seit GGG 1844
GESELLSCHAFT FÜR GEBURTSHILFE UND GYNÄKOLOGIE IN BERLIN

GGG-B
19.9.2018

Blick über die Ländergrenzen

Von Afrika lernen: HPV Screeningprojekte der Klinik für Gynäkologie der Charité in Entwicklungsländern

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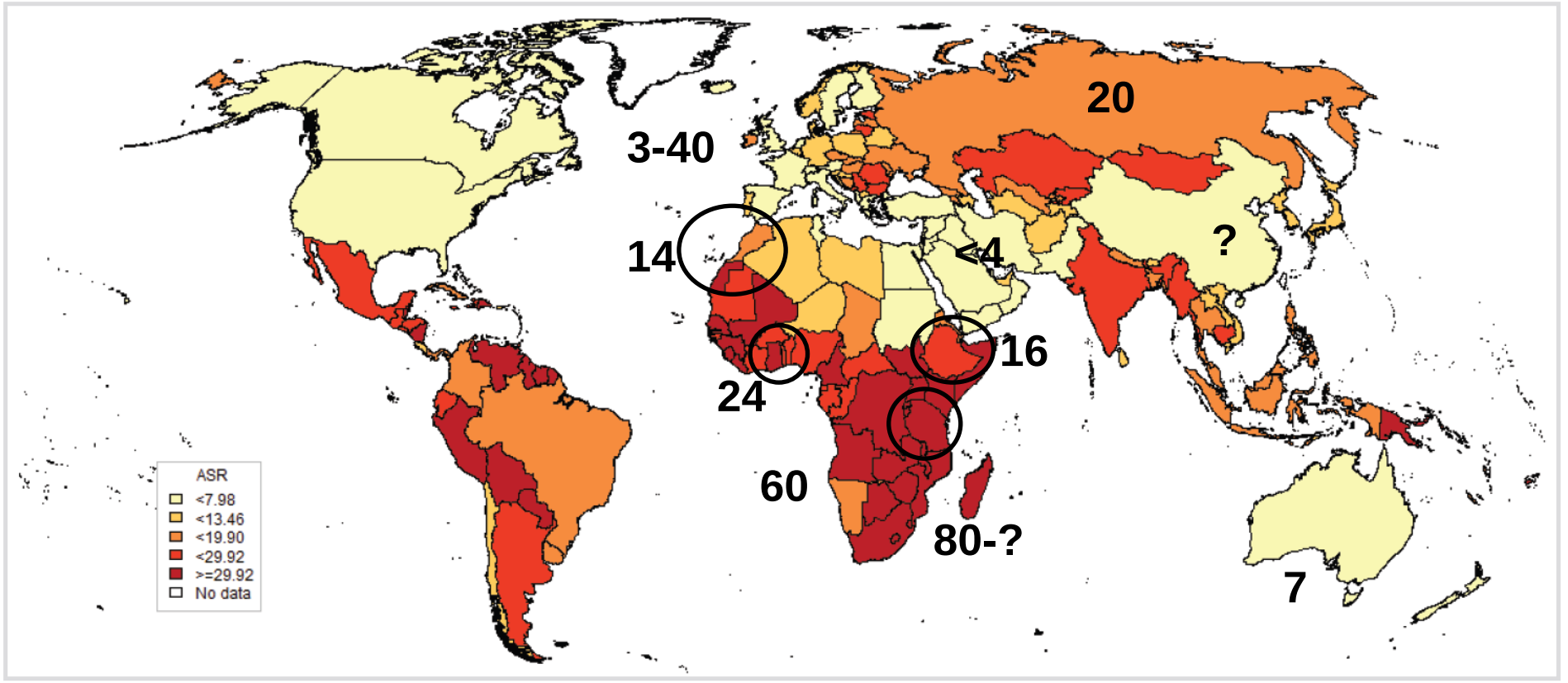
CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Motivation

- Bedarf
- Wissenschaftliches Interesse
- **Bedarf**

- **Global Health Initiative der Charité**
- **Klinik für Gynäkologie, Prof. Jalid Sehouli**
- **Persönliche Verbindungen**

Altersstandardisierte Inzidenzen an CxCa (Rate pro 100.000 Frauen/Jahr)



ASR, age-standardized incidence rates; Rates per 100,000 women per year.

- Adequate Methodik
- Machbarkeit im Gesundheitssystem
- Information für Entscheider

- Ghana
- Marokko
- Tansania
- Ethiopien

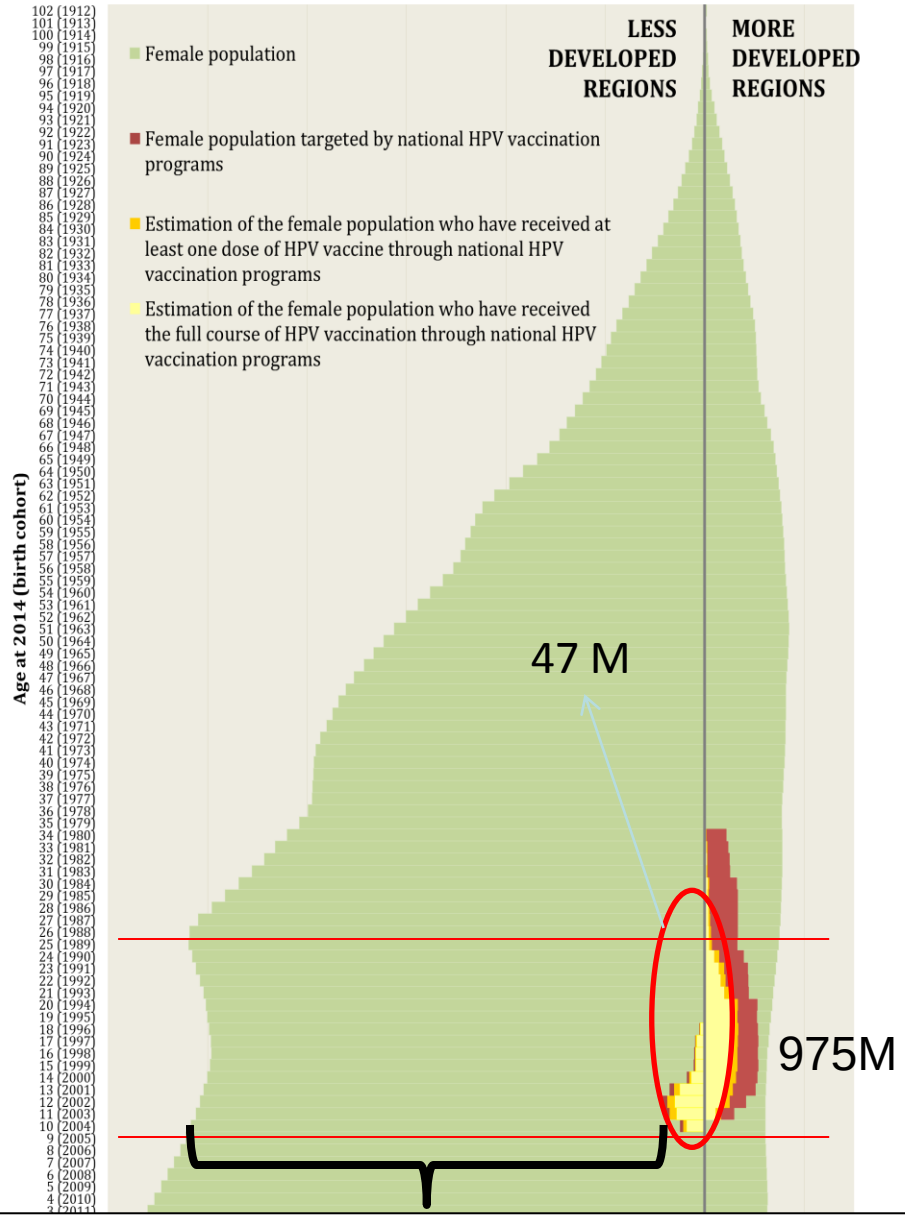
VACCINATION COVERAGES BY REGION

Through 2014, 64 countries nationally, 4 countries in some regions, and 12 overseas territories had implemented publicly funded national HPV vaccination programs

