

CANSA DETECTIVES

Southern African Prostate Cancer Study (SAPCS)



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Southern African Prostate Cancer Study (SAPCS)

Prostate cancer is a lethal disease in much of Africa. Estimating accurate mortality rates within South Africa has been limited. Studies outside of Africa have shown that African ancestry is a significant risk factor for prostate cancer associated mortality.

To narrow this gap in data, the Southern African Prostate Cancer Study (SAPCS) was born. Initiated in 2008 with seed funding from the Medical Research Council (MRC) and with further funds from CANSA over the years, the SAPCS has grown today to include three Universities/Institutes and five collaborating hospitals across the country, recruiting over 3,000 South African men. The SAPCS has therefore become the largest prostate cancer resource for Africa, collecting clinical, epidemiological and pathological data as well as fresh blood and tissue.



The founding members of the SAPCS in Polokwane, Limpopo, in 2010 included Dr Monare, Prof Bornman, Prof Hayes, Prof Venter (retired) and Dr van Zijl. Originally run out of the University of Limpopo, today the SAPCS is headed out of the University of Pretoria under the leadership of Clinical Director Riana Bornman, Urological Director Professor Shingai Mutambirwa and Scientific Director Professor Vanessa Hayes. While initially focused on Limpopo Province, the SAPCS has grown to include the central and northern parts of the country, with 11 contributing urologists.



Left to right: Dr Richard Monare, Prof Riana Bornman, Prof Vanessa Hayes, Prof Philip Venter and Dr Smit van Zijl

SAPCS Research Objectives

- To determine the accurate disease burden of prostate cancer within South Africa, with the inclusion of the most rural communities.
- To provide recommendations for clinical management of prostate cancer of relevance for South African men, in particular Black South African men, and to drive local policy and education related to prostate cancer.
- To identify modifiable environmental or lifestyle risk factors for prostate cancer and specifically those related to the lethal expression of disease observed in Black South African men.
- To identify biomarkers (including genetic, as well as gene-environment interactions) for prostate cancer risk and adverse outcomes of relevance for all ethnicities of South African men, with a focus on identifying contributing factors to observed ethnic-based disparities.
- To identify the molecular mechanisms driving prostate tumour initiation and advanced progression within Black South African men and in turn provide an African-led strategy for diagnosing, treating (therapeutic targets) and ultimately preventing lethal disease.

SAPCS Strategic Objectives

- To provide much needed synergy across prostate cancer studies within South Africa.
- To provide a unique resource for prostate cancer studies of relevance for South Africa and led by South Africans.
- To provide access to expertise in areas such as urology, oncology, pathology, epidemiology, cancer genomics, statistics and bioinformatics via partnership collaborations.
- To provide means for higher education and information transfer via staff and student exchanges between partnership institutions.
- To provide access to state-of-the-art technologies via collaborative access to partnership infrastructure and resources.
- To maintain international standards for research outputs achieving recognition as global leaders in African prostate cancer research.
- To provide a collaborative resource to target much needed funding to meet the research objectives.
- To provide a direct path to community awareness and education based on research outcomes, via mechanisms such as media, direct community engagement, pamphlets and educating local medical services.



SAPCS LEADERSHIP



Profs Riana Bornman, Shingai Mutambirwa and Vanessa Hayes



Professor Riana Bornman, Clinical Director SAPCS

Professor of Health Systems and Public Health, University of Pretoria

Riana Bornman joined the Department of Urology at the University of Pretoria in 1980, trained as an andrologist in Male Reproductive Health and later became head of Andrology dealing with male infertility and the aging male. She received doctorate degrees DSc (Physiology) from University of Pretoria focusing on the biological mechanisms of age-associated erectile dysfunction and MD (Physiology) from the University of the Free State, addressing the pathophysiology of drug-induced priapism.

Professor Bornman found her true passion after she had initiated Community-based Research in the Vhembe District, Limpopo Province, focusing on human and environmental health concerns of insecticides used for malaria control. She is the South African Principal Investigator for USA based National Institutes of Health (NIH) and Canadian Institutes of Health Research (CIHR) funded studies performed at a field office at Tshilidzini Hospital using local VhaVenda women for data collection, processing and storage.

Professor Bornman was a founding member of the SAPCS and took over responsibility as Clinical Director after the retirement of Professor Philip Venter. She is responsible for building partnerships with other South African universities and institutions and heads the administrative duties for the SAPCS out of the University of Pretoria.



Professor Shingai Mutambirwa, Urological Director SAPCS

Professor Shingai Mutambirwa holds M Med (Urology) Medunsa and FCS (Urology) degrees qualifying in 1996. He is head of the Department of Urology at Dr George Mukhari Academic hospital and Sefako Makgatho Health Sciences University in Pretoria, South Africa.

