Advancing Global Equity in Cancer Genomics- Challenges and Opportunities in Sub-Saharan Africa

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Abstract

Developments in genomics in the last decade has improved our understanding of the role of genetics in health and disease. One area where the impact of genomics is very noticeable is in oncology, specifically in terms of diagnosis and elucidating genetic predisposition to rare and common cancers. Molecular Sub-Saharan Africa (SSA) stands to benefit from cancer genomics, given recent spikes in the incidence of various types of cancers in the region. This mini review presents, from a health and science equity perspective, how advances in cancer genomics methods could shape cancer research and clinical care in SSA. We highlight some pan-African genomics and cancer initiatives that are facilitating increase use of genomics for cancer research. We conclude with recommendations on how the ideals of equity may be advanced in cancer genomics in SSA.

Introduction

There continues to be limited representation of indigenous African populations in population genomics research. This is despite the reported human genetic diversity in African populations [1], including high levels of nucleotide and haplotype diversity in both nuclear and mitochondrial genomes compared to other populations [2]. Similarly, structural variations including copy number variation (duplication and deletion), insertions and inversions in the human genome which are typically associated with phenotypic variability differs between African and non-African populations[3, 4]. Recently, whole genome sequencing analyses of 426 individuals across 50 ethnolinguistic groups in Africa has demonstrated a true picture of genome-level population variation of African individuals [5]. These different characteristics of the genetic architecture of African populations makes genetic data from African populations a rich global resource not just for improving our understanding of the genetic risk factors for diseases but also in supporting clinical and translational genomics studies worldwide. This near lack of representation of African populations present a challenge for the implementation of precision medicine in sub-Saharan Africa (SSA) [1, 6]. To fill this gap, a number of initiatives are now focussed on increasing genetic information on African populations in public genomic databases [7].

Currently, there are very few population-wide cancer genomics studies that have included populations in SSA. The risk of this is that while advances in genomics research in other populations may eventually lead to improved cancer care, they may not be translatable to populations in SSA. In this mini-review, we report on some Pan-African initiatives that support cancer genomics research and further discuss some challenges in the use of genomics approaches for both cancer research and clinical care in SSA. We start with a brief report on the cancer burden in Africa with the goal of providing context to why there is an urgent need for population-level cancer genomics studies in Africa. Secondly, we provide an overview of some cancer genomics initiatives in Africa. Thirdly, we propose ways for advancing basic and translational cancer genomics research in SSA. We conclude with recommendations on fast-tracking cancer genomics research and translation in SSA.

Burden of Cancer in Sub-Saharan Africa

The burden of cancer is increasing in SSA [8, 9]. In 2018, 752,000 new cancer cases and 506,000 cancer deaths were reported in the region with breast, cervical, and prostate cancers being the most predominant cancers in SSA [10, 11] . In Zimbabwe and Uganda, for example, breast cancer cases are on a rapid rise with an average annual percentage change of 4.9% and 4.5%respectively between 1991 and 2010 [10]. Epidemiological projections suggest that the cancer incidence and burden in SSA will more than double in 20 years' time [12].

Currently, Africa's cancer mortality rate is between 1.5 and 4-fold higher than in developed countries [13]. This is attributed to inadequate human and infrastructural resources in many SSA countries for the early diagnosis, prevention, and treatment of cancer [14, 15]. Studies in high income countries (HICs) have demonstrated that genomics offers significant promise towards improving and facilitating the prevention, diagnosis, treatment, and management of certain cancers [16, 17]. Therefore, it is anticipated that the introduction of genomics medicine in routine clinical practice in Africa will also yield similar benefits seen in HICs. For example, sanger sequencing and PCR genotyping methods have been used to identify pathogenic variants of BRCA1/2 linked to hereditary breast/ovarian cancers in Senegalese populations [18]. It is therefore hoped that introducing genomics approaches in the healthcare settings in Senegal will facilitate breast cancer screening and clinical management. Similar optimism has been expressed for cell and gene-based therapy for some lymphomas and leukaemia [19]. However, the use of genomic approaches both for cancer research and clinical cares remains a major challenge in much of SSA.

