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Multidisciplinary Cancer Investigation Review Article

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A Review on the Status of Breast Cancer Care in Tanzania

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Tanzania continues to enjoy stability and growth in different sectors similar to other countries; however, some challenges persist in the health sector, especially in the area of cancer care. The current study aimed at reviewing social economic status (SES), as well as factors contributing to the increased burden of breast cancer (BC) in Tanzania. The current study reviewed different literature ranging from nationally/internationally published statistics, academic publications, health information of non-governmental organizations, academic researchers, and other sources of health information to better understand the socioeconomic and BC care status in Tanzania. The current review showed that BC is still the second most prevalent malignant disease in Tanzania, and most of the patients referring to medical centers are in the advanced stage of the disease due to shortage and unaffordability of health care services. The majority of health-related interventions and investments target infectious diseases, including HIV-AIDS, tuberculosis, malaria, as well as maternal and child health-related conditions, compared to noncommunicable diseases (NCDs) such as BC. In spite of some setbacks and improvements in healthcare facilities (e g, novel techniques for early detection), the best way to address BC care is affordable fees for clinical and laboratory investigations, accessible treatment, palliative care, follow-up, rehabilitative care, and better management and allocation of resources.

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INTRODUCTION

The major challenges of breast cancer (BC) care in low- and middle-income countries (LMICs) including Tanzania are early diagnosis and disease prevention, as well as providing the patients with pre- and post-therapies at effective cost. BC is second to cervical cancer (CC) in Tanzania due to its high mortality rate, poor survival and the fact that it affects both females and males similarly and negatively impacts the economically active population. The current review study was conducted to understand the status of care services directed at this disease in Tanzania. Since its independence in the early 1960s, Tanzania has continued to maintain socio-political stability and economic growth among different sectors, thus

providing more support to foreign investors compared to its neighboring countries. With an estimated population of 52 million, Tanzania's population grows at an annual rate of 2.3%-2.7%, triggering the rise in demand for social comforts and infrastructure according to the 2012 Population and Housing Census [1, 2]. As claimed by the Business Monitoring Intelligence and the National Bureau of Statistics, a robust economic growth based on the infrastructure investment in standard-gauge electrical railways, ports, and harbors, as well as expansion and improvement of roads are expected to be among the main drivers of gross domestic product growth from 2017 to 2026, with a constant average of around 6.2% [1, 3].

Following the Deloitte Touché Tohmatsu Limited report in 2016 and The Citizen Tanzania newspaper in 2018, despite the promising implementation and growth in telecommunication (via mobile financial service), agriculture and industrialization focusing on agricultural food processing and employment of about 65% of the population [1, 4], certain gaps in the public health system still exist, including poor water, hygiene, and sanitation as well as health care facilities, which may contribute negatively to the perceived socio-economic status of the country. Due to increased incidence (7.2%) and number of deaths occurring each year, BC becomes the second major public health concern for women worldwide, specifically in Tanzania, which is often diagnosed in an advanced stage largely due to lack of reliable screening settings, early detection, and thus, making it fatal for 56% of the women diagnosed according to the Foundation of Cancer Care in Tanzania. Despite being the second cause of death among women after CC in Tanzania, BC incidence is higher in LMICs, where case-fatality rates are disproportionately higher. The current study aimed at reviewing the current status of BC care in Tanzania, focusing on involved socioeconomic factors and identifying possible diagnostic and prognostic targets and treatment affordability in the country.

For this purpose, a review of the literature was conducted on related academic publications, health information data of non-government organization/ civil societies, health care institutions, academic research, and other health-related sources (MEDLINE and Google Scholar), for better understanding of BC, socio-economic, and health status in Tanzania (Figure 1).