WOMEN VACCINATED AGAINST HPV THROUGH PUBLICALY FUNDED VACCINATION PROGRAMS

FULL COURSE VACCINATION

- By 2014, 47M women received a full course and 59M women at least one-dose HPV vaccine through national programs.
  - 32M in more developed regions
  - 15M in less developed regions
- 3-dose coverage:
  - 40% of targeted cohorts
  - 1.4% of total female population



Zukünftige Erkrankungslast

Bruni et al. 2015

Gebärmutterhalskrebsprävention auf WHO Agenda

19th May 2018: Cervical cancer is one of the most preventable and treatable forms of cancer as long as it is prevented with HPV vaccination, detected early, and managed effectively. Prevention and early treatment are highly cost-effective. Worldwide however, cervical cancer remains one of the gravest threats to women's lives, and globally, one woman dies of cervical cancer every two minutes. This suffering is unacceptable, and cannot continue. In recognition of this, WHO Director-General, Dr Tedros Adhanom Ghebreyesus today made a global call for action towards the elimination of cervical cancer.

Read the call to action
pdf, 82kb

Dr Tedros Adhanom Ghebreyesus, WHO Director-General

Read the call to action
pdf, 82kb

Projekte

- Ghana
- Marokko
- **Deutschland**

HPV research in Ghana

Update on ACCESSING

Adequate Cervical cancer Capacity building, Education and Screening by new Scientific INstruments in Ghana

Andreas M. Kaufmann, Amrei Krings, Anna-Lisa Behnke
Aleksandra Pesic
Gynäkologische Tumor Immunologie, Clinic for Gynecology
Charité Campus Benjamin Franklin
Wolfgang Siebert
German Rotary Voluntary Doctors
Kofi Effah et al.
Battor Catholic Hospital, Ghana

BUILDING A COMPREHENSIVE CERVICAL CANCER SCREENING AND TRIAGE SYSTEM FROM BOTTOM UP: THE ACCESSING APPROACH*

ESTHER GERMANY

CATHOLIC HOSPITAL BATTOR

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

Rotary GRVD

giz Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH

ROVERS MEDICAL DEVICES BV

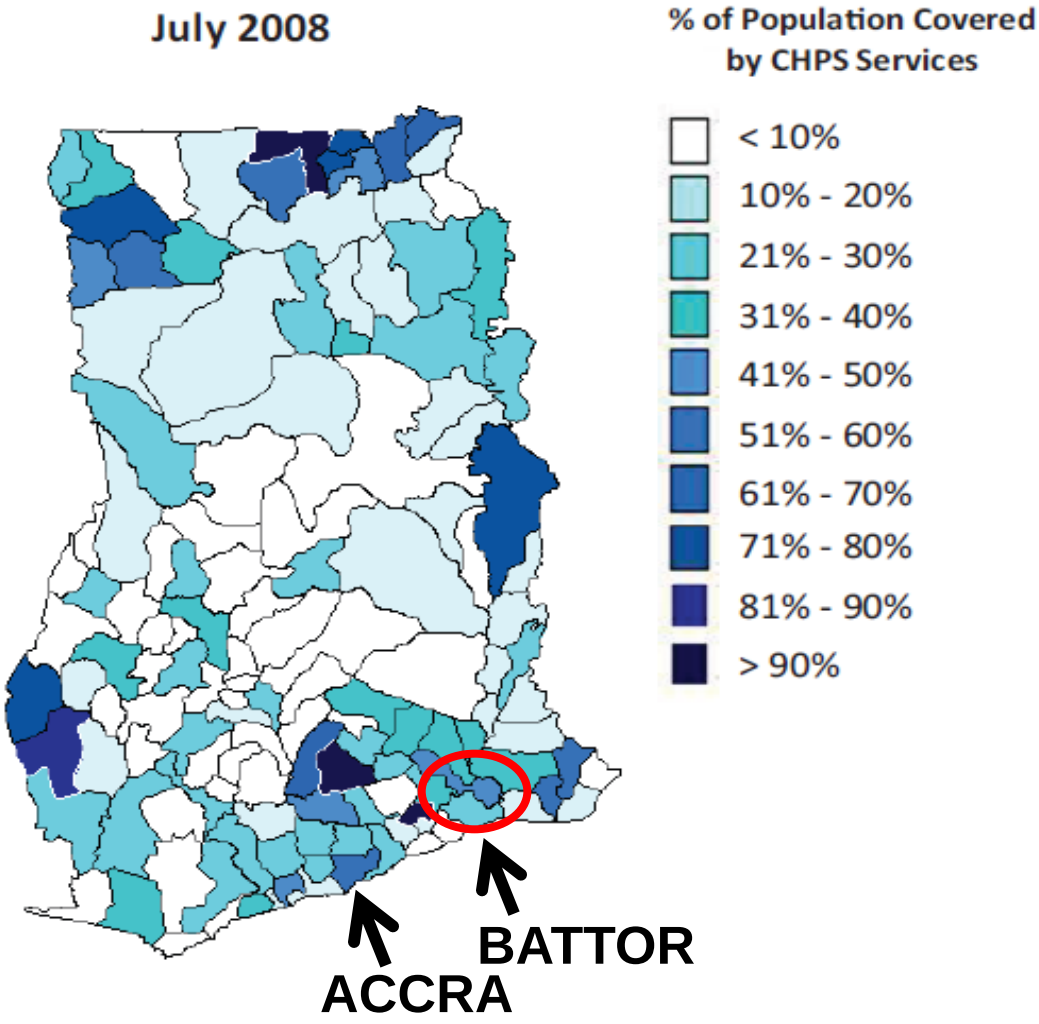
AID AUTOIMMUN DIAGNOSTIKA GMBH

ARBOR VITA

Ownership of African partners!

ACCESSING: **Adequate Cervical cancer Capacity building, Education and Screening by new Scientific INstruments in Ghana**

Community Health Immunization Planning and Services (CHIPS), Ghana



Catholic Hospital Battor (CHB) Ghana, North Tongu District, Adidome/Battor

Dr. Wolfgang Siebert (GRVD), Sr. Dr. Edgitha Gorges (retired), Dr. Kofi Effah (PI; Battor) (v.l.)