Pan-African Genomics Initiatives and Cancer Genomics Research

A number of Pan-African genomics initiatives have been established to advance the course of genomics research on African populations [20-22]. The Human Heredity and Health in Africa consortium (H3Africa) consortium [21] which is one of the largest genomics research consortia in Africa, has over 30 genomics projects, of which two are investigating genetic risks factors and susceptibility for breast and cervical cancer in in African populations. Other initiatives have conducted Genome Wide Association Studies for prostate and breast cancer in African-American populations [23, 24]. However, in Southern Africa, it has been reported that the European-defined genetic risk loci shows no association with prostate cancer in the Southern African Prostate Cancer Study (SAPCS), with only three (rs6983561, rs1859962, and rs13254738) of 46 tested loci were found within the SAPCS [25]. This limitation is brought about by the use of a genotyping array content that is not African-based and a lack of sufficiently powered resources [25]. The development of MADCaP Array, by the Men of African Descent Carcinoma of the Prostate (MADCaP) Network, to detect novel genetic variants in SSA and the use of OncoScan® in clinical research settings in South Africa [26] are efforts made to introduce cancer genomics methods (CGMs) to improve cancer care in low resource settings.

The study of risk factors of cancer in SSA populations could provide useful information into the biology of cancer that would have otherwise been missed. For example, the discovery of Epstein-Barr virus as the causative agent for Burkitt's lymphoma was made possible because of research done in African populations on this cancer type [12]. African Americans, which are admixed with most of them having an African origin but still presents with stark genetic differences with the continental

Africans, are reported to have the highest genomic risk for prostate cancer worldwide compared to any other population. Screening for the prostate cancer risk allele with SNPs rs7584330 located at 2q37 containing melanophilin (MLPH) and prolactin releasing hormone (PRHL) genes, showed higher frequencies in African Americans and Africans but lower frequencies in European-descent individuals [27]. Additionally, research has shown that the Southern Africa KhoeSan ancestry is linked to high risk prostate cancer [28]. These data support the need for wider inclusion of SSA populations in genomics studies to enable the development genomics technologies that will be applicable to populations in SSA.

The limited cancer genomics research in SSA is further worsened by the near absence of national cancer registries that could be used to facilitate cancer genomics research [26]. However, the African Cancer Registry Network (AFRCN) was set up with the overarching goal of regulating population-based cancer registries in SSA (www.afcrn.org). The network was established in 2012 with the aim of bringing together existing cancer registries across SSA; fostering the establishment of new registries in SSA countries that do not have cancer registration systems; as well as functioning as a surveillance of the registries. To qualify as a member of AFRCN, a population-based cancer registry at the time of entry, must have enrolled at least half of their population of interest and are expected to achieve three quarters of the population coverage by the third year following registration. Annual activities carried out by the members of the advisory group include but are not limited to site visits to each member country to assess the current statuses of their registries as well as offer professional advice where necessary. Although their focus is not cancer type-specific, it is worth mentioning that cancers of the breast, cervix, prostate as well as non-Hodgkin lymphomas appear frequently in their list of annual activities as stated on their website. In addition, a focus on childhood cancer in SSA is reflected in their Childhood Cancer Staging Rules that was developed for use by African cancer registries. With over thirty cancer registries to date, the AFCRN is making invaluable strides to improve the effectiveness of cancer surveillance in SSA even though not all the member registries have in the past 10 years, provided continuous data. These different factors contribute significantly to the limited number of cancer genomics studies in SSA.