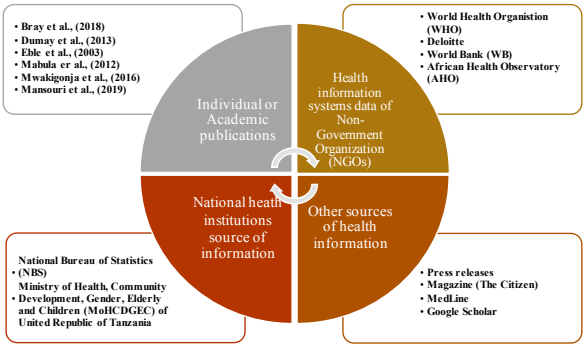

Figure 1: Assessment of Literature Review

Health Status

The healthcare sector funding in Tanzania and other LMICs is steadily increased over the years, as reflected by the continuous expansion of services, as well as the quality of care; although there is still plenty of room for further improvement [5], including the possibility for increasing healthcare spending per capita from about US$44 currently to at least US$54, as recommended for the developing countries by the high-level Taskforce on Innovative International Financing for Health Systems [1, 6]. Notably, communicable diseases; maternal, newborn, and childhood illnesses; other diseases-e.g. neglected tropical diseases; noncommunicable diseases (NCDs); and malnutrition are among the main causes of morbidity and mortality in the country [7-10]. Under such circumstances, it is therefore desirable that the demand on healthcare delivery system at all levels in terms of drugs, equipment, and medical supplies be matched with a corresponding level of funding, in order to allow sustainability in healthcare provision. Such a level of funding helps to prevent deterioration of the physical health care infrastructure, including public utilities (energy, water, and sanitation), and the supply of health-related logistics at the healthcare facilities, following the African Heath Observatory and UNICEF report [6, 11, 12]. Furthermore, the availability of requisite funding might support and sustain poor healthcare management in addition to the regulatory frameworks, wages, and other incentives for healthcare workers [13]. Naturally, improved funding results in improved health care, which subsequently results in a decreased burden of disease in the country and ultimately increased

productivity [3, 6, 12]. Since women make the majority of productive force in LMICs such as Tanzania, improved BC care directly and positively impacts productivity and economic growth thus results in the improved community, as well as individual welfare.

Burden of Noncommunicable Diseases

Broadly speaking, there is an evidence of the increased global burden of NCDs, particularly in developing countries such as Tanzania, compared with developed ones -e.g. USA, Eastern Mediterranean, and Europe [14, 15]. In Tanzania, NCDs, such as cardiovascular diseases, chronic respiratory diseases, diabetes, cancer, and injuries, are reported as the major public health issues that significantly contribute to increased mortality and morbidity across all age groups and genders [14, 16] (Figure 2 and Figure 3).

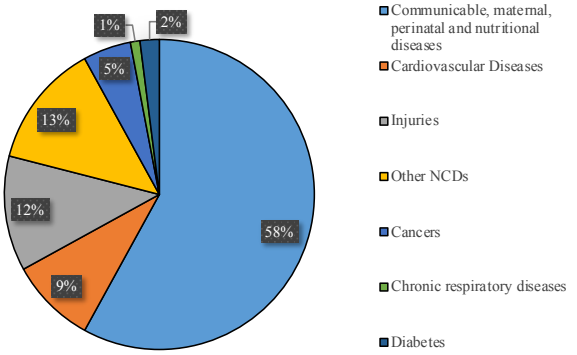

Figure 2: Proportion of Mortality in Tanzania
Source: The World Health Organization, 2014. Noncommunicable diseases (NCDs) Country Profiles [17].

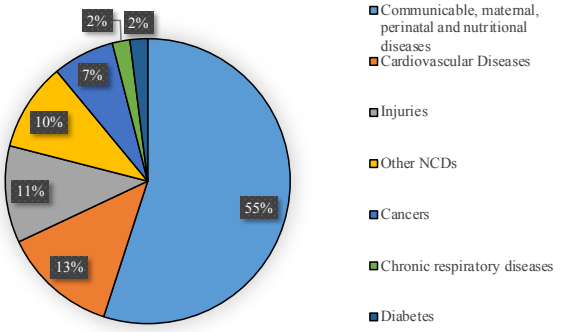

Figure 3: Proportion of Mortality in Tanzania
Source: The World Health Organization, 2018. Noncommunicable diseases (NCDs) Country Profiles [18].

