted in clinical contexts focused primarily on understanding the effects of gender affirming hormonal therapies on microbiota. For example, research examining the effects of exogenous testosterone administration on the vaginal microbiome of transgender men relative to cisgender women, documented decreased abundance of Lactobacillus, increased abundance of over 30 different species of microbiota, and greater alpha-diversity (Winston Mcpherson et al., 2019) that is considered healthy. This suggests that steroidal hormones play an important role regulating microbiome diversity. There is also need for ethnographically informed cross-cultural studies examining global variation in experiences of gender affirming care or transition. Finally, research that focuses on TGD youth are urgently needed with respect to all aspects of transition, growth and development, and long-term health.

### 2.3 Social relationships

Research with cisgender individuals strongly and consistently supports a direct association between health outcomes and the quality of involvement in family relationships (Repetti, Taylor, & Seeman, 2002), romantic relationships (Braithwaite & Holt-Lunstad, 2017), and friendships (Holt-Lunstad, Smith, & Layton, 2010). In addition, characteristics of close relationships moderate the associations between physiological stress systems and health outcomes (Pietromonaco & Powers, 2015) and increase or lower resilience to stressful experiences like discrimination (Mereish & Paul Poteat, 2015). Notably, these effects may vary in important ways by race, ethnicity, and sexual orientation (Whitton, Dyar, Newcomb, & Mustanski, 2018). Published research on these issues with TGD people is currently limited, but is beginning to confirm the importance of close relationships on health outcomes (Fuller & Riggs, 2018; Meier, Sharp, Michonski, Babcock, & Fitzgerald, 2013; Puckett,
Matsuno, Dyar, Mustanski, & Newcomb, 2019; Riggs, von Doussa, & Power, 2015; Sansfaçon et al., 2018; Wilson, Chen, Arayasirikul, Wenzel, & Raymond, 2015). Although there is strong evidence that structural, interpersonal and individual manifestations of stigma are related to poorer health for TGD people (White Hughto et al., 2015), there is little investigation of how stigma affects the initiation, maintenance, and experience of relationships and how variation in these may help explain health outcomes.

At present, no published studies have yet examined the links of TGD close relationships to health outcomes using MICBS. MICBS are especially useful in close relationship research because they allow interpersonal interactions to proceed naturally while gathering immediate, daily, or longer term physiological responses to those interactions (Hostinar & Gunnar, 2013; Powers, Laurent, Gunlicks-Stoessel, Balaban, & Bent, 2016). Stress-responsive systems (eg, neuroendocrine, cardiovascular), cumulative stress (eg, AL), immune functioning, and sex hormones are a few of the physiological factors that have high potential for informing our understanding of psychological processes that might alter or explain the associations between close relationships and health of TGD people.

2.4 | HIV/AIDS and global health

A prominent area of research that has been inclusive of TGD people and integrates MICBS targets HIV prevention, treatment, and factors impacting disease progression. This research, however, often has small sample sizes and some studies conflate cisgender men who have sex with men (MSM) and transgender women (Poteat, German, & Flynn, 2016). Nonetheless, this work remains unique in TGD health-focused research as it includes samples of TGD people living outside of North America and Europe. The urgency of this issue is apparent; estimates of between 15 and 19% of transgender women worldwide are living with HIV (Baral et al., 2013; Becasen, Denard, Mullins, Higa, & Sipe, 2019; WHO, 2015) with transgender women of color disproportionately burdened (Hirshfield et al., 2019). Data for transgender men is limited but estimates range from 0 to 10% (Becasen et al., 2019; Reisner & Murchison, 2016; WHO, 2015) compared to 0.8% for all individuals ages 15-49, globally (WHO, 2018). Global research addressing the needs of various sub-groups within the transgender population is strongly needed (Poteat, Keatley, Wilcher, & Schwenke, 2016a).