Challenges to Implementation of Cancer Genomics Methods in Sub-Saharan Africa

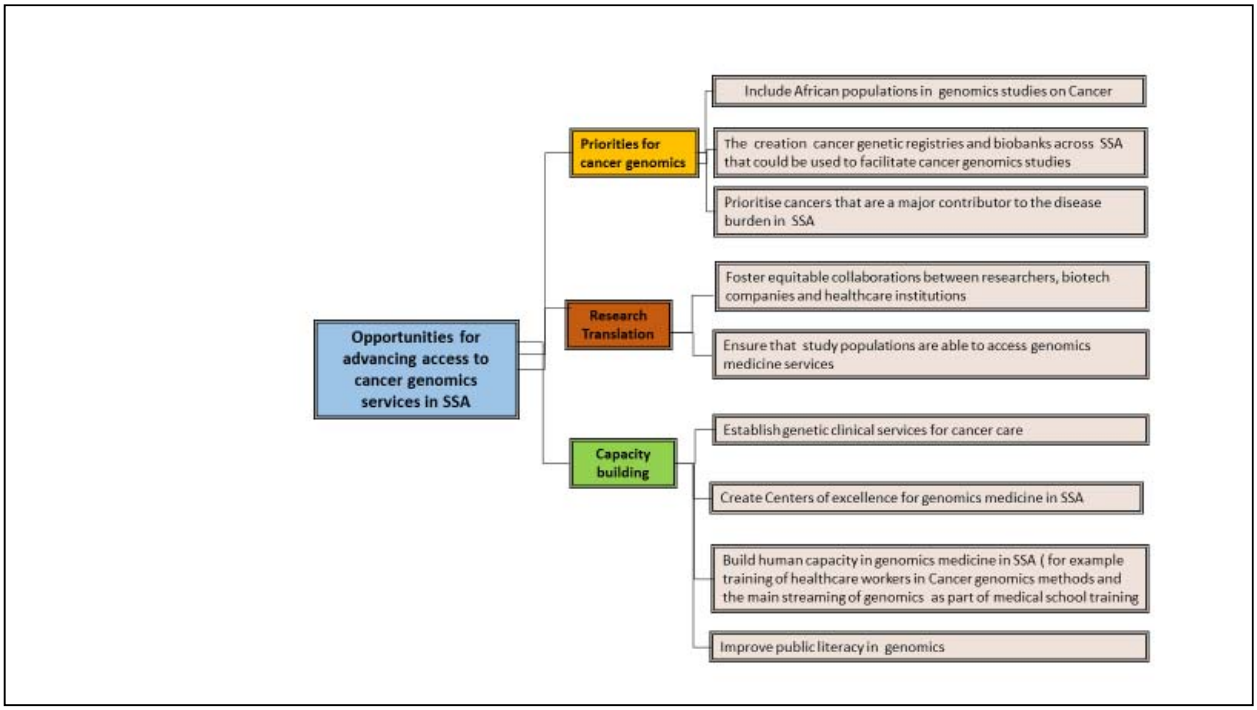
African researchers and a number of Pan-African research initiatives continue to make strides towards integrating cancer genomics methods (CGMs) either as part of clinical care for cancer or to improve the representation of Africa populations in genomics databases or genotyping arrays [29, 30]. However, the implementation of these CGMs is still met with several challenges. For instance, most CGMs including customized arrays, genetic markers testing, and genetic risk prediction models lack representation of the SSA population and as a result might be inaccurate or not suitable for use in

SSA. Similarly, the current use of artificial intelligence, machine-learning and big data in genomics as models for possible diagnostic and therapeutic approaches in cancer would only be beneficial in SSA if large-scale population genomic data of SSA are included. Furthermore, limited large-scale SSA population specific genomic studies of hereditary cancers may hinder implementation of current CGMs because of differences in the frequency of mutations found in genes like BRCA1/2 between SSA and non-SSA populations [31]. It is therefore suggested that ancestry-specific models that make use of genetic variants such as ancestry-specific genomic markers or variants associated with disease of a specific race, would be more useful than self-identified ethnicity or race [12] in developing and implementing genetic testing. Hence, the inclusion of SSA population in current CGMs will be particularly useful not only to this population but Africans in diaspora because of their shared genetic and genomic resemblances.

Equity in Genomics Medicine and Cancer Care

A number of high-income countries now use molecular approaches for clinical diagnosis and care for persons with various forms of cancer [15, 16]. There are however concerns that genomics medicine and services may not be easily available to populations in SSA and that this may further widen global health inequities [19, 32] . On a whole, three equity-oriented activities can help increase access to genomics medicine for cancer care by populations in sub-African Africa. These include supporting cancer genomics research in SSA; the translation of genomics research outcomes to interventions clinical interventions; and capacity building for genomics medicine in SSA (Fig 1). While there are a number of cancer genomics studies ongoing in different countries across Africa, there are limited translational genomics initiatives to facilitate a transition from bench to bedside. This is due to several reasons, but what stands out is the near absence of translational genomics research and capacity in sub-Saharan Africa. Overcoming this challenge requires fostering equitable collaboration between institutions biotechnology companies-and healthcare institutions. This will not only facilitate the translation of research findings but could also allow for research facilities to be used to support clinical care in resource limited settings.

Fig 1: Opportunities for advancing access to, and use of, genomics approaches to support cancer research and clinical care in Sub-Saharan Africa



South Africa is one of few SSA countries that have incorporated genetic testing for cancer in its public health programs. Genetic testing for breast cancer was introduced in this country in 2005. However, this service is primarily offered in tertiary healthcare settings and by private laboratories. This will suggest that a vast majority of the south African population will be unable to access clinical cancer genomics services therefore widening health disparities within the country.