He is a Founding member of the Prostate Cancer Foundation of South Africa, Head of the Academic Committee for the South African Urological Association, sat on the Review Board for "The South African Guidelines for Prostate Cancer" and is Academic Committee Chair for the Urological

Colleges of Medicine of South Africa.

He is also a published book and article author and a peer reviewer for several journals including The Journal of Urology, The African Journal of Urology and Hindawi online publications.



Professor Vanessa Hayes, Scientific Director SAPCS

Born and raised in South Africa, Professor Hayes started her career in cancer genetics during her Honours and Masters degrees at the University of Stellenbosch. Completing her PhD in 1999 at the University of Groningen in The Netherlands, she established and refined a then new genetics technology to translate genetic variants in key oncogenic regulator genes into clinical practice.

Returning to South Africa, she briefly headed a research team focused on genetic susceptibility to HIV/AIDS and disease progression. It was during this time and her placement within the Urology Department at the University of Stellenbosch, headed by the late Professor Chris Heyns, that she became aware of the significant devastating impact of prostate cancer in South Africa.

She moved to Sydney, Australia, and the Garvan Institute of Medical Research in January 2003 to head up a team focused on the genetics of prostate cancer. She is head of the Laboratory for Human Comparative and Prostate Cancer Genomics at the Garvan Institute and is the Petre Chair of Prostate Cancer Research within the University of Sydney. She never forgot her roots in South Africa and was determined to initiate the first African-based prostate cancer resource. She has led the field in defining the genetic-basis to African-based prostate cancer health disparity.

Together with South African colleagues the now retired Professor Philip Venter (University of Limpopo) and Professor Riana Bornman (University of Pretoria), she founded in 2008 the SAPCS. She remains the SAPCS Scientific Director, is an Extraordinary Professor at the University of Pretoria and an Honorary Professor at the University of Limpopo.



SAPCS RESEARCH OUTCOMES TO DATE

SAPCS shows that men living in rural Limpopo of South Africa are at a 1.6-fold greater risk of presenting with lethal prostate cancer than men from urban areas (Gauteng).

African Americans are two to five times more likely to die from prostate cancer than any other population in the United States (Singh et al; 2017). Studies have however been lacking within Africa and South Africa, in particular Black South African men. The SAPCS leaders have shown that compared with African Americans, age-matched Black South African men are at a 2-fold higher risk of presenting with lethal disease (Tindall et al; 2014). This is further exaggerated when considering men of non-African ancestry and/or men living in rural over urban localities.

SAPCS shows the risk for lethal prostate cancer is significantly increased within the Vhembe district of Limpopo

Within the SAPCS the team identified significant increased prostate cancer risk associated with men from the Vhembe district of Limpopo (Tindall et al; 2013). The team has therefore established a dedicated study site in Vhembe with the aim to investigate both genetic and/or environmental factors that could explain the observed associations (see SAPCS-Vhembe).

SAPCS shows that PSA screening will greatly alleviate the burden of prostate cancer in South Africa

The SAPCS shows that serum prostate specific antigen (PSA) screening is the most important indicator for determining prostate cancer risk in South Africa (McCrow et al; 2016, Tindall et al; 2014, Tindall et al; 2013). Compared with global studies, South African men are more likely to present 2-5 years later at urological clinics and in turn are more likely to present with advanced disease (Tindall et al; 2014).

SAPCS identifies a 1.8-fold increased prostate cancer risk associated with diabetes in South African men

Within the SAPCS we observed an increased risk for aggressive prostate cancer in South African men, which was directly associated with a pre-existing diabetes diagnosis (Tindall et al; 2013). International studies have associated diabetes with increased prostate cancer mortality rates (Lee et al; 2016). This study holds potential that dietary / lifestyle factors could change prostate cancer mortality in South Africa. This is being explored further within the context of the SAPCS.

SAPCS team identifies a link between aggressive prostate cancer presentation in South African men and the DNA inherited from their mothers

Using the SAPCS as a resource, we identify a link between the maternally inherited mitochondrial DNA and risk for aggressive prostate cancer (Mc Crow et al; 2014). Specifically, we show a link between both the inherited profile and the acquired mutational burden and a diagnosis of pathologically advanced disease.

SAPCS leaders are the first to include Africans in the genomic revolution

Members of the SAPCS team generate the first complete human genomes for the African continent, including South African prostate cancer survivor, ARCHBISHOP EMERITUS DESMOND TUTU (Schuster et al; 2010). As such, South Africa leads the way to bring the genomic revolution to Africa.

