Novel screening and treatment of cervical precancer:

Experiences from around the world

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Financial Disclosures

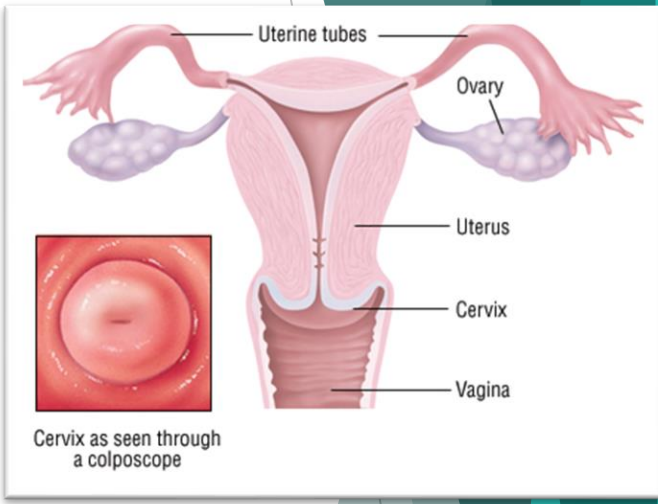
- Merck Speakers Bureau

Objectives

- Review worldwide cervical cancer statistics
- Discuss current screening tests, their limitations, and alternatives under investigation
- Present current treatments, their limitations and alternatives under investigation

The problem:
Epidemiology of cervical cancer (2018)

- 570,000 new cases/year
- More than 311,000 women die every year, mostly in low and middle income countries
- Completely preventable: 99.7% of cases are caused by infections of the human papillomavirus (HPV), a sexually transmitted disease



The New York Times

Wider Racial Gap Found in Cervical Cancer Deaths

By Jan Hoffman

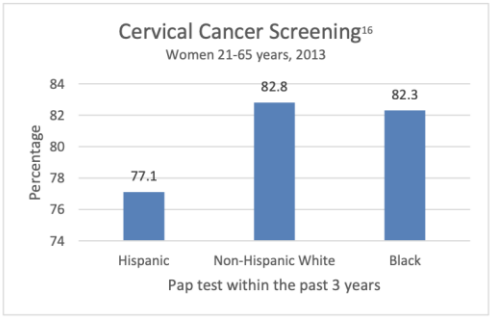
Jan. 23, 2017

The death rate from cervical cancer in the United States is considerably higher than previously estimated and the disparity in death rates between black women and white women is significantly wider, according to a study published Monday in the journal Cancer.

The rate at which black American women are dying from the disease is comparable to that of women in many poor developing nations, researchers reported. What makes the findings especially disturbing, said experts not involved in the research, is that when screening guidelines and follow-up monitoring are pursued, cervical cancer is largely preventable.

Cervical Cancer Disparities: Hispanic/Latina Women

- **Low Rates of Screening:** Despite having one of the highest incidence of cervical cancer, Hispanic/Latina women **undergo significantly fewer Pap tests** than non-Hispanic white and black women.[2]
  - Women of Cuban and Central/South American origin have the lowest rates of Pap tests in the past three years among all Hispanic/Latina women in the U.S.[2]
  - Hispanic/Latina women who have been in the U.S. for less than 10 years are significantly less likely to have had a Pap test in the last three years compared to those who have been in the country for 10 or more years.[12]



American Cancer Society Cancer Action Network | 555 11th St. NW, Ste. 300 | Washington, DC 20004 | @ACSCAN FB/ACSCAN | acscan.org

Socioeconomic Factors Increasing Cervical Cancer Rates for Some in the U.S. Despite Downward Nationwide Trends

Business Wire January 23, 2020

AmeriHealth Caritas Shares Advice to Help Women Prevent Cervical Cancer

Cervical cancer is a preventable disease, yet a large number of Americans are still dying from it--especially black and Hispanic women.[1] While deaths are decreasing as more women have been vaccinated against HPV, the leading cause of cervical cancer, there are still an estimated 11,900 new cases of cervical cancer being diagnosed in the U.S. each year. To prevent these results, it is crucial that women keep themselves informed as recent cervical cancer testing recommendations[2] and HPV vaccination age limits[3] have changed.

This press release features multimedia. View the full release here: https://www.businesswire.com/news/home/20200123005041/en/