There is need for SSA countries to establish genetic clinical services for cancer care. This will first require building capacity in genomics medicine including the acquisition of infrastructure; training of health care workers (medical geneticist; genetic counsellors, data scientist) and biocomputational capacity. A sustainable approach to human capacity building is through mainstreaming of genetics as part of medical school training. Partnerships between research and clinical services infrastructural sharing (computational and laboratory-based) may be a more feasible approach in the short run.

Currently, the cost of genomics medicine may be a deterrent to access to cancer genetic services. Although there is a general argument that the cost of genomics is on the decline, it remains relatively high for many persons in Africa. For example, genetic testing in south Africa for certain cancers could range from about 100-1000USD [33].

Given that many African countries still do not have national universal health coverage, and where it exists, cancer care is hardly covered, introducing a cancer genomics service that adds an extra cost to the national health expenditure may be challenging. This will suggest that genomics cancer services may come at a huge cost to patients or persons who require such services.

Conclusion

There is a need to support cancer genomics research and clinical translation in Africa to help ease the increasing cancer burden in SSA. This call to action has recently been echoed in a 2019 WHO Expert Meeting on Genomics and Genetics Disorders held at the University of Pretoria (https://www.who.int/genomics/expert-meeting-2019/en/index1.html), which brought together experts from different spheres including genomics research, healthcare profession, clinicians, patient advocacy groups and the WHO Secretariat to discuss the need for integration of genomics methods as part of routine care in the health systems in SSA. Although continuous efforts by Pan African initiatives to promote cancer genomics research and clinical care in SSA, has yielded noticeable progress [34, 35], much is still to be done to overcome some of the inherent challenges faced in its implementation.

Sub-Saharan Africa undoubtedly needs centres of excellence for translational genomics that can provide multidisciplinary training and research in genomics medicine. Such a centre of excellence would have the responsibility of strengthening collaboration between research institutions, biotech companies and the health systems in African countries. The centres could build on the model of The Cancer Association of South Africa (CANSA) which uses a of a public-private partnership approach to provides care and support to cancer patients, improve public awareness and understanding of cancer; train clinicians in cancer care and provide funding for cancer research. These centres could also facilitate the establishment and operations of regional initiatives that will manage laws on trade, investment, cross border sharing of cancer genomics data, the implementation of proprietary and innovative cancer genomics approaches, and the harmonization of genomics policies and guidelines across the region. This will go a long way to boost both basic research on cancer as well as translational cancer genomics in SSA.

Conflict of interest statement

Nothing declared

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References

1. Popejoy, A.B. and S.M. Fullerton, *Genomics is failing on diversity.* Nature, 2016. **538**(7624): p. 161-164.

2. Chimusa, E.R., et al., *A Genomic Portrait of Haplotype Diversity and Signatures of Selection in Indigenous Southern African Populations.* PLOS Genetics, 2015. **11**(3): p. e1005052.

3. Campbell, M.C. and S.A. Tishkoff, *The evolution of human genetic and phenotypic variation in Africa.* Current biology : CB, 2010. **20**(4): p. R166-R173.

4. The 1000 Genomes Project Consortium, *A global reference for human genetic variation.* Nature, 2015. **526**(7571): p. 68-74.

5. Choudhury, A., et al., *High-depth African genomes inform human migration and health.* Nature, 2020. **586**(7831): p. 741-748.

6. Landry, L.G., et al., *Lack Of Diversity In Genomic Databases Is A Barrier To Translating Precision Medicine Research Into Practice.* Health Affairs, 2018. **37**(5): p. 780-785.

7. Bentley, A.R., S. Callier, and C. Rotimi, *The Emergence of Genomic Research in Africa and New Frameworks for Equity in Biomedical Research.* Ethnicity & disease, 2019. **29**(Suppl 1): p. 179-186.

8. Globocan, *Cancer incidence and mortality statistics worldwide and by region*, International Agency for Research on Cancer, Editor. 2018: https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf.

9. Pilleron, S., et al., *Cancer incidence in older adults in selected regions of sub-Saharan Africa, 2008-2012.* Int J Cancer, 2019. **144**(8): p. 1824-1833.

10. Joko-Fru, W.Y., et al., *The evolving epidemic of breast cancer in sub-Saharan Africa: Results from the African Cancer Registry Network.* International Journal of Cancer, 2020. **n/a**(n/a).

