Gynecologic Cancer InterGroup
Cervix Cancer Research Network


# Cervical Cancer Research in South Africa

Lynette Denny

Department Obstetrics and Gynaecology, University of Cape Town/
Groote Schuur Hospital and SA Medical Research Council
Gynaecology Cancer Research Centre

Cervix Cancer Education Symposium, January 2019, South Africa

## Gynecologic Cancer InterGroup
## Cervix Cancer Research Network

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Introduction

- Globally, non-comunicable diseases are responsable for the majority of deaths and cancer is predicted to be the single most important cause of death in the 21st Century as well as a major barrier to prolongation of life expectancy
- The reasons for the increase in incidence and mortality from cancer range from ageing populations to the prevalence and changes of risk factors for cancer
- GLOBOCAN 2018 (produced by the International Agency for Research on Cancer: IARC)*, estimates that there will be 18.1 million incident cancers in 2018 and 9.6 million deaths globally
- At least one half of all cancer deaths will be diagnosed in Asia (where 60% of the world's population live), 20.3% of deaths will occur in Europe, 14.4% in the Americas and 7.3% in Africa

Cervix Cancer Education Symposium, January 2019, South Africa

*Bray F et al. CA CancerJ Clin 2018;68:394 424

# Cervical cancer

- Risk factors for cervical cancer:
  - Persistent infection with high-risk types of Human papillomavirus, particularly HPV16/18
  - Immunosuppression (HIV)
  - Smoking
  - High parity
  - Prolonged oral contraceptive use
  - Failure to screen for cervical cancer precursors
  - High incidence of Sexually Transmitted infections
- While some countries have demonstrated decreases in cervical cancer over the past decades, in others without effective screening programmes have steadily risen e.g Uganda and Zimbabwe where data is available

# Human development index and Age standardised incidence rates (ASIR) and age standardised mortality rates (ASMR) of cancer in women in 2018

| | ASIR | ASMR |
|---|---|---|
| Low HDI | 128.4 | 91.1 |
| Medium HDI | 112.8 | 68.6 |
| High HDI | 178.3 | 87.8 |
| Very High HDI | 268.5 | 80.9 |
| World | 182.6 | 83.1 |

# Burden of cancer

- Incidence and death rates for all cancers combined globally are nearly 50% higher in males than females
- There is also significant variation geographically, with deaths in Eastern Europe ranging from 171/100 000 to 64/100 000 in Central America
- However the risk of dying from cancer in East Africa (11.4%) is higher than in North America (8.6%), Northern Europe and Australia (9.1%)/New Zealand(8.1%)
- Lung cancer remains the leading cause of cancer incidence and mortality with 2.1 million cases and 1.8 million deaths predicted for 2018, representing 18.4% of all cancer deaths

# Burden of cancer

- Female breast cancer had the highest number of cases diagnosed (n = 2 088 849 with 626 679 deaths) accounting for 1 in 4 cancer cases among women globally in 2018
- Followed by 569 847 cases of cervical cancer and 311 365 deaths – the fourth most commonly diagnosed cancer in women for both incidence and mortality
- Cervical cancer is the fourth most common cancer in 28 countries and the leading cause of death in 42, the vast majority being in Sub-Saharan Africa and South-East Asia
- Over 85% of incident cases and mortality from cervical cancer occur in low and middle income (LMICs)
- Cervical cancer research has increased significantly in past decades, particularly in terms of biomedical, behavioural and policy development

# Burden of cancer in South Africa

- Cancer overall is under-reported in South Africa due to the lack of a comprehensive cancer surveillance system
- There is also a shortage of health care personnel with 5,4 doctors/10 000 compared to a similar country Chile, which had 15.7 doctors /10 000* in 2011
- Cancer surveillance data in SA are provided by three registries:
  - South African National Cancer Registry (NCR)
  - Eastern Cape Province Cancer Registry
  - South Africa Paediatric Tumour Registry
- The current NCR was established in 1986 as a pathology based cancer registry and was a collaborative venture between Cancer Association of South Africa and National Dept of Health
- The NCR has an archive of 1.2 million cases and adds approximately 55 000 – 80 000 new cases per year from both the private and public sector
- The lifetime risk for cancer is estimated to be 1:8 for men and 1:9 for women in South Africa

*Singh E. et al Lancet Oncology 2015; 16(8):e414 – e421

# Eastern Cape Province Cancer Registry

- Just over a million people in 8 districts located in the former Transkei are covered by this population based registry, which includes 15 hospitals and one public health laboratory
- From 2003 to 2007, 2808 cancers were reported, 60% were women and girls and just under 70% were histologically or cytologically confirmed
- In women the commonest cancers were oesophageal, cervical and breast cancers