Catholic Hospital Battor / Ghana

CHB/Charité ESTHER clinical partnership

Accessing health care is difficult

Gynecology ward CHB

Diagnostic Laboratory

Established Infrastructure in Ghana

CHPS System and Community Health Worker

Comprehensive Program

<u>Feasibility</u>:

combination of self-sampling in villages…

With HPV test or

low-tech Biomarker test possible…

Screening of women in remote rural areas

Treatment in District Hospital Battor

HPV genotyping for prevalence in Berlin

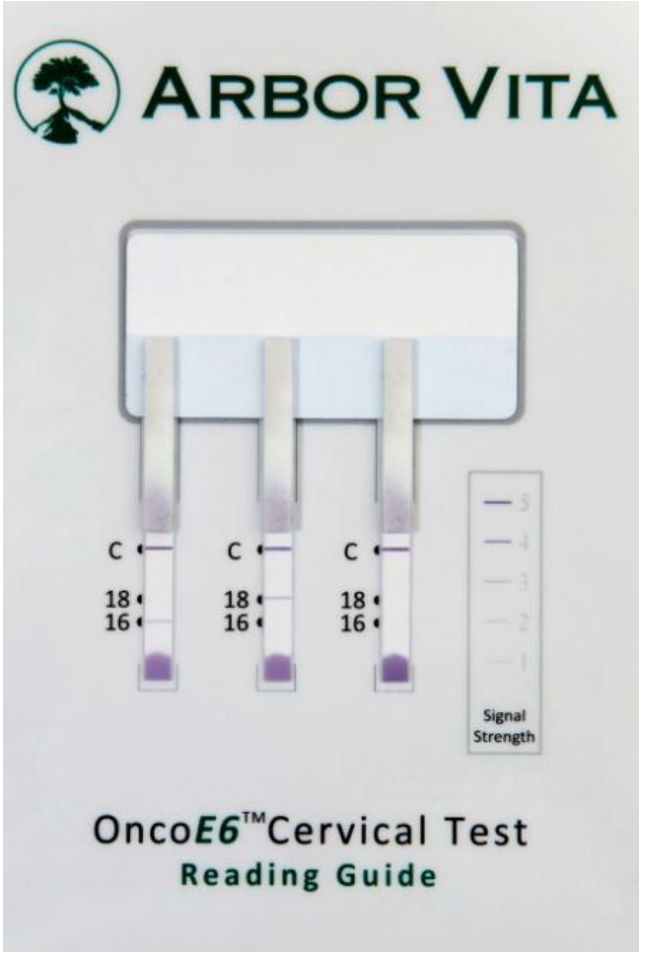
ESTHER & GIZ financed clinical partnership

Simplicity of Oncoprotein E6 Cervical Test (Workstation Setup)

Oncoprotein E6 Cervical Test (Biomarker for disease)

- Lateral flow Immunoassay Test
- Detection of HPV16 and 18 (typing)
- 9 samples in <3 h (hands on time appx. 2 h)

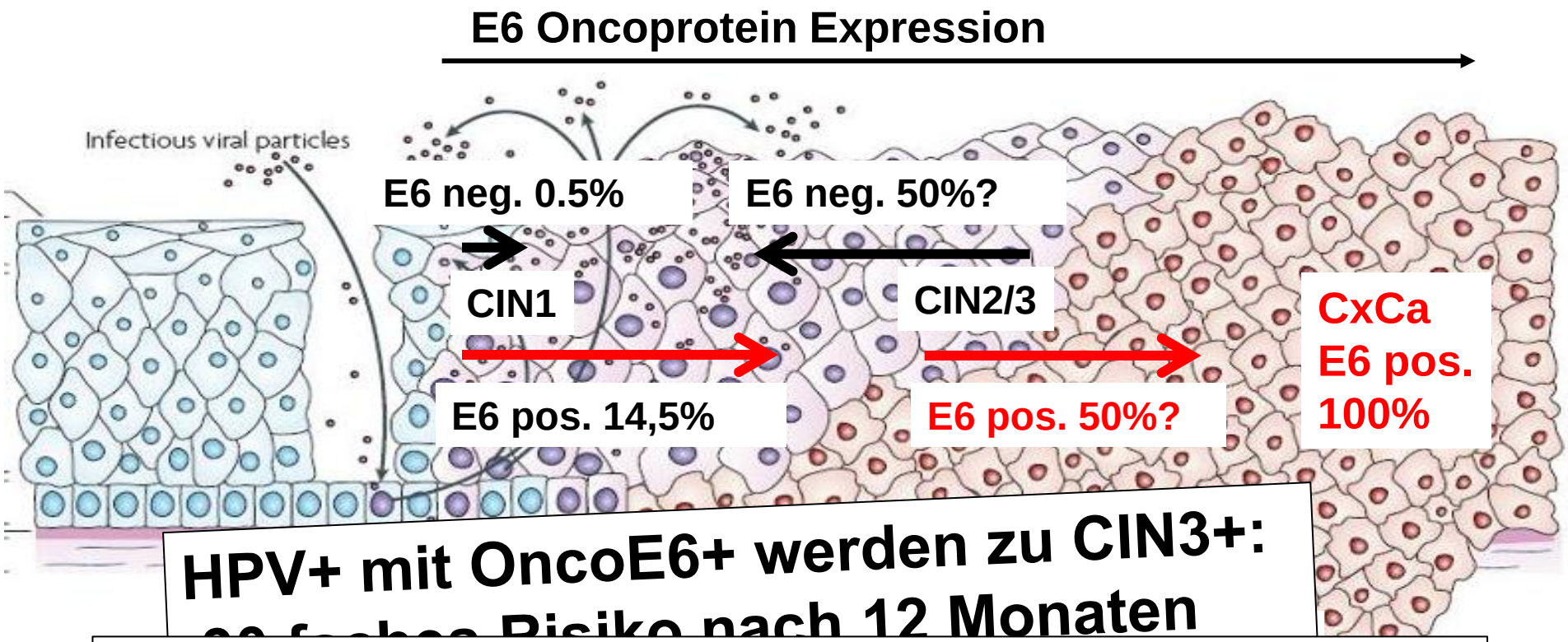
• Sensitivity	for CIN3+	53.5%
	for CervixCa	91.7%
• Specificity	for CIN3+	98.9%
• PPV	for CIN3+	40.8%
• NPV	for CIN3+	99.37%



⇒ High specificity for disease
⇒ Simple, robust technology
⇒ Low resource settings

Zhao et al., 2013

E6 Onkogen:
Biomarker for high-grade and progressive dysplasia



HPV+ mit OncoE6+ werden zu CIN3+:

110 faches Risiko nach 10 Jahren

! => Test mit prognostischer Aussage

Nur ... detektierbare Mengen von E6 Onkoprotein.

Pilot trial HPV Testing in high incidence HIV+ Population

1) self-sampling in referral population

- **91% (228/250) self-sampled.**
- **85% found this easy/very easy and comfortable/very comfortable**
- **Technically feasible (logistics, lab)**

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2) HPV in referral population

Ergebnis	HIV+ (n=100)	HR Group (n=150)
CIN2+	14% (14)	3% (5)
HPV+	80% (80)	38% (57)
hrHPV	72% (72)	30% (45)
Multi hrHPV	47% (47)	17% (25)

HPV testing => No specificity for disease!

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HPV testing => No specificity for disease!