11. The Cancer Atlas. *Sub-Saharan Africa*. 2018 [cited 2020 27 July].

12. Rebbeck, T.R., *Cancer in sub-Saharan Africa.* Science, 2020. **367**(6473): p. 27.

13. Parkin, D.M., et al., *Cancer in Sub-Saharan Africa*. 2018: International Agency for Research on Cancer.

14. Boyle, P., et al., *Cancer in Africa: the way forward.* Ecancermedicalscience, 2019. **13**: p. 953-953.

15. Williams, M.S., *Early Lessons from the Implementation of Genomic Medicine Programs.* Annual Review of Genomics and Human Genetics, 2019. **20**(1): p. 389-411.

16. Hill, S., *Introducing genomics into cancer care.* BJS (British Journal of Surgery), 2018. **105**(2): p. e14-e15.

17. Turnbull, C., *Introducing whole-genome sequencing into routine cancer care: the Genomics England 100 000 Genomes Project.* Annals of Oncology, 2018. **29**(4): p. 784-787.

18. Ndiaye, R., et al., *Evidence for an ancient BRCA1 pathogenic variant in inherited breast cancer patients from Senegal.* npj Genomic Medicine, 2020. **5**(1): p. 8.

19. Pepper, M.S., et al., *Cell and gene therapies at the forefront of innovative medical care: Implications for South Africa.* South African Medical Journal; Vol 109, No 1 (2019), 2018.

20. Gurdasani, D., et al., *The African Genome Variation Project shapes medical genetics in Africa.* Nature, 2015. **517**(7534): p. 327-332.

21. H3Africa Consortium, *Enabling the genomic revolution in Africa.* Science, 2014. **344**(6190): p. 1346-1348.

22. Pepper, M.S., *Launch of the Southern African Human Genome Programme.* S Afr Med J, 2011. **101**(5): p. 287-8.

23. Tan, S.-H., G. Petrovics, and S. Srivastava, *Prostate Cancer Genomics: Recent Advances and the Prevailing Underrepresentation from Racial and Ethnic Minorities.* International journal of molecular sciences, 2018. **19**(4): p. 1255.

24. Zheng, Y., et al., *Inherited Breast Cancer in Nigerian Women.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2018. **36**(28): p. 2820-2825.

25. Hayes, V.M. and M.S.R. Bornman, *Prostate Cancer in Southern Africa: Does Africa Hold Untapped Potential to Add Value to the Current Understanding of a Common Disease?* Journal of Global Oncology, 2017(4): p. 1-7.

26. Ambele, M.A., et al., *Amplification of 3q26.2, 5q14.3, 8q24.3, 8q22.3, and 14q32.33 Are Possible Common Genetic Alterations in Oral Cancer Patients.* Frontiers in oncology, 2020. **10**: p. 683-683.

27. Lachance, J., et al., *Genetic Hitchhiking and Population Bottlenecks Contribute to Prostate Cancer Disparities in Men of African Descent.* Cancer Res, 2018. **78**(9): p. 2432-2443.

28. Petersen, D.C., et al., *African KhoeSan ancestry linked to high-risk prostate cancer.* BMC Medical Genomics, 2019. **12**(1): p. 82.

29. Bentley, A.R., S.L. Callier, and C.N. Rotimi, *Evaluating the promise of inclusion of African ancestry populations in genomics.* NPJ genomic medicine, 2020. **5**: p. 5-5.

30. Harlemon, M., et al., *A custom genotyping array reveals population-level heterogeneity for the genetic risks of prostate cancer and other cancers in Africa.* bioRxiv, 2019: p. 702910.

31. Rebbeck, T.R., et al., *Mutational spectrum in a worldwide study of 29,700 families with BRCA1 or BRCA2 mutations.* Hum Mutat, 2018. **39**(5): p. 593-620.

32. Munung, N.S., B.M. Mayosi, and J. de Vries, *Genomics research in Africa and its impact on global health: insights from African researchers.* Global Health, Epidemiology and Genomics, 2018. **3**: p. e12.

33. CANSA, *Fact Sheet on Genetic Testing for Cancer*, Cancer Association of South Africa (CANSA), Editor. 2017: https://www.cansa.org.za/files/2017/04/Fact-Sheet-Genetic-Testing-for-Cancer-web-April-2017.pdf.

34. Adebamowo, S.N., et al., *Cohort profile: African Collaborative Center for Microbiome and Genomics Research (ACCME) study.* Journal of Clinical Oncology, 2016. **34**(15_suppl): p. 5524-5524.

35. Kuguyo, O., et al., *Genetic Susceptibility for Cervical Cancer in African Populations: What Are the Host Genetic Drivers?* Omics, 2018. **22**(7): p. 468-483.