# Temporal trend analysis of cervical cancer in South Africa

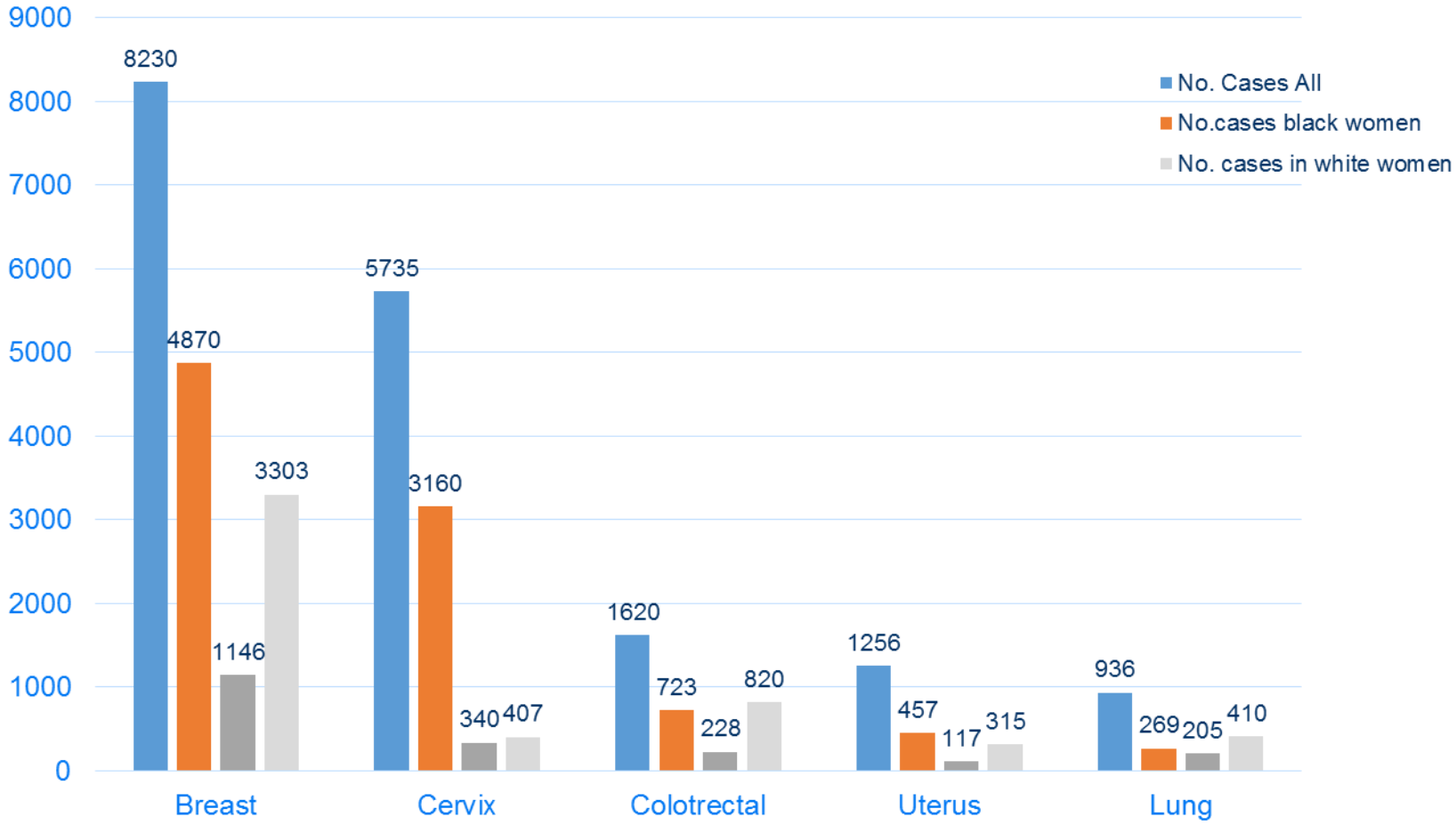
- ASIR rates  of CC were analysed from 1994 – 2009 and ASMR from 2004 – 2012, using data from the NCR and Stats SA by Olurunfemi G et al*
- The group conducted a temporal trend analysis of cervical cancer in South Africa from 1994 – 2009* during which 75 099 incident cases of cervical cancer were reported and the average number of cases per annum were 4694 – the majority were diagnosed in public sector laboratories and were of squamous cell type
- 79% of all CC cases occurred in black women compared to 1.4% among Indian/Asian women with a mean age at diagnosis of 50.9 years
- The highest ASIR was among black women (27.2/100 000) compared to 11.5/100 000 in white women
- The ASIR in 1994 was 22.1/100 000 and 23.3/100 000 in 2009 with an annual average incline of 0.9% per annum