Numerous factors, including modifiable (i.e. tobacco use, unhealthy diet, insufficient physical activities, alcohol consumption, occupation, etc.) and non-modifiable factors (i.e. aging, gender, race, and genetic dynamics) contribute to increased disease burden [19-21]. Following the World Health Organization (WHO) STEPwise approach to Surveillance conducted in Tanzania from 2012 to 2013, statistics showed that 14.1% of the population were tobacco smokers, 29.3% were associated with alcohol consumption, 26% were overweight and hypertensive, and only 2.8% followed a healthy diet [22]. As a result, many people spend their non-standard form of employment revenue for diverse healthcare needs. Urgent measures should then be taken in order to mitigate the burden of NCDs in developing countries including Tanzania [8-10].

Cancer Burden

Cancer is one of the major life-threatening diseases in the world. Globally, BC is the most frequently diagnosed malignant disease and the leading cause of cancer death among females, accounting for 23% of the total cases and 14% of the cancer deaths [16, 23, 24]. The current report from WHO estimated that more than 17 million new cancer cases were diagnosed, with more than 9 million accounting for death [25]. According to gender, lung cancer (2.1 million cases) and prostate cancer (1.2 million cases) are the first and most common cancers globally among males, with more than 1.5 million deaths annually. With more than 2 million cancer cases among females, the most commonly encountered cancers are CC, BC, and colorectal cancer, all being responsible for up to 522,000 deaths worldwide every year [26, 27]. However, BC was the second cause of death among females in Tanzania, following CC in 2012, with approximately 2732 (14.4%) newly diagnosed cases [28, 29]. Over the years, the status of BC disease remained unchanged in Tanzania in contrast to developed countries (Figure 4, Figure 5, and Figure 6). It was partly due to limitations in timely screening, early diagnosis, low availability of immunohistochemistry (IHC) test for receptor status, and lack of cancer registries. The fact that individuals still seek traditional health remedies in this part of the world instead of conventional medicine increases the burden, thus causing delayed diagnosis and treatment, as well as underreporting [16, 28, 30-34].

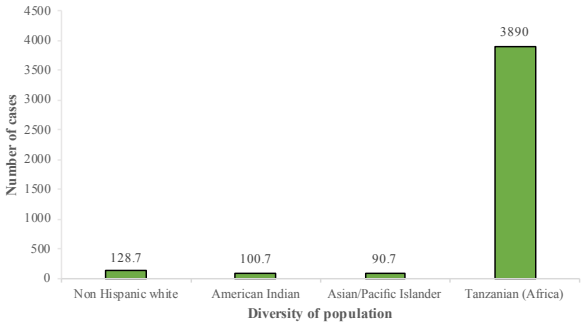

Figure 4: The Incidence of Breast Cancer in Tanzanian and Other Races in the US in 2014
Source: American Cancer Society [36] and MoHCDGEC of Tanzania [28]

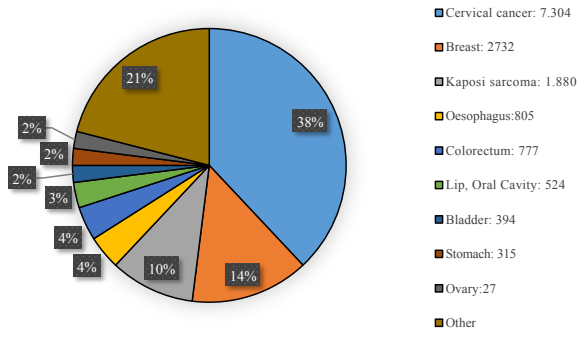

Figure 5: Cancer Incidence in Tanzania in 2012
Source: MoHCDGEC of Tanzania [28]

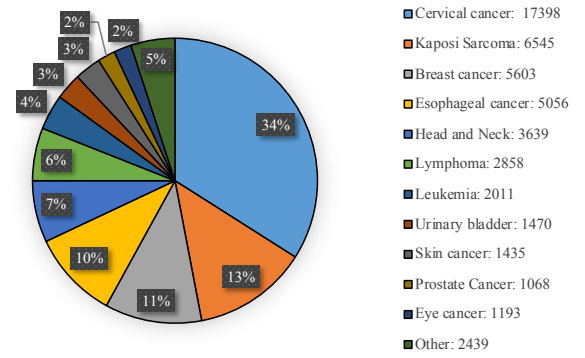

Figure 6: Cancer Incidence in Tanzania in 2016
Source: MoHCDGEC of Tanzania [28]

Most of the time, many diseases, including BC, are diagnosed at a late/advanced stage in most developing countries, resulting in the inability to reduce the frequency and consequences of the disease [16, 28, 30-33]. It is thus a challenging, but noble and important task to find appropriate strategic plans to diagnose (including molecular tests) and effectively treat BC, and reduce its incidence [35].