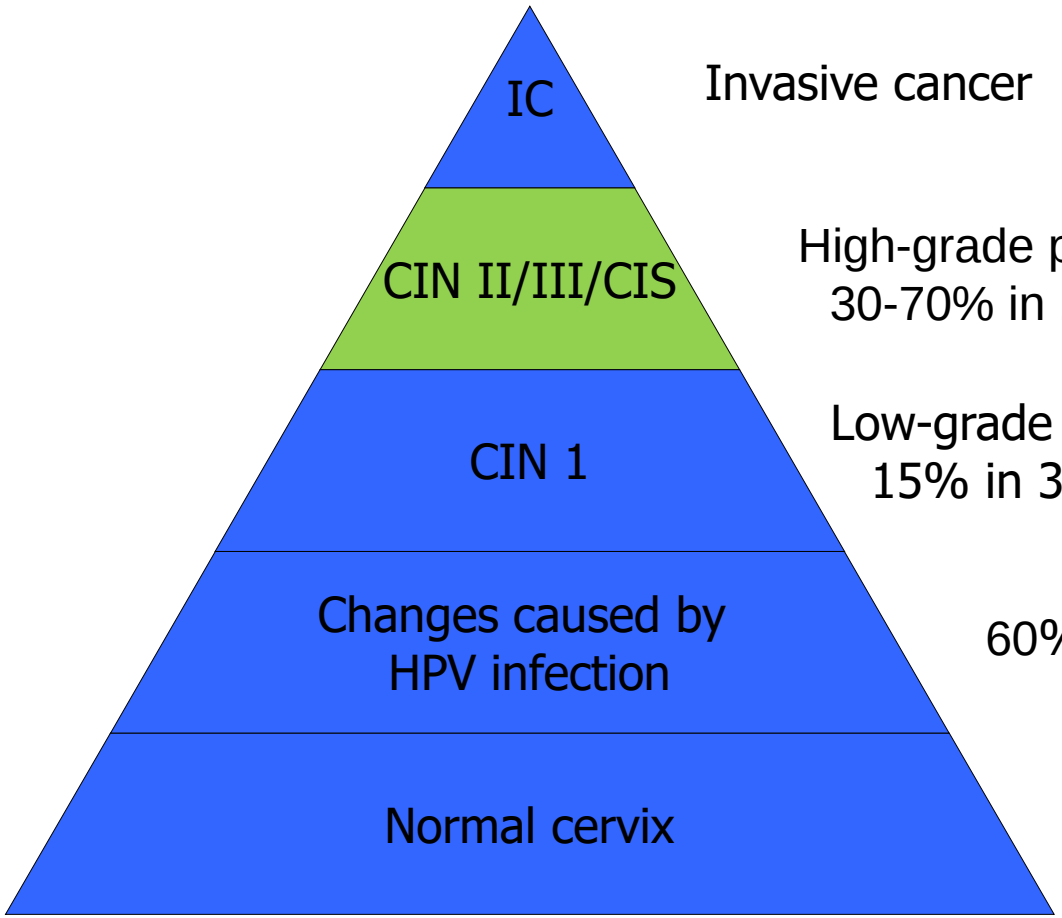
Cervical Cancer in Alaska

- Alaska Incidence:[1]
  - Range from 1996-2015 = 5.0 – 12.5 per 100,000 (CI 2.8-18.3)
  - In 2015: 8.2 per 100,000
    - U.S. overall (2014): 7.6 per 100,000
- Mortality: [1] 2.3 per 100,000, approx. the same as US overall
- Disparity:[2]
  - AN women have higher incidence rates of cervical cancer compared with White women (11.0 vs 7.1; RR = 1.55)
  - AN are more often diagnosed with later-stage disease (RR = 1.84 for regional stage and RR = 1.74 for distant stage)
  - AN are TWICE as likely to die from cervical cancer than White women (4.2 vs 2.0, RR = 2.11)

[1] Alaska Cancer Registry. Health Analytics and Vital Records Section (HAVRS), Division of Public Health, Alaska Department of Health and Social Services and **North American Association of Central Cancer Registries** (NAACCR), CiNA analytic public use file, accessed via SEER*Stat software. Includes incidence data from CDC's National Program of Cancer Registries (NPCR) and NCI's SEER registries.

[2] Am J Public Health. 2014 June; 104(Suppl 3): S415–S422.Published online 2014 June. doi: 10.2105/AJPH.2013.301681 PMCID: PMC4035877 PMID: 24754650

Normal cervix → Invasive cancer



Invasive cancer

High-grade precancer:
30-70% in 10 years

Low-grade precancer
15% in 3-4 years

60% of women

Goals of BHI Research

- **To develop patient-centered, comfortable, affordable and accessible screening and treatment options for women around the world, particularly those in low resource and remote settings.**

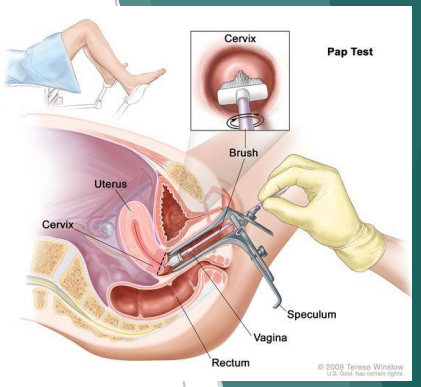
The perfect screening test is:

- Inexpensive
- Easy to perform by all level of providers, and
  - preferably by the woman herself
    - self-sampling not yet FDA approved in the U.S.
- Point of care
  - Able to make a diagnosis in real time
- Good accuracy
- High reproducibility

Screening tests for cervical precancer

- Pap Smears (cytology)
- Visual Inspection with Acetic Acid
- Human Papillomavirus (HPV) tests
- HPV Genotyping
- Artificial Intelligence (AI) algorithm-driven image diagnosis (*experimental*)