*Olurunfemi G et al. Int Journal Cancer 2018; 143:2238 - 2249

# Mortality trends in SA

- Overall 5 year relative survival rates for cervical cancer from 2004 – 2009 ranged from 37.9 – 45.7%
- There was a 7.6% per annum increase in cervical cancer incidence between 1994 and 1998 which may be a reflection of better access to services and identification of cases and reporting to NCR post apartheid
- However, from 2001 – 2009 incidence rates of CC decreased by only 0.9% per annum, which may be a reflection of HIV prevalence, low ART coverage and improved CC prevention programmes
- ASMR declined by 0.6% per annum from 2004 – 2012: initially between 2004 – 08 there was a 3% decline in mortality (? due to ART roll-out) followed by an increase of 0.8% from 2008 – 2012 (? due to better access and recording of CC cases)
- Over the time period (2004 – 2012) 25 101 mortalities were recorded and the average number of deaths per annum was 2789, of which 69.4% occurred in black women with a mean age of death of 56.1 years
- One third of deaths occurred  in women of reproductive age

# Burden of cancer in women in South Africa, number of cases reported in all women and in black women, 2014*




*National Cancer Registry, NICD, South Africa 2014

# Cervical cancer treatment and research in Africa

- Systematic review*:
  - Searched for publications from 2004 – 2014
  - 380 articles identified with majority on screening (55%) or secondary prevention, 23.4% on primary prevention (HPV vaccination) and 18% on treatment of cervical cancer and its precursors
  - Only 4% of studies focussed on quality of life in women with cervical cancer and 11% focussed specifically on CC and HIV
- Khayelitsha Cervical Cancer Screening Project (KCCSP)
  - Collaboration between UCT and Columbia University, New York
  - Funded by Alliance for Cervical Cancer Prevention via Gates Foundation from 1995 – 2016
  - Screened over 40 000 from 1995 to current

*Finocchario- Kessler S et al. BMC women's health 2016: 16:29


K1278

# Alternative approaches to cytology based secondary prevention

- Visual inspection methods
  - Visual inspection with acetic acid
  - Immediate result
  - Primary care level
  - Low technology using mid-level providers
- HPV DNA testing as a primary screening test
  - Expensive
  - Laboratory-based
  - Objective and reproducible
  - However, virtual point of care test now developed use GeneXpert cartridge based PCR technology, initially formulated for detection of TB and rifampicin sensitivity

# Cross-sectional studies of VIA/HPV testing

- Link screening to treatment
  - Identify 1:5 or 1:4 women as having a positive test and requiring treatment
  - Better sensitivity than a cytology-based program but lower specificity and PPV
  - High NPV
  - Overtreatment


www.KWIKSPACE.co.za

# KCCSP

- In 2000
  - Prospective three - arm randomized trial
  - Evaluate *safety, acceptability and effectiveness* of 'screening and treating' women with positive screening tests
  - Without the intermediate steps of colposcopy and histological sampling

# KCCSP

- Screening tests were VIA and HPV DNA testing (Hybrid Capture II, Digene)
- Treatment: Cryotherapy
- Nursing sisters at a primary care level
- Groups:
  - Treat if VIA positive
  - Treat if HPV DNA positive
  - Delayed treatment for 6 months regardless of screening test result (control group)

*Denny et al JAMA 2005;294:2173 - 2181

# Performance characteristics of HPV and VIA as screening tests in the control group for CIN 2+

| | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| **HPV test** | | | | |
| 6 months | 93.9 | 82.6 | 15.4 | 99.7 |
| **36 months** | **89.5** | **84.5** | **24.9** | **98.8** |
| **VIA** | | | | |
| 6 months | 54.5 | 79.2 | 8.0 | 98.5 |
| **36 months** | **48.6** | **79.7** | **13.2** | **96.9** |