SAPCS team are the first to observe a unique genomic signature driving lethal prostate cancer in African men

Generating the first whole genome profiling for prostate cancer within Africa, the SAPCS team identify a unique genomic signature that defines a disease course that is different to populations outside of Africa (Jaratlerdsiri et al; 2018, Hayes et al; 2018). This work is instrumental to understanding the presentation of lethal disease observed within South Africa and has led to potential mechanisms for treating aggressive disease within the context of South Africa, via immunotherapy. The SAPCS team has been funded via the National and Medical Research Council (NHMRC) of Australia to explore this further.

SAPCS team generates the first complete prostate cancer genome map

The SAPCS team were the first globally to use the next generation optical mapping technology to unravel the genomic complexities of human cancer. Using this technology, in parallel with next generation sequencing, we have identified complex chromosomal genomic rearrangements driving prostate cancer in a single South African patient (Jaratlerdsiri et al; 2017). This study was the first demonstration of how these state-of-the-art technologies could be used for the clinical management of prostate cancer – bringing precision medicine to South Africa.

SAPCS team identifies a link between high-risk prostate cancer and KhoeSan ancestry

A large majority of South African's carry a percentage of their DNA representing KhoeSan ancestry. In this study, the SAPCS, together with colleagues from Stellenbosch University, linked KhoeSan genetic ancestry to high-risk prostate cancer defined both by advanced pathology and/or elevated prostate specific antigen (PSA) levels (Petersen et al., 2019).

SAPCS team calls for urgent evaluation of androgen deprivation therapy in Black South African men

The most common androgen regulated mutation in prostate cancer includes a large gene fusion, identified in 50% of prostate carcinomas from men of European ancestry. The SAPCS, however, identified this mutation to be relatively rare in Black South Africans, with a prevalence rate of 13%, a frequency of half that reported for African Americans (Blackburn et al; 2019). Additionally, this fusion mutation was associated with low-grade disease at younger age of presentation, calling for an evaluation of translating current hormone-based therapies from European-predominant populations to Black South Africans.

SAPCS teams with Australian and Chinese researchers to identify a common prostate microbiome across the three continents

In a first-of-its-kind study, the SAPCS, together with their Australian and Chinese counterparts identify a common prostate microbiome across the three continents (Feng et al; 2019). The elevated microbial diversity and content within Black South Africans calls for further controlled investigation for a potential pathogenic contribution to aggressive disease presentation within South Africa.



EMERGING RESEARCH FOCUS AREAS

SAPCS-Vhembe

SAPCS-Vhembe is a dedicated SAPCS site in the furthest northern region of Limpopo. A high malaria risk area, Vhembe district is a rural region and home to roughly 5 million people, with most living as subsistence farmers. The SAPCS has a focused study site in Vhembe at Tshilidzini Hospital, after identifying increased prostate cancer risk and specifically lethal prostate cancer in the region.



The dedicated staff at the VHEMBE field office working on the VHEMBE study (Venda Health Examination of Mothers and Babies and their Environment). This facility was built with funding from the NIEHS, USA to Prof Brenda Eskenazi. UC Berkeley, USA is to establish a mother-baby birth cohort in the insecticide exposed population. Currently the office is sustained with CIHR funding to Dr Jonathan Chevrier, McGill University, Montreal, Canada. Photo credit: Vanessa Hayes

This site is sustained through merging of different projects and sharing of staff and infrastructure to ensure optimal use of resources. By empowering people from the community a research hub can be established in Vhembe, which may benefit both academic institutions and communities.

Risk for lethal prostate cancer is significantly increased within the Vhembe District

Vhembe district is in the malaria belt of South Africa, with the highest number of cases and reported deaths. Consequently, villages in Vhembe have been sprayed since the early 1950's. While resulting in a decline in the incidence of malaria, it remains to be determined if pesticide usage in Vhembe has contributed to the increased risk for aggressive prostate cancer observed in the now adult men of Vhembe.

Is insecticide use in the malaria belt of South Africa, contributing to the observed increased incidence of lethal prostate cancer in the region?



Insecticide spraying in Vhembe, Limpopo, South Africa;
Photo credit: Riana Bornman

Professor Bornman heads a focused research team as part of a University of Pretoria initiative within Vhembe to understand the link between malaria, in particular the use of insecticides, and hypospadias in newborn males and prostate cancer in elderly males.