MICBS are widely used in HIV-related research and more recently are being utilized in studies with TGD people (e.g., Madera et al., 2017). Specific MICBS include: DBS to assess systematic inflammation (Morgan, Taylor, Ryan, D’Aquila, & Mustanski, 2019), both DBS and saliva to access HIV incidence, prevalence and treatment efficacy (Flores, Brown, León, Sánchez, & Galea, 2018; Zalla, Herce, Edwards, Michel, & Weir, 2019), and finally DBS and hair samples to assess pre-exposure prophylaxis (PrEP) uptake and adherence (Gandhi et al., 2015, 2017; Marins et al., 2019). A number of studies have also established the feasibility of rapid HIV testing with TGD people with increased attention being paid to measuring the efficacy of PrEP (Grinsztejn et al., 2018).

Future work integrating MICBS into both local and global health research would facilitate the development of effective approaches and interventions to reduce the global burden of HIV/AIDS among TGD people. Beyond measuring efficacy of PrEP, MICBS could contribute to understanding of syndemic interactions between non-communicable disease risk and social conditions including poverty and stigma (Mendenhall, Kohrt, Norris, Ndetei, & Prabhakaran, 2017; Singer, Bulled, Ostrach, & Mendenhall, 2017) and gender minority stress (Rich et al., 2020). Integration of multiple MICBS measuring immune function, metabolism, and stress in the context of HIV/AIDS research are recommended. An ongoing study is moving forward the integration of MICBS by taking an intersectional approach to identify pathways linking stigma to health among trans women of color living as HIV+, providing a rich model for future work in this area (Rich et al., 2020).

2.5 | Structural violence and biologies of everyday life

To date, MICBS have not been utilized to investigate structural inequalities shaping TGD peoples’ lives. TGD people face increased risk for experiencing houselessness (Henderson, Jabson, Russomanno, Paglisotti, & Bloshnic, 2019; Shelton, 2016), financial hardship (Lenning & Buist, 2013), and food insecurity (Russomanno, Patterson, & Jabson, 2019). Due to continued sociopolitical marginalization in many countries around the world, TGD people encounter harmful policies that endanger their very lives, resulting in forced displacement. These forms of structural violence likely shape variability in the day-to-day experiences and physiologic function of TGD people. Employing MICBS in TGD-focused human biology research will enhance biocultural understandings of gender experience and global patterns of health.

Future research might model human biology research that routinely combines MICBS with psychosocial
frameworks. For example, social determinants of health frameworks (see Marmot, 2005) have been used to understand multilevel environmental exposures (see Dufour, 2006) within socioeconomic and political contexts (Levy et al., 2016; Liebert et al., 2013; Martínez, Ruelas, & Granger, 2017; Thompson, Nicholas, Watson, Terán, & Bentley, 2019; Wutich & Brewis, 2014). Investigating the social, economic, and political factors shaping the biologies of everyday life among TGD people is critically important for future research. Elucidating these factors is necessary for understanding how culturally specific forms of structural violence as well as resilience strategies mediate variation in health outcomes among TGD people.

2.6 | Health disparities

Research focused on health disparities other than HIV experienced by TGD people has been sparse compared to other marginalized groups. However, we do know that TGD people are at greater risk for many negative mental and physical health outcomes in comparison to the general population (Meyer, Brown, Herman, Reisner, & Bockting, 2017; Reisner et al., 2016; Su et al., 2016). In their most extreme form, health risks include high rates of suicidality, often in response to intense social stigma and inequality. TGD people also report more depression and anxiety symptoms (Budge, Adelson, & Howard, 2013; Puckett, Matsuno, et al., 2019) than the general population. Data from the 2014 to 2016 Behavioral Risk Factor Surveillance System found TGD people have a higher burden of chronic medical conditions, disabilities, and poor mental health than cisgender people (Downing & Przedworski, 2018). There is also evidence of increased risk for cardiovascular disease and incidence of myocardial infarction, particularly for transgender men (Alzahrani et al., 2019; Defreyn et al., 2019; Irwig, 2018). Future work integrating MICBS is needed to assess integrated pathways of risk including exogenous hormonal administration, endured stigma, discrimination, and structural inequalities (e.g., poverty, houselessness, migration, environmental injustices) and the contribution of these factors to health disparities for TGD people. Work that applies an integrative biocultural approach to understand the complex processes impacting health and well-being are desperately needed.