# Capacity of two SAT strategies to reduce cumulative prevalence of CIN 2+ by 36 months

| | HPV (HC II) | VIA |
|---|---|---|
| % Disease prevented | **73.1 (60.7 – 85.3)** | 32.7 (11.6 – 53.9) |
| Cases prevented per 100 women SAT | **4.42 (3.08 – 5.77)** | 1.98 (0.44 – 3.52) |
| Number needed to SAT to prevent one CIN2+ | **22.6 (15.7 – 29.5)** | 50.5 (11.2 – 89.7) |

# Self sampling*

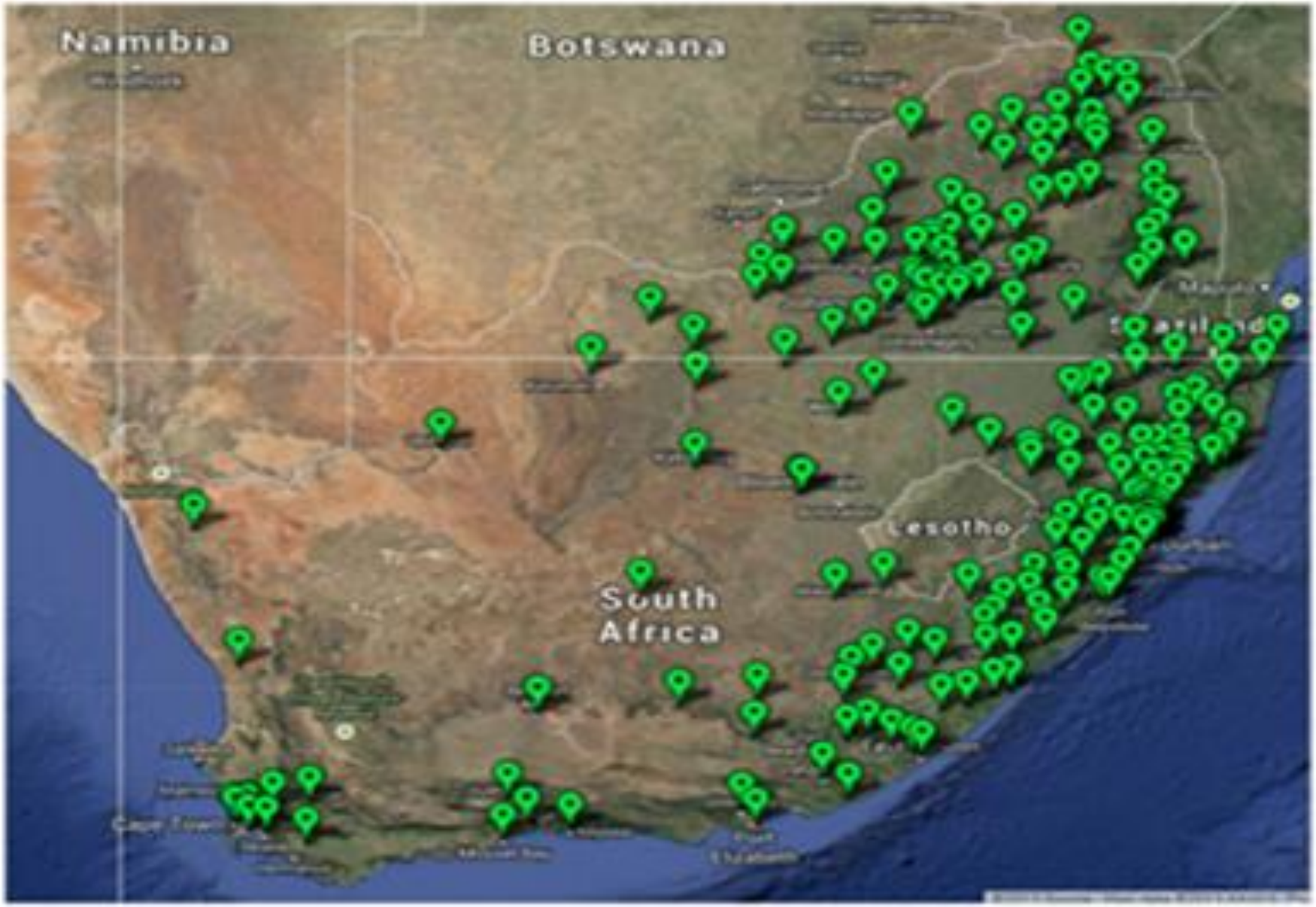
- Updated meta-analysis of detecting cervical cancer precursors and reaching underserved women showed that using PCR based high-risk HPV testing on self and clinician obtained samples resulted in similar accuracy between the two but was superior to amplification hrHPV tests
- Offering kits to women was more successful than sending invitations and increased participation (Arbyn et al, 2018)
- Saidu et al+ (KCCSP) performed a mixed method study on women's perspectives on self sampling, which included 822 women who answered a structured questionnaire and 41 who participated in focus group discussions
- While the majority of women were comfortable with self sampling, 70% preferred clinician obtained samples for fear of the self sampling not being accurate or correctly collected