SAPCS-CANSA driving prostate cancer awareness

SAPCS and CANSA are working together to conduct an intervention to impact knowledge and awareness of prostate cancer in men in the Vhembe district of Limpopo. Making use of the community engagement platforms already established by SAPCS, this study will aim to increase knowledge and awareness of prostate cancer and screening in men, health care providers and traditional healers; and uptake of prostate cancer screening at the newly established Men's Health Care Clinic at Tshilidzini Hospital, Thohoyandou. This is a dedicated clinic with trained medical and nursing professionals able to access prostate health, perform prostate biopsies and manage prostate disease in men from rural Limpopo.



Bringing the SAPCS to the people
Photo credits: (Left) Vanessa Hayes, (Right) Riana Bornman

SAPCS – making precision medicine a reality for South African men

Teaming with their International partner at the Garvan Institute of Medical Research in Sydney, Australia, the SAPCS team has access to state-of-the-art genomic technologies, bioinformatics and high-performance computational infrastructure. As such, the SAPCS has performed the first whole genome tumour-normal sequencing project for the African continent. This study resulted in the SAPCS team members being awarded in 2019 a \$1.2 Million Australian National Health and Medical Research (NHMRC) grant to generate a genome profile of aggressive prostate cancer for Black South African men. Consequently, the SAPCS has been invited to join the Global Pan Prostate Cancer Group (PPCG) with the aim to make prostate cancer precision medicine a reality.

SAPCS Moving beyond our borders

Built on the success of SAPCS, in 2018 i-DZOMO was launched. In the Tshivenda language of the Vhavenda, DZOMO means 'to provide a voice for those who have none'. This first-of-its-kind initiative, i-DZOMO will provide a voice for the unknown impact of prostate cancer, while fostering collaborative research efforts into this deadly disease, within the African continent.

i-DZOMO is globally unique, as it allows for a single study design to be replicated across multiple partner sites. In turn, studies may be replicated and findings validated between countries, increasing the power of the research findings, which largely do not align with those performed outside of Africa.



The launch of i-DZOMO in 2018 has resulted in the establishment of two parallel SAPCS collaborations in Namibia, the Namibian SAPCS (NamSAPCS) and in Kenya, the East African Prostate Cancer Study (EAPCS).

www.idzomo.org



18-20 April 2018, launch of i-DZOMO, University of Pretoria, South Africa

Funded by the National Research Foundation (NRF) South Africa, University of Pretoria

Left to right: Dr Micah Onger Oyar (Kenya), Dr Sean Patrick (South Africa), Professor Riana Bornman (South Africa), Professor Shingai Mutambirwa (South Africa), Professor Vanessa Hayes (Australia), Professor Mungai (Peter) Ngugi (Kenya), Dr Africa Gasana (Rwanda), Dr Raymond Campbell (South Africa). Absent from photo: Professor Emile Rwamasirabo (Rwanda) and Dr Johan Becker (Namibia)

SUMMARY

The SAPCS is a uniquely integrative team, merging basic science with public health and clinical presentation, which is already changing our understanding of prostate cancer in South African men. Discoveries from environmental factors, to genetic risk to significant possibilities for treating advanced disease of relevance to Black South African men, is already highlighting the impact of this devastating, yet largely silent disease, in South Africa. Additionally, the SAPCS is providing South African scientists access to new and advanced scientific technologies, changing policy and providing awareness that reaches the most rural of our communities.

The SAPCS team and Directors are excited about the next decade. Welcoming new team members, expanding research capacity both within South Africa and beyond our borders, while improving health outcomes for South African men. All these efforts would not be possible without the dedication of the many patients, their families, the clinical staff and all funders and support staff who have helped establish the SAPCS over the 10 years. We especially thank CANSA for their ongoing dedication to the SAPCS.

Future of the SAPCS

The future of the SAPCS is highly dependent on sourcing funds to maintain and continue to recruit patients and biospecimens, to train nurses and academic staff, to provide outreach, awareness and infrastructure, and to continue the research efforts to ensure favourable outcomes for a disease that is significantly lethal within our Black South African community. Specific future directions include; (i) developing of a dedicated awareness programme within the rural communities, (ii) identifying and training of nurses to facilitate the prostate cancer screening clinic at Tshildzini Hospital, (iii) measuring the impact of environmental exposures within Limpopo (in contrast to the rest of South Africa), (iv) further interrogating the expanded SAPCS biobank for risk factors, both lifestyle and genetics, that will facilitate in preventing lethal disease, (v) establishing a genomic signature for high-risk aggressive prostate cancer in South African men that may explain ethnic-based disparities in outcomes, (vi) tailoring prostate cancer treatment in South Africa towards the genetic makeup of South African's and (vii) training the next generation of South African prostate cancer researchers.



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