3) AVE6 in referral population (HPV16/18 positive)

7 CIN3+: 4 (57%) detected, 1 CxCa

19 CIN2+: 7 (37%) detected

HR-Group: Longitudinal HPV follow-up

- Initial genotyping study 500 women, Ghana Natl. Lab. 2011
- Recruitment into ACCESSING 104 women and genotyping again 2014
- No follow-up or treatment in between !!!

93.3% (97/104) **had cleared** original HPV type

21.2% (22/104) **had new infection** with other genotype

6.7% (7/104) **had persistent same genotype**

Disease found **only in persistence group**:

3 CIN2+

1 invasive CxCa (HPV16)

! => genotype-specific persistence is prerequisite for dysplasia

Main study: Screening 2000 in North Tongu, in rural communities by AVE6 Cervical Test and PCR Genotyping

Women representatively selected from census from villages
Age 18-64, non-pregnant (anamnestic)

- **Feasibility (logistics): 2000 samples in 5 weeks collected August-November 2015**
- **Acceptance; Risk factors questionnaire: highly accepted (>90%)**
- **HPV prevalence of individual types: 36% HPV positive!**
  With mean age 34 years
- **Therapy referral and performance rate: problem low compliance to travel to hospital**

Screening results and disease burden

	AVOncoE6	HR-HPV Test
screening positive	2.1% (41/1999)	37.6% (752/2000)
triageing	85% (35/41) colpo	38.4% (298/752) cyto
treatment referral	28.5% (10/35) w/changes	5.5% (16/298) ASCUS
disease found	100% (10/10)	6.25% (1/16)

! => We need a test with high sensitivity and even more specificity!

Conclusion Self Sampling and Molecular Triage Testing

- **Self-sampling well accepted and not inferior** in detecting dysplasia than swab sampling.

- Self-sampling **in conjunction with OncoE6 cervical test** can be used in communities to detect and triage women with **highest risk for severe dysplasia or cervical cancer.**

- **Molecular Triage** with Arbor Vita OncoE6 Cervical Test **more efficient than PAP** testing.

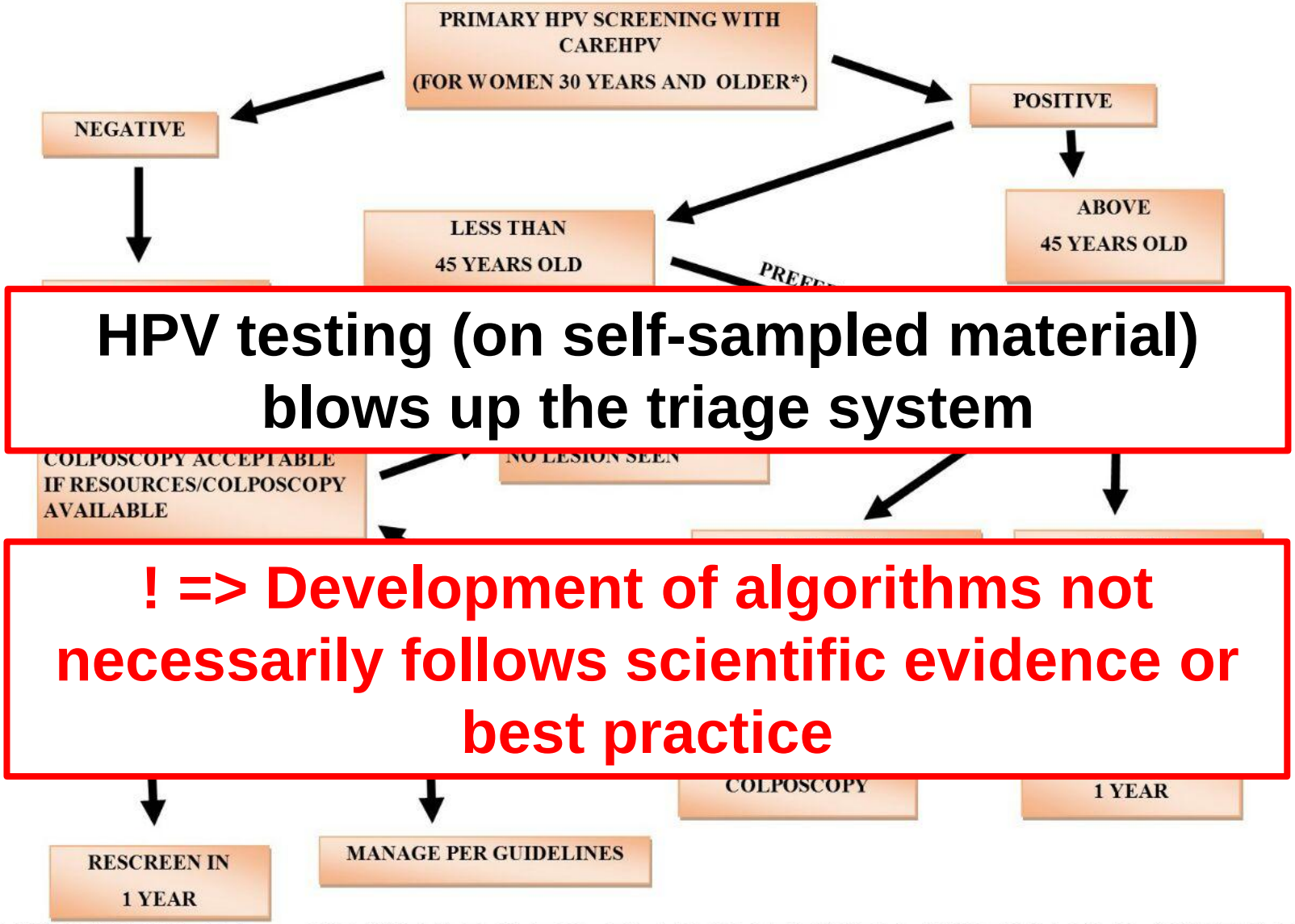
- This allows **secondary cancer prevention** 'on the doorstep' **in remote locations**.

! => Local **needs, beliefes, ownership, key stakeholders**, …..**particular interests**…. influence decision on the system to be established…..

Colleagues decided on local screening algorithm

- Kofi Effahs decision
- After visiting conferences
- Own contacts to industry
- Own capacity building
- Use of Ghana internal resources
- Independent decision on screening algorithm
- For women who have to pay out of pocket…

ALGORITHM FOR SCREENING WITH CAREHPV



HPV testing (on self-sampled material) blows up the triage system

! => Development of algorithms not necessarily follows scientific evidence or best practice

*** WOMEN 21— 29 YEARS TO BE SCREENED WITH PAP SMEAR**

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GCIG-PARSGO Conference 5-7.4.2018 Marrakesh

Cervical Cancer Screening Feasibility Study *MorocOncoE6* comparing VIA with Molecular HPV E6 Oncogene Expression Testing

Andreas M. Kaufmann, Karima Bendahhou, Jalid Sehouli, Abdellatif Benider

+all the MorocOncoE6 Study Consortium

andreas.kaufmann@charite.de

Partners

- **Lalla Salma Foundation**

- **Direction Régionale du Ministère de la Santé, Les Centres de Santé (CS): Dradeb, Bni Makada, Al Amal, Msalah, Breich, Had Gharb Beni Arouss, (Tanger/Larache)**