*Arbyn M et al. BMJ 2018;363:k4823; +Saidu et al SAMJ 2018.v109/1.13278

# Screen and treat

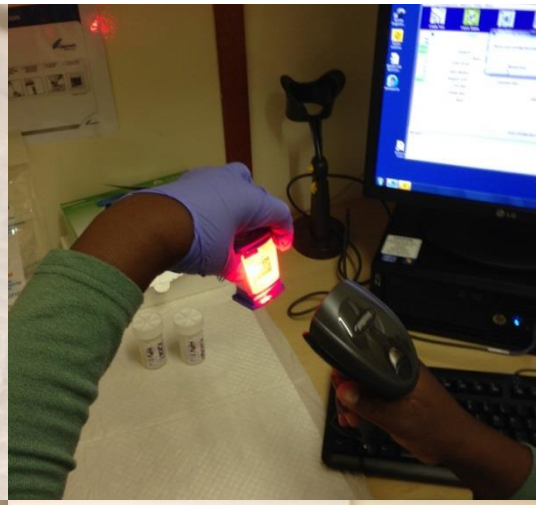
- New PCR based technology
- Tests for 14 high-risk types of HPV
- Same technology as used to detect AFBs for TB and rifampicin resistance – GeneXpert, Cepheid
- Same technology for HPV DNA testing, different reagents in cartridges, takes one hour to produce result and does not require sophisticated laboratory systems

**Figure 10:** *Placement of GeneXpert Instuments*



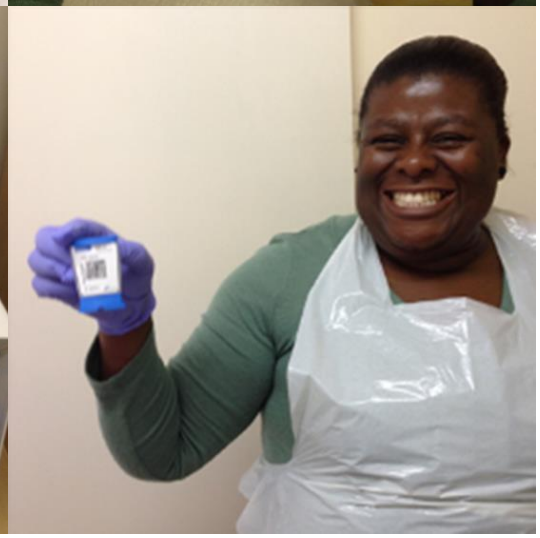
# Advantages of Xpert HPV as point-of-care test

Cartridge is preloaded with all required reagents

No specialized lab skills required

Fully automated real-time PCR instrument Doesn’t require “batching”



<1 min of operator “hands-on” time

UCT GXIV-4 805050 GXIV-4 805052

17/03/15 10:34:11

## Test Report

Sample ID: G1027
Test Type: Specimen
Sample Type:

Assay Information

| Assay | Assay Version | Assay Type |
|---|---|---|
| HPV HR AND GENOTYPE RUO ASSAY | 2 | Research Use Only |

Test Result:

HPV 16 NEG;
HPV 18_45 POS;
OTHER HR HPV POS

Test and Analyte Result

| Analyte Name | Ct | EndPt | Analyte Result | Probe Check Result |
|---|---|---|---|---|
| SAC | 36.8 | 45.0 | NA | PASS |
| HPV 16 | 0.0 | 0.0 | NEG | PASS |
| HPV 18_45 | 30.9 | 322.0 | POS | PASS |
| P3 | 26.6 | 366.0 | POS | PASS |
| P4 | 0.0 | 7.0 | NEG | PASS |
| P5 | 0.0 | -3.0 | NEG | PASS |

User: Signoria vathiswa kamkam
Status: Done Start Time:
Expiration Date*: 26/12/49 End Time:
S/W Version: 4.4a Instrument S/N:
Cartridge S/N*: 234594192 Module S/N:
Reagent Lot ID*: 11051 Module Name:
Notes:
Error Status: OK

Errors
<None>

Cepheid
A better way.