2.7 | Life course approaches and health

TGD people experience heightened levels of discrimination and stigma, (Grant et al., 2011) but little is known of how the developmental timing of these life experiences affects health, resilience, and disease risk. Work in this area is particularly relevant for youth (Birkett, Newcomb, & Mustanski, 2015; Reisner, Gretyak, Parsons, & Ybarra, 2015). A clinical cohort study conducted among TGD youth found associations between greater inflammation via DBS, greater gender-based psychosocial stress, and decreased social support (McQuillan et al., 2020). Understanding health impacts of chronic stress for TGD people in early life presents a clear research priority. The developmental origins of health and disease (DOHaD) framework suggests that chronic stress during certain stages of development could increase risk for negative health outcomes later in life such as risk for metabolic and cardiovascular disease (Barker, 1997; Gluckman, Hanson, & Mitchell, 2010). To date, however, we know of no published work that applies a DOHaD framework with MICBS to understand the health of TGD people.

Future work might draw on recommendations for employing MICBS to examine experience across the life span (Sievert & Brown, 2016). For example, model longitudinal health disparities research is being conducted with SM people. Recent analyses of data from the Cebu Longitudinal Health and Nutrition Survey drew on anthropometric data to test hypotheses about prenatal androgen exposure, sexual orientation, and growth. In contrast to studies attributing sexual orientation-based differences in adult stature to prenatal androgen exposure, this study of Filipino males found only minimal differences by sexual orientation and attributed these to adverse postnatal exposures encountered during childhood and adolescence (Gibb, McDade, & Schillaci, 2020). Another example based on longitudinal research integrating DB found parental support protective against the inflammatory effects of discrimination among SM people (Wood & Cook, 2019). Applying life course approaches to research inclusive of TGD people is much needed to enable informed development of public health policy promoting healthy growth, development, and aging among TGD people over the life course.

3 | IDENTIFYING AND MEETING CHALLENGES

Overall, the lack of studies integrating MICBS in research inclusive of TGD people reflects an unmet need in trans health research specifically and gender/sex research more broadly. There are some significant challenges to overcome to conduct this work in ways that are ethically guided, community-based, and inclusive. Central issues include: (a) obtaining reliable and valid data on variation in gender identity and sexual orientation; (b) advancing
professional training; (c) collecting MICBS respectfully and involving TGD communities in MICBS research; and (d) improving analysis, interpretation, and synthesis of data from studies incorporating broader understandings of gender/sex, MICBS and a variety of intersectional factors. In addressing each of these issues, our field could expanding our leadership and participation with multi-disciplinary teams integrating MICBS in their research. These types of collaborations would ensure expertise and resource support across multiple key areas of training and analyses, rather than requiring that a single investigator have expertise across all domains.

3.1 Collecting gender identity and sexual orientation data

In the United States, data about TGD and SM people is extremely rare due in part to a lack of standardized data collection that specifies gender identity and sexual orientation. Arguably, this lack of data collection reflects a number of issues including tendencies to conflate sex and gender (Westbrook & Saperstein, 2015). Also, there is a lack of attentiveness to, and education regarding, the degree to which sex and gender are varied and complex (Hart, Saperstein, Magliozzi, & Westbrook, 2019; Štrkalj & Pather, 2020), and misunderstandings that gender identity and sexual orientation are not synonymous (Reisner, Conron, et al., 2015; Reisner, Greytak, et al., 2015).