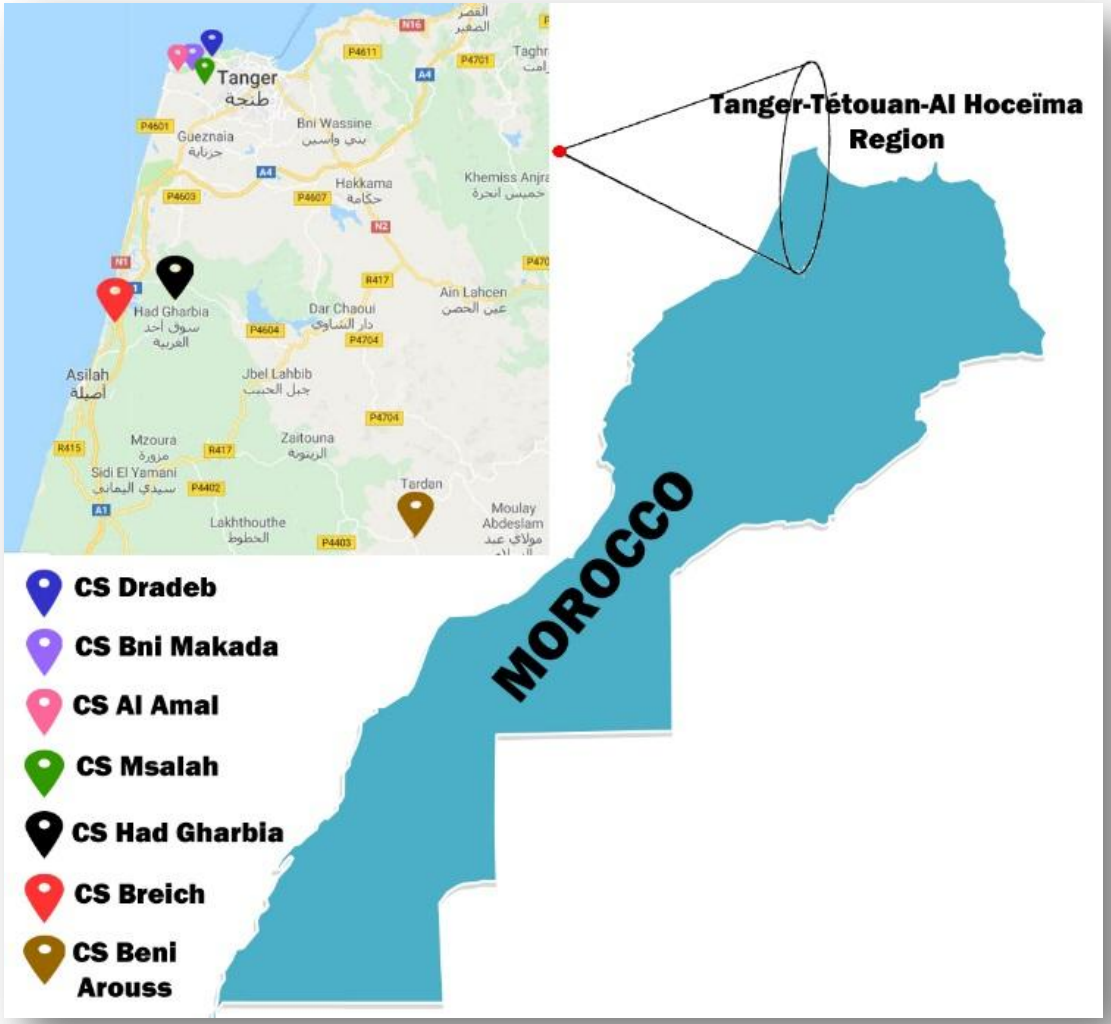
- **University Hassan II, Mohamed VI Cancer Center**

- **Charité-Universitaetsmedizin Berlin**

- **Zenith Pharma / Arbor Vita**

Study Sites in Tanger Area

- Access to underserved women
- Cervical Cancer Screening
- Self-sampling
- Adequate test format
- VIA vs molecular HPV test
- Acceptability questionnairs
- HPV epidemiology



4 urban sampling sites
Centre de Santé:

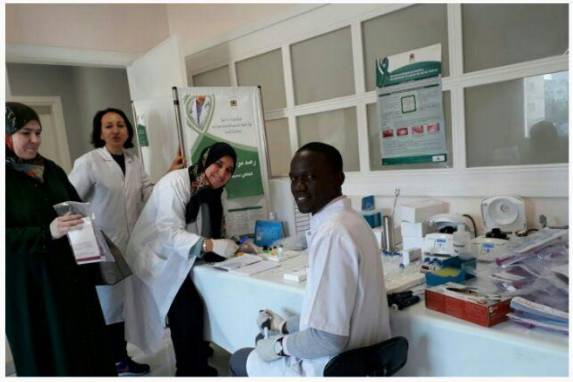
- Dradeb
- Bni Makada
- Al Amal
- Msalah

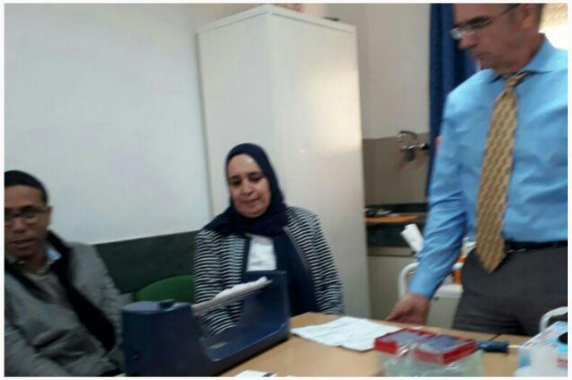
3 rural sampling sites
Centre de Santé:

- Had Gharbla
- Breich
- Beni Arouss

Self-sampler Evalyn Brush

Training Casablanca Cancer Center 5-6 Dec 2017





VIA and Colposcopy: Preparation of Materials

! => VIA is not well known by the nurses…

Concordance VIA and OncoE6 test

Coefficient Kappa =0,001

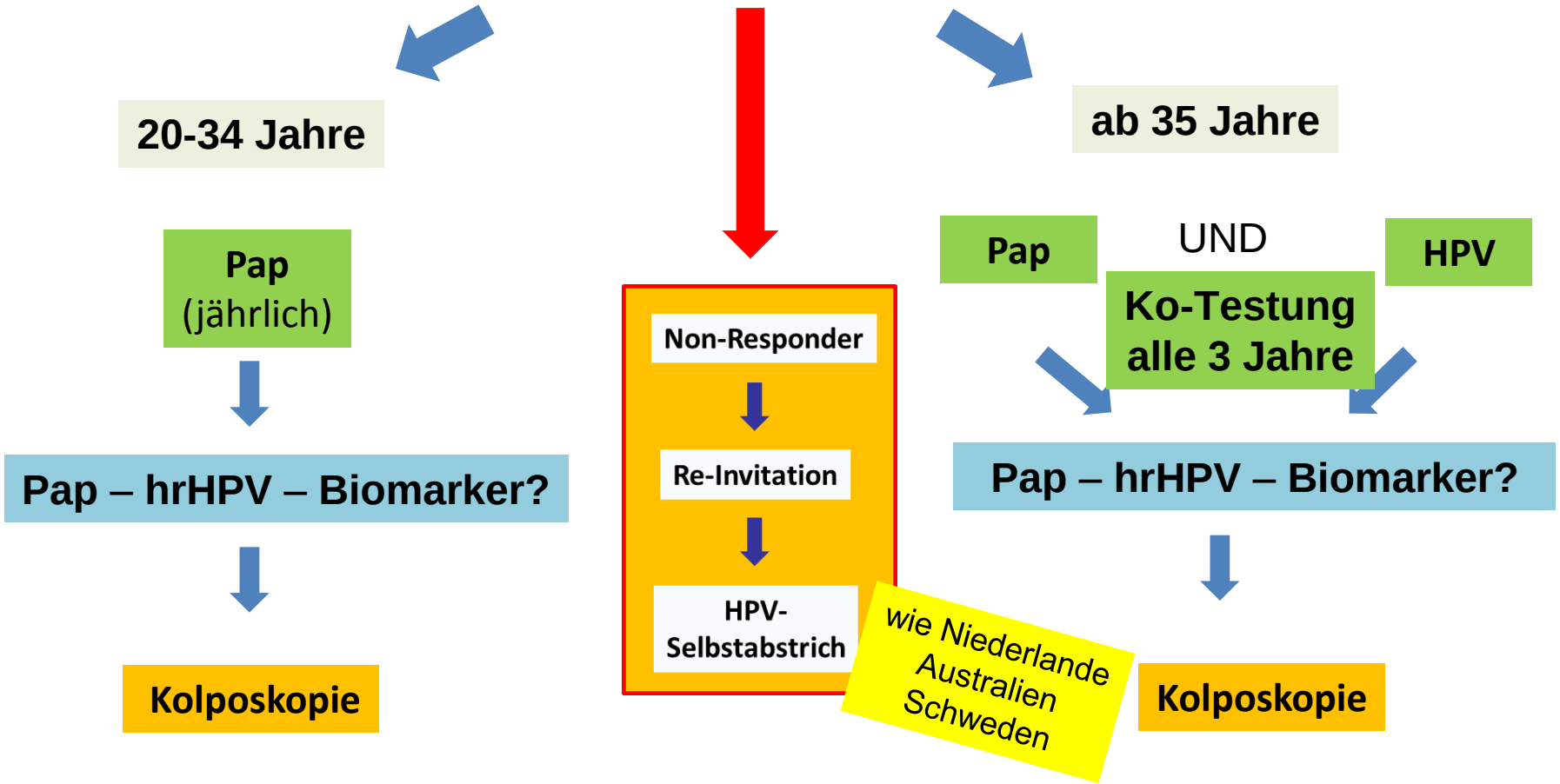
	VIA		
	Negative	Positive/ suspicious	total
OncoE6 -	181	30	211
OncoE6 +	4	1	5
Total	185	31	216

6 fold more positives by VIA!
=> over referral, cost of triage
=> wrong cases

Lernen

- Impfung: wäre wichtig
- Screening: bleibt wichtig
- **Triage : wird wichtig**

G-BA: Organisiertes Screening mit Einladungsmodell (KV Anschreiben ab 1/2019)



Registrierung der Teilnahme, Ergebnis, follow-up….

Problem: HPV Prävalenz und Triage

ICO Information Centre on HPV and Cancer

Germany

Human Papillomavirus and Related Cancers, Fact Sheet 2017 (2017-07-27)

Table 3. Burden of cervical HPV infection Germany

	No. Tested	% (95% CI)
HPV prevalence in women with normal cytology	38684	8.2 (7.9-8.5)
HPV 16/18 prevalence:		
Normal cytology	10988	3.2 (2.9-3.5)

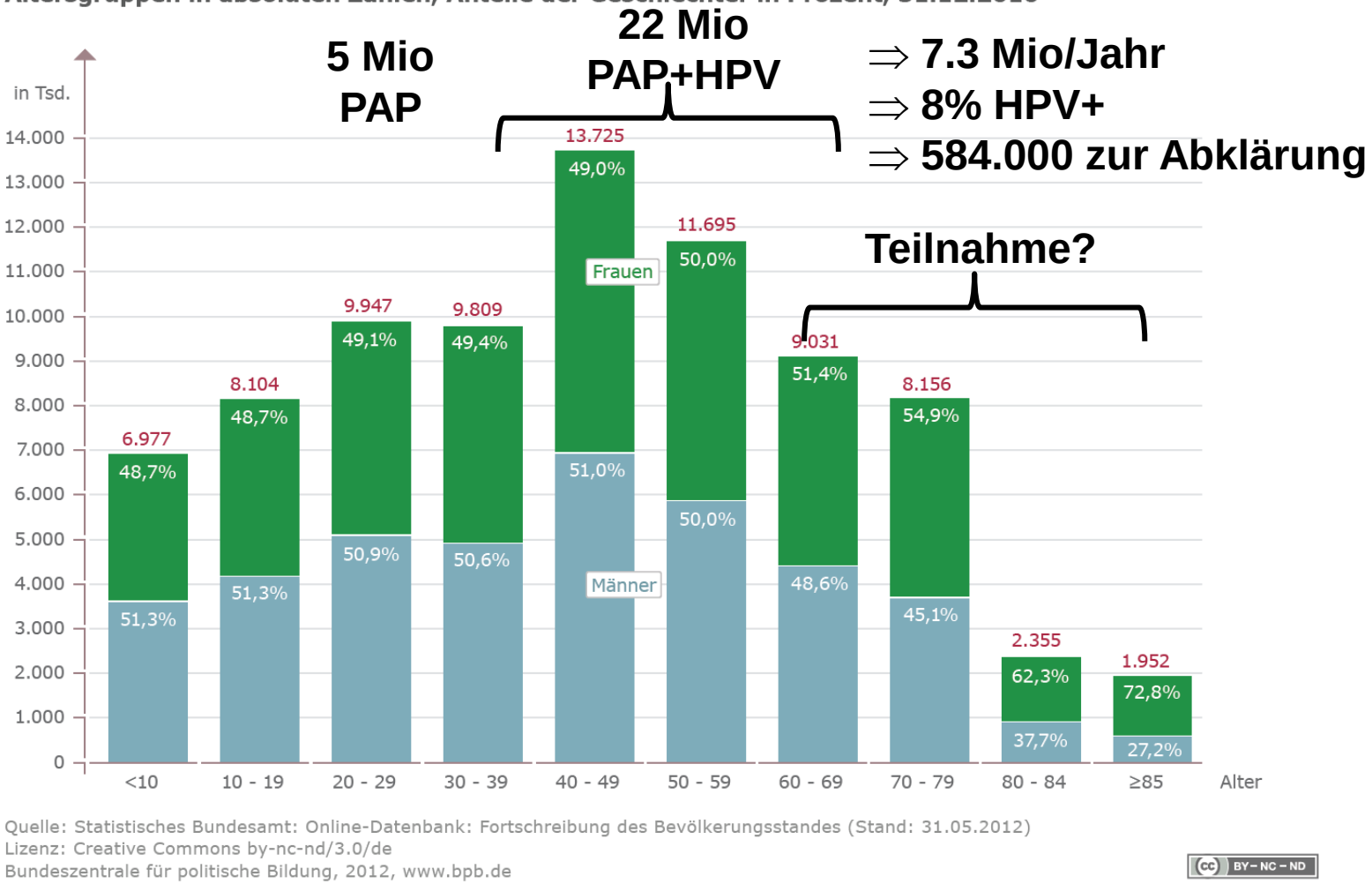
Auffällige Zytologien bei **0,3%**

Primäres HPV Screening => Positive zur Triagierung

http://www.hpvcentre.net/statistics/reports/XWX.pdf

Screening Zielpopulation

- Bevölkerung nach Altersgruppen und Geschlecht



Quelle: Statistisches Bundesamt: Online-Datenbank: Fortschreibung des Bevölkerungsstandes (Stand: 31.05.2012)