Non-Molecular Breast Cancer Screening Approaches in Tanzania

Surgery was the predominant and standard treatment for BC in the past century until the past decade. However, treatment modalities underwent drastic changes over the years due to novel research discoveries, which include elucidation of more prognostic factors, histological and immunohistological characterization, and cytogenetic diagnosis, leading to a wider range of therapeutic options, including customized/targeted therapies. Self-examination characterized by a palpable mass or lump most frequently located in the upper outer quadrant of the breast, nipple discharge, peau d'orange, skin ulceration, and fungating mass are most often discovered by the patient [37, 38]. Besides, mammography screening is one of the conventional examination techniques, providing information about prognostic factors (tumor size, lymph-node involvement, and metastasis) helping to classify a patient with benign condition or malignancy. Comprehensive molecular profiling of tumors is widely studied over the past few years in a variety of cancers, leading to the development of a new discipline termed "personalized medicine" [34, 37-39].

Molecular Biomarker Screening of Breast Cancer in Tanzania

Numbers of proteins and germline markers for BC are identified, qualified for clinical examination, validated, and reported by the National Comprehensive Cancer Network (NCCN) for which the targeted drugs are discovered and exploited; the proteins include estrogen receptors (ER), progesterone (PR), human epidermal receptor (HER-2), the BRCA1/2, PIK3CA, PD-L1, and tumor suppressor (p53) [40]. Other proteins such as Ki-67 and anti-apoptotic cell protein (BCL-2) also attracted the attention of researchers; although they were also studied as potential prognostic markers of BC, they are not recommended for clinical assessment by NCCN yet. Although many laboratories and medical centers do not assess molecular profiles of BC, such as ER, PR, and HER-2 as standard procedure for patients in Tanzania, studies show the

correlation of Ki-67, p53, and BCL-2 with clinical presentations of the disease such as histopathology grade and prognosis among patients, regardless of their low applicability in clinical trials [35, 41-43]. The p53 is an oncoprotein (also called TP53) encoded by p53 tumor suppressor gene that normally limits cell growth by monitoring quickly dividing cells, restoring inconsistent DNA, and regulating apoptosis, but it is also a key prognostic marker in the early detection of BC [35, 44, 45]. Moreover, BCL-2, on the other end, is an anti-apoptotic cell protein encoded by the BCL-2 gene with an imperative effect on cell survival through inhibiting the pro-apoptotic antigen activity. The BCL-2 is also associated with hormone receptor status due to its manifestation in normal breast glandular epithelium and upregulation by estrogen [46-48]. Besides, Ki-67, p53, and BCL-2 are the most significant and helpful predictive variables presently accessible for endocrine treatment targets [35, 43, 49, 50]. Further studies and investigations on molecular markers are required for therapeutic success. This can only be sustained through the strengthening of clinical settings, as well as laboratory facilities and services, leading to effective treatment.