Nationally representative studies that integrate effective measures of sexual orientation and gender identity are critically needed. For example, the National Health and Nutrition Survey presently includes sexual identity and sexual behaviors but does not collect information on participants’ gender identity or sex-assigned at birth. One way to address this gap in data collection would be a 3-item questionnaire including both sex assigned at birth and gender identity with additional recommendations made for broader inclusivity (Bauer, Braimoh, Scheim, & Dharma, 2017) (see Table 3). This and similar items are effective in much of North America and Europe, but researchers should adapt instruments appropriately for specific linguistic and cultural contexts (Reisner et al., 2014). Recommendations from TGD people regarding how to ask about their gender include a number of suggestions, such as specifying “cisgender” instead of simply “men” or “women” when a response option is given to represent cisgender men or women (Puckett et al., 2020). Given the complexity of addressing these issues of measurement and inclusivity, transdisciplinary collaborations can enable the most comprehensive use of current and future sexual orientation and gender identity measures. Inclusion of these measures would facilitate researchers’ capacity to effectively disentangle intersectional factors impacting health and development across the life span beyond WEIRD populations (Bauer & Scheim, 2019a; Gibb et al., 2020).

3.2 Training in MICBS and trans & gender-focused research

Currently, there is a lack of training and/or lack of significant interest in integrating MICBS collection by those who have experience working with TGD people. This could be addressed through multidisciplinary training opportunities including short courses in human biology and biomarker sample collection methods, and/or workshops offered at disciplinary meetings or within graduate curricula. Collaborative potential also exists to bridge gaps in training, particularly if transgender and transgender health researchers collaborate with researchers who have experience using MICBS. Similarly, biomarker-based researchers could benefit from training opportunities and short courses to enhance inclusivity of TGD and SM people in studies. Collaborative teams should ideally work with community advisory boards to help best identify the MICBS most appropriate for the research questions (see Table 4).

### Table 3: Example TGD-inclusive measure of gender/sex

<table>
<thead>
<tr>
<th>Q1. What sex were you assigned at birth (meaning on your original birth certificate)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Female</td>
</tr>
<tr>
<td>2. Male</td>
</tr>
<tr>
<td>3. Undetermined</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q2. What is your current gender identity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Woman/Female</td>
</tr>
<tr>
<td>2. Man/Male</td>
</tr>
<tr>
<td>3. Trans woman/Trans female</td>
</tr>
<tr>
<td>4. Trans man/Trans male</td>
</tr>
<tr>
<td>5. Indigenous or other cultural gender minority identity (e.g., Two-Spirit)</td>
</tr>
<tr>
<td>6. Genderqueer/Gender Non-Binary/Gender Fluid</td>
</tr>
<tr>
<td>7. Different identity (please specify)________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q3. What gender do you currently live in your day to day life?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Woman/Female</td>
</tr>
<tr>
<td>2. Man/Male</td>
</tr>
<tr>
<td>3. Sometimes a man/male sometimes a woman/female</td>
</tr>
<tr>
<td>4. Something other than a man/male or woman/female</td>
</tr>
</tbody>
</table>

3.3 | Building trust in biomarker research with TGD people

Although there have been significant advances in recent years, TGD people continue to be harmed in the name of “science” and rightful distrust exists among members of this highly medicalized community. Research harm can occur through overt unethical conduct and misrepresentation but also through outright exclusion. This can stem from a failure to include community input or “give back” to the community. As a consequence, barriers of trust exist particularly between TGD people and cisgender researchers. These barriers can be exacerbated when MICBS are included in studies without explanation of the risks and benefits to the community. One way to address this is to include trainings that enhance researchers’ capacity to explain the community benefits of providing biological samples, in addition to hands-on training in the clinical basics of sample collection.

Whenever possible, it is essential to include TGD community members via community advisory boards and ideally trans identified researchers in the design and implementation of data collection protocols. Research teams in collaboration with community advisory boards can define important research goals and plans for dissemination of findings. Transparent consent processes detailing “levels” of consent regarding the sampling, storage, and use of biomarkers is essential as is building “applied” outcomes into the research design (e.g., developing interventions, impacting policy; see Table 5). In addition to respectful treatment, compensation for time is ethical and essential; TGD people endure high rates of poverty, unemployment, and violence, particularly trans women of color, and have voiced the need to be fairly compensated for their time and emotional labor (Leppel, 2019; Madera et al., 2017). The use of MICBS can facilitate this capacity by reducing the overall financial cost of data collection, compared to the expertise and materials required for the collection of whole blood. This would enable funds to be redirected to incentives for study participants.