Bundeszentrale für politische Bildung, 2012, www.bpb.de

http://www.bpb.de/system/files/datei/SO-01_04-svg-standard.svg#

Lernen…

Self-sampling für Nicht-Teilnehmerinnen: z.B. in unterversorgten Regionen, Altersgruppen, Randgruppen, Migrantinnen….
=> RKI Studie; FACTS Studie

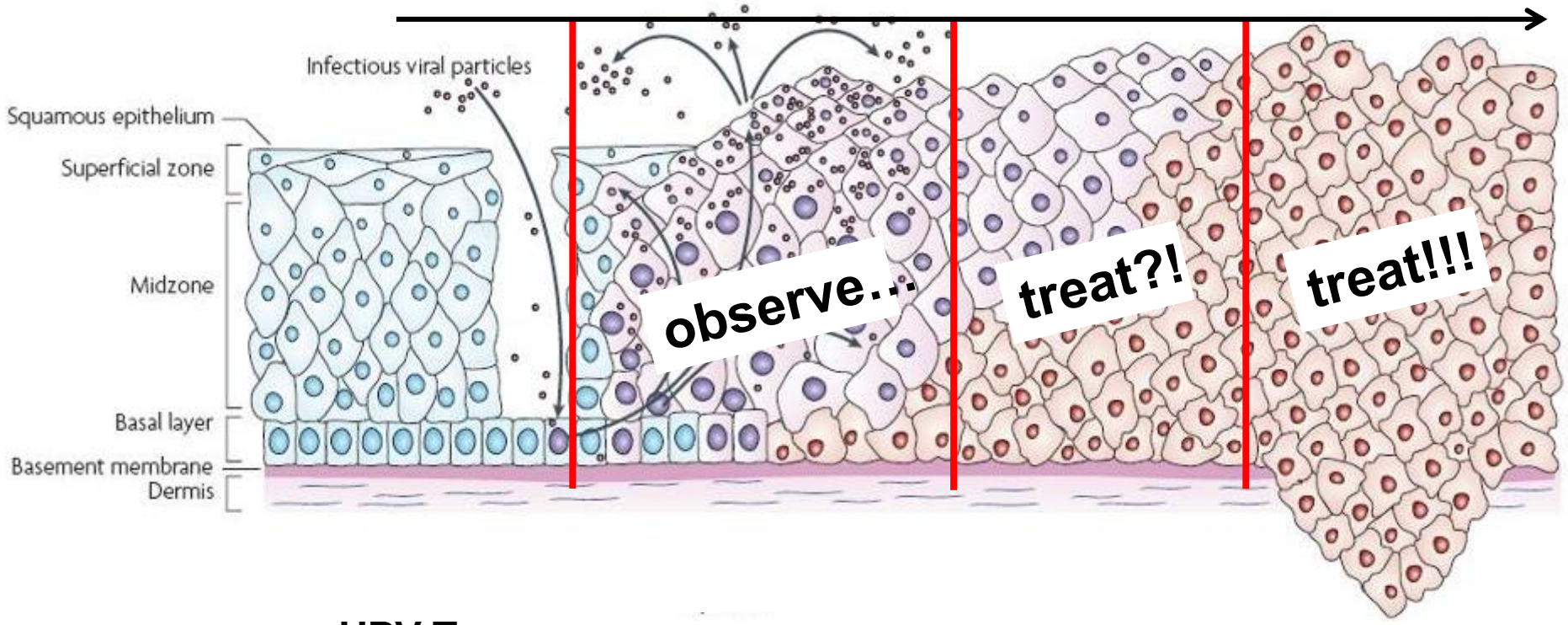
HPV Testung: genotypisierender Test mit longitudinaler Ergebnisregistrierung: => Persistenz = Risiko
=> Typwechsel = KEIN Risiko
=> Genotypisierende HPV Tests

Molekularer Markertest für Triage zur Kolposkopie
=> zu wenig Kapazität der Dysplasiezentren
=> Test mit hoher Aussagekraft zum Stadium
=> Therapieentscheidung! – oder nicht?
=> „Dysplasie“ statt „HPV“ Test

HPV induzierte Progression zu Zervixkarzinom (Charité: inhouse Cerviclaire Test) von LBC Screeningabstrich durchführbar

~50% ~50%

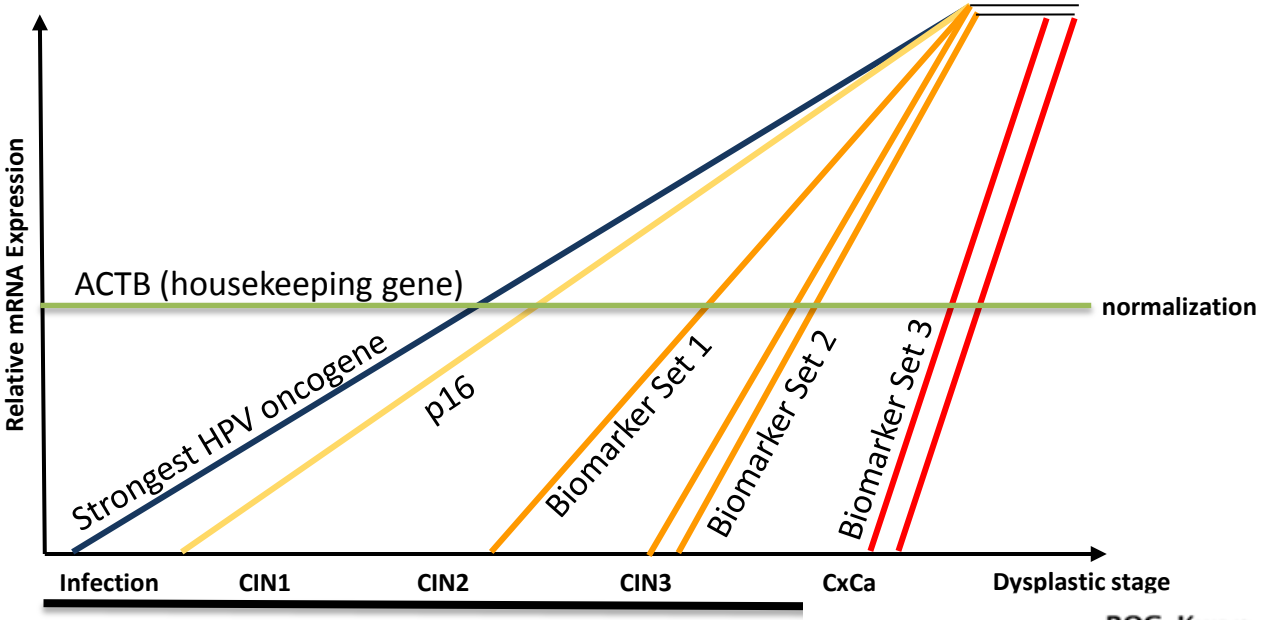
Infektion ⟷ CIN 1 ⟷ CIN 2/3 → Invasives CxCa