Breast Cancer Diagnosis and Treatment Services in Tanzania

BC screening and diagnosis involve self-observation, physical examination by a physician, breast ultrasonography, mammography, FNAB/FNAC, and core-needle biopsy (or incisional biopsy where cores are not available), as well as chest radiography to rule out metastasis once the cancer is confirmed [51]. In addition, where the core-needle biopsy is not available and patients do not express or respond to endocrine therapy, FNAC smears coupled with cell blocks as well as more target molecular markers could have a comparable diagnostic value in addition to their economic advantages. Most often, the treatment and diagnosis of BC require multiple healthcare facilities and professionals- i.e., clinicians (surgeons, oncologists, and others), ultra-sonographers, radiographers, radiologists, pathologists or cytologists, histo-technologists, cytotechnologists, or a general lab scientist as an alternative [32, 52, 53]. These highly-skilled professionals might not be readily available and accessible to many individuals in need of BC diagnostic services in LMICs. Some of the laboratory procedures are available in Tanzania, including fine-needle aspiration biopsy / cytology (FNAB/FNAC) and core-needle biopsy utilized for tissue microarrays (TMAs). These methods need to be optimized to allow early and accurate BC diagnosis in more medical centers [54, 55]. Moreover, the routine IHC test for BC receptors at molecular levels (ER, PR, and HER2) used as the most early, rapid, accurate, and cost-effective diagnostic measure for BC is currently available at the Histopathology Unit of the Central Pathology Laboratory of Muhimbili National Hospital (MNH) in Dar es Salaam [29, 33, 35]. However, there are only about five regions in Tanzania that currently have at least one pathologist as well as surgical pathology/cytology services [32]. The current practice to treat BC in Tanzania depends on the stage of the disease and includes neoadjuvant therapy, followed by mastectomy or mastectomy with adjuvant therapy [51]. Patients destined to experience recurrence can be candidates for systemic adjuvant therapy, and the ones who are not at the risk of recurrence do not require adjuvant therapy, which is cost-effective to the health system. Such decisions are made by the specialists of both MNH and Ocean Road Cancer Institute (ORCI) through a multidisciplinary tumor board. Patients with BC are generally categorized as premenopausal and postmenopausal. However, both categories are treated with surgery, chemotherapy, radiotherapy, and hormonal therapy [tamoxifen-α selective estrogen receptor modulator (SERM)], depending on the stage of the disease and expression level of hormone receptors (HR) [16, 30, 35, 51, 56]. On the other hand, for postmenopausal women not responsive to tamoxifen (an anti-HR drug), an aromatase inhibitor (AI) drug (Anastrozole) is currently prescribed at MNH alongside surgery and chemotherapy. Radiotherapy is given as well when surgical margins and regional lymph nodes are positive for tumor. Other forms of hormonal manipulation, including selective estrogen receptor degrader (SERD like fulvestrant) and luteinizing hormone-releasing hormone (LHRH) analogs such as zoladex are not yet used to treat BC in MNH, although zoladex is currently used to treat prostate cancer. However, the medical fraternity in MNH should also consider the possibility of adding zoladex just like anastrozole to tamoxifen non-responders,

as it is already available locally. In addition, patients strongly overexpressing the HER2 marker may be eligible for receiving an immunotherapeutic monoclonal antibody agent such as trastuzumab or herceptin as well.

Tanzania is one of the few countries in the Eastern, Central, and Southern African sub-region that has a well-established and longstanding cancer treatment institute, named ORCI. Furthermore, new and upcoming oncology centers are at different stages of the establishment at Bugando Medical Center (BMC) in Mwanza, as well as the Kilimanjaro Christian Medical Center (KCMC) in Moshi; although they may not be still sufficient to serve the whole Tanzanian population, majority of those may also be rural-based [32, 52]. Nevertheless, this is no small feat including the fact that these centers serve the neighboring countries. This situation makes cancer diagnosis and therapy still expensive for many ordinary Tanzanians. Patients with BC in the lake regions (around Mwanza) are relatively younger premenopausal women mostly referring to medical centers at advanced stage of the disease and high rate of lymph-node metastasis [57]. Altogether, this makes BC care (including cancer diagnosis generally) a complex, multistep, and multicentric practice, with subsequent high-cost implications to the patient and/or his/her family and the country as a whole. This may be economically prohibitive to the underprivileged patient. Hospital-seeking behavior is also determined by the educational and socioeconomic status of the patient and/or his/her family. Consequently, a significant number of patients seek traditional remedies/healers only or prior to consulting conventional medicine, resulting in delayed diagnosis, advanced stage of the disease at diagnosis, and poor outcome of treatment. There is a need therefore to improve public awareness on BC, including setting up screening centers to promote early detection and thus allowing timely intervention [16, 31, 32, 58].