3.4 | Challenges interpreting biomarkers

Accurate interpretation of biomarker data necessitates inclusive sex and gender diversity data. This also includes the recognition that analyses of sex often include effects of gender (Springer, Stellman, & Jordan-Young, 2012). As recent work has shown, important data on TGD health outcomes often gets lost in conventional data analysis (Bauer et al., 2017). We suggest that where possible data be analyzed using a combination of nonbinary sex and gender categories, and that ranges and standards of deviation be used to acknowledge variation within sex and gender categories instead of simple mean differences comparing binary groups (Hart et al., 2019). Importantly, we also suggest that “sex-specific” cutoffs for biomarkers consider variation among TGD people derived from
sample-based distributions rather than clinical norms that are based on binary sex categories and cisgender samples (Juster, Ouellet, et al., 2016; Juster, Pruessner, et al., 2016).

Collectively, these considerations would enable analysis to preserve variation in datasets instead of collapsing variation for interpretation through pre-existing binary categories. Finally, effective interpretation of MICBS in multimethod studies that include inclusive sex and gender data, interview, ethnographic, and/or survey data may require additional training in qualitative data analysis as well as statistical methods such as multilevel modeling (DuBois et al., 2017) and principal components analysis (Pelletier, Ditto, & Pilote, 2015) as well as expertise in TGD health. This would be further enhanced through additional capacity building in quantitative data analysis that enables analytical intercategorical intersectionality such as decomposition analysis (Bauer & Scheim, 2019b; Jackson, 2017; Jackson & VanderWeele, 2019). As noted above, enhanced opportunities for training in these areas might be most rapidly advanced through interdisciplinary collaborations in research projects and in focused short-term training workshops.

4 | CONCLUSIONS

Integration of MICBS into research has contributed important findings regarding the physiological, social, and structural pathways through which experiences impact marginalized groups. But overall, MICBS have not been extensively used to understand embodied experience or health among TGD people. The current lack of studies integrating MICBS reveals an unmet need in trans health research specifically and gender/sex research more broadly. This gap reflects a lack of expertise in trans health among those with experience in biomarker measurement. Among transgender health researchers, there is a need to increase training, capacity, and interest in conducting research integrating MICBS. Measurement of biomarkers from minimally invasive biological samples such as saliva and DBS enable assessment of health and the identification of pathways through which experiences impact health. Particularly important for work with marginalized communities, these methods effectively reduce participant burden and harm from invasive procedures while enabling impactful community-based research. Finally, integrating MICBS into research focused on the interacting and distinct aspects of gender/sex can enable our work to capture embodied experiences and their impacts on health and well-being while taking into account the full range of human gender/sex diversity.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Josh Snodgrass and Dr. Geeta Eick for organizing the conference session focused on biomarkers and their measurement. We would also like to thank the study participants in the Transition Experience Study, the study of Trans Resilience and Health Across Sociopolitical Context and the Trans Collaborations Community advisory board for providing invaluable feedback on sampling for biomarker measures that informed some of the recommendations made here. We are also grateful to Dr. Jae Puckett for their feedback on early drafts of this manuscript. Dr. Robert-Paul Juster acknowledges salary support from the Fonds de recherche Québec—Santé and is a holder of a Sex and Gender Science Chair from the Canadian Institutes of Health Research.

AUTHOR CONTRIBUTIONS

L. Zachary DuBois: Conceptualization; writing-original draft; writing-review and editing. James Gibb: Writing-original draft; writing-review and editing. Robert-Paul Juster: Writing-original draft; writing-review and editing. Sally Powers: Conceptualization; writing-original draft; writing-review and editing.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed as part of the development of this manuscript.

ORCID

L. Zachary DuBois https://orcid.org/0000-0001-5459-2863
James K. Gibb https://orcid.org/0000-0002-1334-5433


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