**Xpert® HP V**

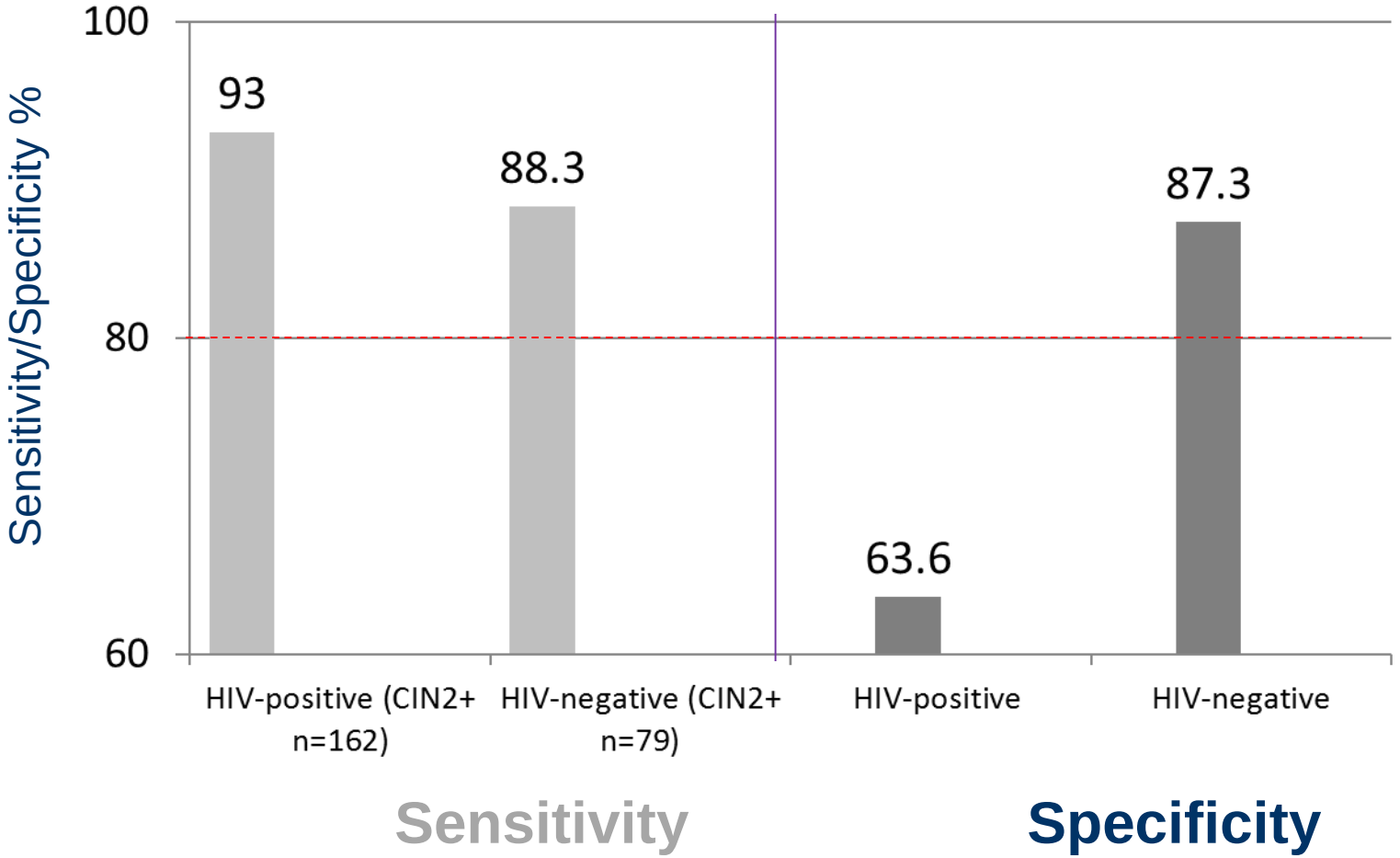
Real-time PCR for 14 targeted HPV types in 5 channels plus sufficiency control:

**HPV16;**
**HPV18 45;**
**[P3] HPV31, 33, 35, 52, 58;**
**[P4] HPV51 59;**
**[P5] HPV39, 56, 66, 68**

# Evaluate Xpert HPV “as is”

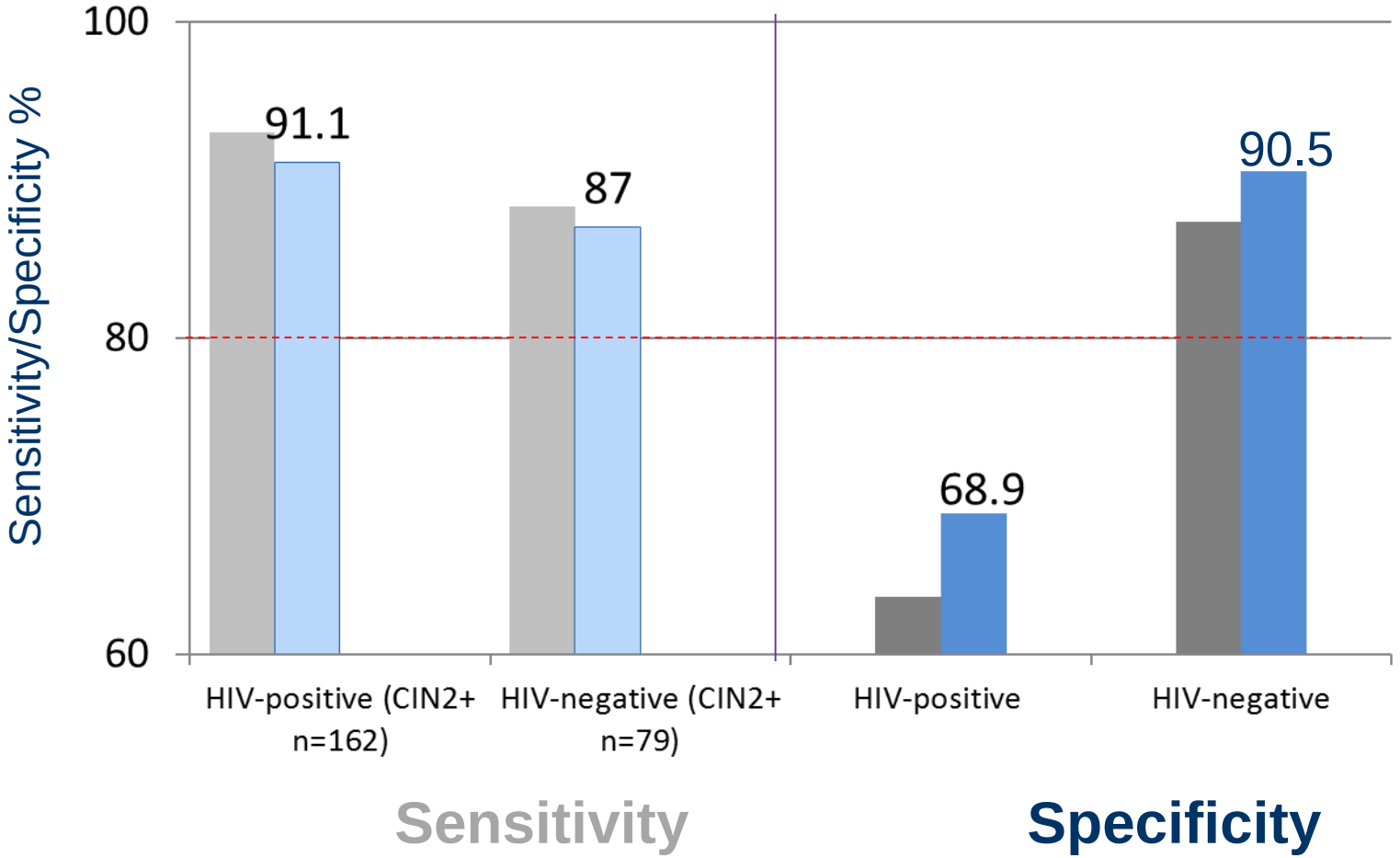
Positive for any of

16,18,45,31,33,35,52,58,51,59,39,56,66,68



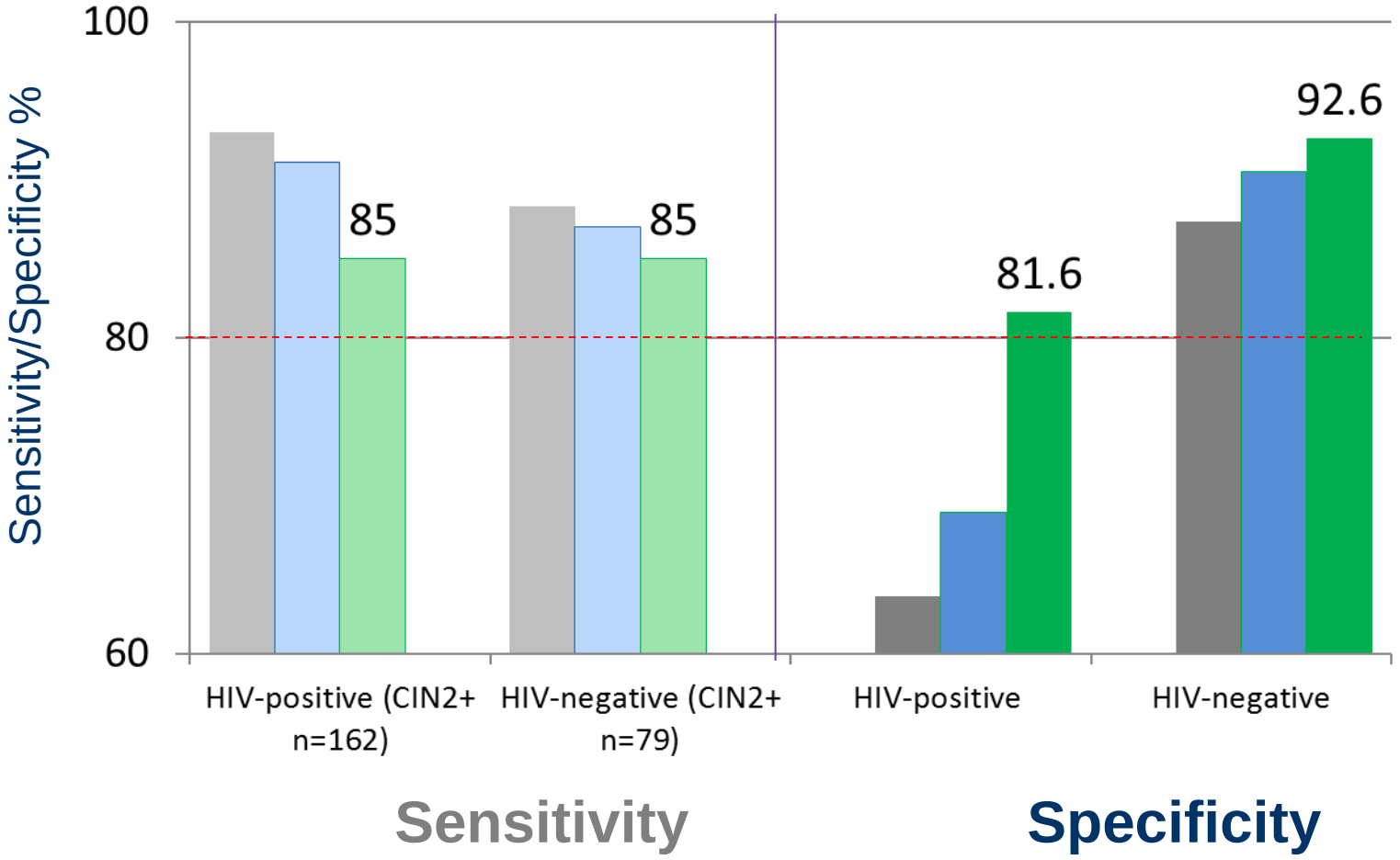
# Restrict to specific HPV types

Positive for **16**, **18,45**, **31,33,35,52,58**, ~~51,59,39,56,66,68~~



# Optimize Ct thresholds for specific HPV channels

Ct thresholds for **16**, **18,45**, **31,33,35,52,58**



# Conclusions from phase 1

- The best algorithm optimized **Ct values** in the three channels that detect HPV types **16**, **18,45**, **31,33,35,52,58**
- For HIV-negative women, at 85% sensitivity, specificity of 93% could be attained
- For HIV-positive women, at 85% sensitivity, specificity of 82% could be attained
- Xpert HPV, run as a point-of-care test, is robust and practical to implement the most disadvantaged communities in South Africa
- Xpert HPV can be adapted to make it suitable for "screen-and-treat" for both HIV-pos women and HIV negative women.

# Key secondary prevention studies in KCCSP

- Phase 2 of screen and treat now completed – an additional 3000 women recruited and being followed for 12 months with high risk HPV DNA testing, colposcopy and histology
- Over 90% of women chose to wait the hour for their results and return rates at 6 months have been over 90%, 12 months return rates still need to be analysed

# Conclusion

- Phase two will show impact of screen and treat on cervical cancer precursors and cervical cancer
- Plan is to move into implementation phase with strong partnership with Western Cape Government DOH
- Add in robust evaluation of impact of the algorithm on health system efficiency and strength
- Negotiate costs!