Limited Access to Breast Cancer Care and Tumor Markers Testing in Tanzania

One of the constraints on BC diagnosis in Tanzania is the molecular characterization of tumor markers in patients. Several investigations put forward that African BC is largely caused by overexpression of hormone receptors [59]. Pathologists and researchers working in low-resource countries face challenges with regard to Standard Operating Procedures (SOPs) for IHC staining due to many reasons, including outperformance of surgery, pre-treatment of tissue samples, low-quality specimens from large and necrotic tumors, doubtful quality of fixative materials, a lengthy stay in the fixative agent (regularly for several weeks), poor laboratory techniques and low-quality assurance/quality control practices, which often lead to the inapplicability of advanced IHC techniques [60]. In Tanzania, there is a small number of studies on BC diagnosis using IHC or other techniques for the assessment of BC molecular markers such as Ki-67, p53, and BCL-2 [31, 33, 35, 61]. In total, there are 169 district hospitals and 30 regional referral hospitals in which four are public referral and zonal hospitals including MNH for the coastal zone, Mbeya Referral Hospital in the Southern highlands zone, BMC in the lake zone, and KCMC in the Northern zone [32]. Unfortunately, not all healthcare activities related to BC care are conducted as planned, since most of them face limited human resources and poor supply of important health commodities. The four public referral and zonal hospitals, as well as Aga Khan Hospital (AGH), are the most prominent medical centers offering cancer screening and diagnostic services. However, chemotherapy and palliative therapy are only offered by ORCI. Moreover, most of these centers lack diagnostic facilities such as the IHC technique. All patients with cancer in the regional and peripheral zones are directed to MNH for hormonal receptors and Her-2 examination or other IHC tests. This institution offers an original assessment of BC categories in Tanzania, where they lack a population-based registry [30, 32]. This limitation on facilities with IHC capacity calls for government efforts to provide IHC facilities to the abovementioned centers. Burson et al., (2010) performed a two-year survey in Tanzania using medical records of patients with BC admitted to ORCI from July 2007 to June 2009. Their results revealed that the frequency or molecular characteristics of BC in Tanzania are scarcely understood [30]. The MNH provides radio- and chemo-therapy for patients with BC in partnership with ORCI. However, this collaboration offers an extremely specific treatment in both overcrowded clinics with long waiting times for critical practices such as surgery and pathological assessment [32], making treatment outcomes hardly sensitive. Improvement of healthcare facilities

for early diagnosis and management of cancer is therefore imperative.

A study in 2017 by the Ministry of Health, Community Development, Gender, Elderly, and Children (MoHCDGEC) of Tanzania showed that the fraction of patients with BC expressing hormone receptors in the various medical center could be substantial and significantly affected by therapeutic plans (endocrine therapy) [32]. But the current queries are: if patients are not substantial for endocrine therapy, how are other prognostic biomarkers, such as Ki-67, p53, and BCL-2, expressed vis-à-vis the age, stage, and grade in patients with BC in these specialized hospitals? Is there any correlation between the expression of these biomarkers and clinical and histopathological features of BC cases admitted to MNH? These further questions were partly addressed in a research study conducted by Mansouri et al., (2019), where a significant association among biomarkers (Ki-67, p53, and BCL-2) expression and clinico-histopathological features (age, tumor grade, stage of the disease, tumor size, and lymph-node status) of BC were observed [35]. However, further studies are required to comprehensively elucidate the association of BC biomarkers, the pathogenesis, histopathology, prognosis and therapeutic options to improve patient care and wellbeing and positively enhance the socioeconomic status of patients, the community and country as a whole. Furthermore, the future of BC care in developing countries should include targeted therapeutic modalities based on cytogenetics and other ancillary molecular diagnostics, including gene microarrays [7, 62]. These might serve as the second frontline in the quest for improved care and outcome of patients with BC in Tanzania.

CONCLUSIONS

BC is still a global public health concern, but mostly in developing countries such as Tanzania where a significant proportion of the population may also be affected by poverty and limitations in availability, accessibility, and affordability of appropriate healthcare services. The healthcare system of the country needs to be strengthened particularly in the area of cancer diagnosis and care. To positively affect the survival of patients with BC through personalized therapy systems, BC management in Tanzania should discover routes to improve the pathology facilities, including IHC for screening biomarkers in a regular cancer management process. The increased investments in the healthcare system, including novel and pre-existing techniques for early detection of BC and other cancers, affordable laboratory diagnostic fees for patients, availability of comprehensive and customized treatment modalities and palliative care, improved patient follow-up and management, and generally the allocation of resources could be the best way to tackle this particular health challenge and improve the quality of life of patients and thus positively affect the productivity.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

ETHICS APPROVAL

Not applicable.

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