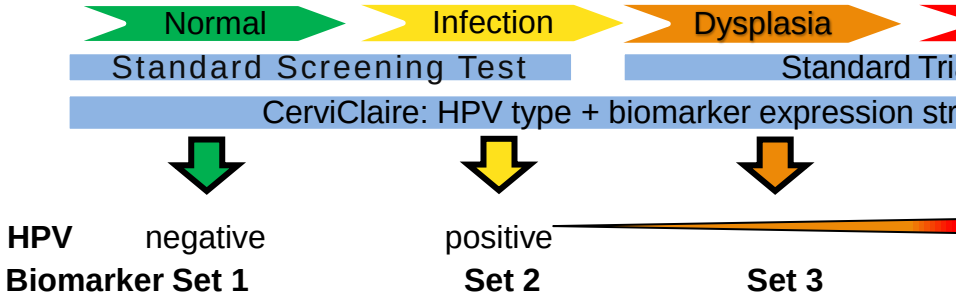


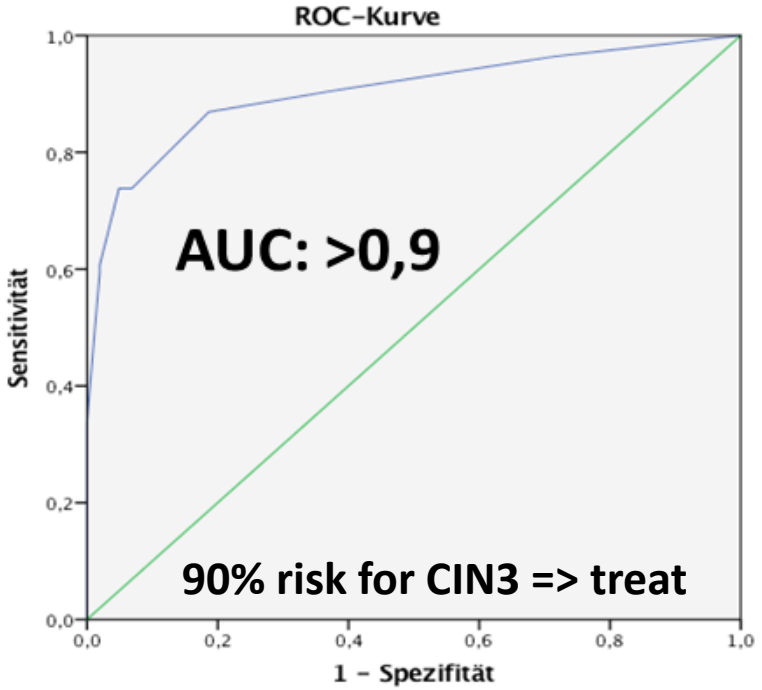
mRNA von:	HPV Type Present?	biomarker set 1	biomarker set 2	biomarker set 3

Seeing a women once: One step screening for dysplasia

Detektion/Quantifzierung von Biomarkern als Maß des Stadiums







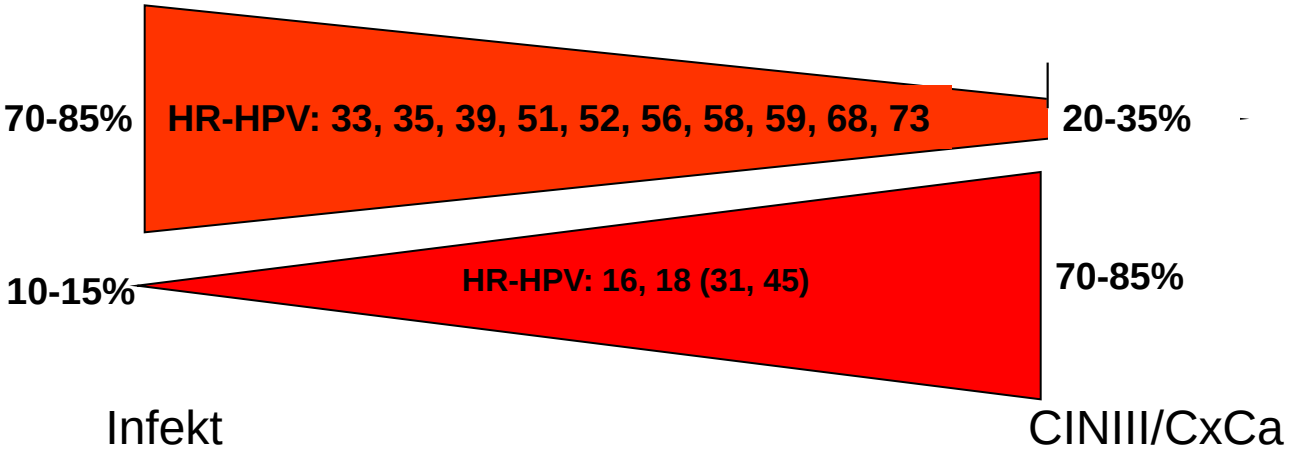
! => Good for Africa…

Aber vielleicht nicht nur….


Thank you !
Please do not forget vaccination!
Rwanda vaccinated 90% eligible girls against HPV!

Welchen Mehrwert kann die HPV Genotypisierung haben?

- **Multiple Typen abbilden**
- **Hochrisiko-Typen differenzieren**
- **Persistenz desselben HPV Typs nachweisen vs Typenwechsel**
- **Test of cure – Dysplasie-verursachender Typ eliminiert, Reinfektion mit anderem Typ?**
- **HPV Impfstofftypen identifizieren (Durchbruchsinfektion?)**



Ziele der Forschungs- und Versorgungsansätze in der Gynäkologie

promote => enable => change

- **Verbesserung der PatientInnenversorgung**
  - **Klinikpartnerschaften**
  - **Expression VI Studie**
- **Stärkung der Forschung**
  - **PARSGO Consortium**
  - **TOC: Tumor Bank Ovarian Cancer Network**
- **Translation in das Gesundheitssystem**
  - **HPV/Zervixkarzinom Screening**
    - **Ghana**
    - **Äthiopien**
    - **Tansania**
    - **Marokko**

Klinikpartnerschaften (BMZ/GIZ)

Ghana: Charité / Catholic Hospital Battor => CxCa Screening

Marokko: Charité / Hassan II, Casablanca => gyn-onkologische Versorgung
/ MoH, Lalla Salma F. => CxCa Screening

Koop. Partner: HPV / CxCa-Screening Kompetenz

Äthiopien:

Charité / Halle	Addis Ababa	=> HPV Test, Laboraufbau
	Butajira	=> Populations-Screeningstudie
Charité / Heidelberg	Gondar	=> Populations-Screeningstudie

Tansania:

Charité / LMU München	Mbeya	=> HPV in HIV+, Immunologie