Screening tests for cervical precancer



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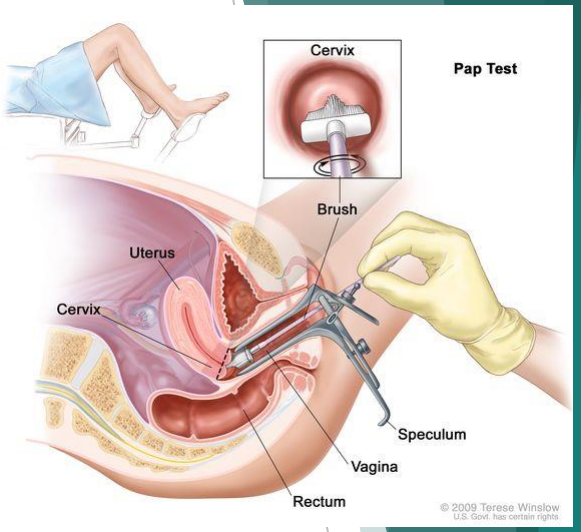
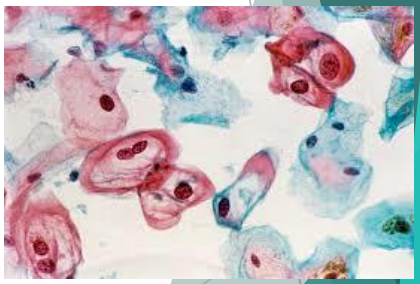
Pap Smear and its limitations

- Pap: Provider visit, speculum exam with cells scraped from the inside and outside of the cervix, send specimen to lab for analysis

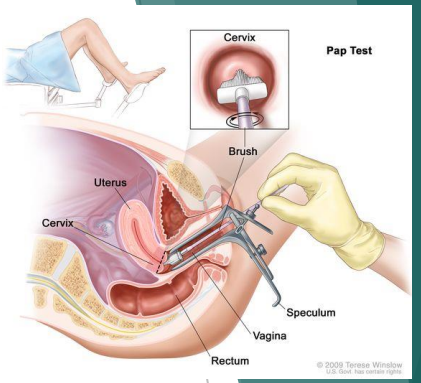


Limitations:

- Analysis of cytologic and histologic specimens is very user dependent for quality
  - sample, laboratory, pathologist
- Requires a multiple-visit approach
  - Abnormal pap → Colposcopy → Treatment



Pap Smears (Cytology)



- Inexpensive
- Easy to perform by all level of providers, and
  - Preferably by the woman herself
- Point of care
  - Able to make a diagnosis in real time
- Good accuracy (only if done frequently)
- High reproducibility (with good pathologists)

Screening tests for cervical precancer

- Pap Smears (cytology)
- Visual Inspection with Acetic Acid
- Human Papillomavirus (HPV) tests
- HPV Genotyping (16+18)
- Artificial Intelligence (AI) algorithm-driven image diagnosis

Visual Inspection with Acetic Acid (VIA)

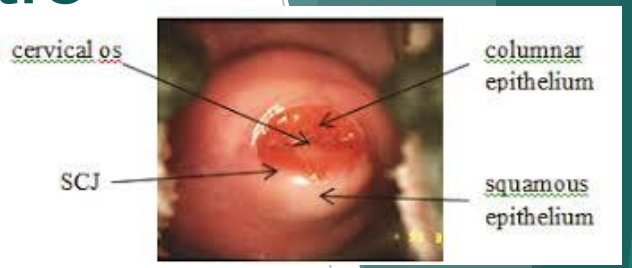
Apply white vinegar (acetic acid) to the cervix, wait one minute, and look for changes consistent with HPV

Negative

Positive

Photo source: JHPIEGO

Visual Inspection with Acetic Acid (VIA)



- Inexpensive
- Easy to perform by all level of providers, (but they need to be trained and have regular QA, which is costly)
  - Preferably by the woman herself
- Point of care
  - Able to make a diagnosis in real time
- Good accuracy
- High reproducibility
- Leads to overtreatment

Screening tests for cervical precancer

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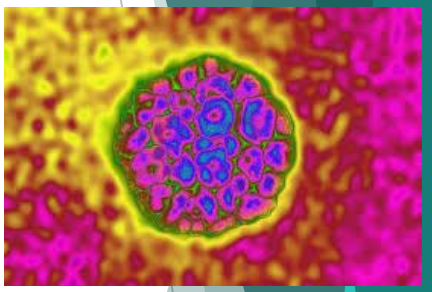
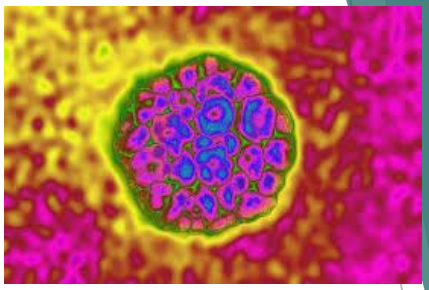
- Artificial Intelligence (AI) algorithm-driven image diagnosis

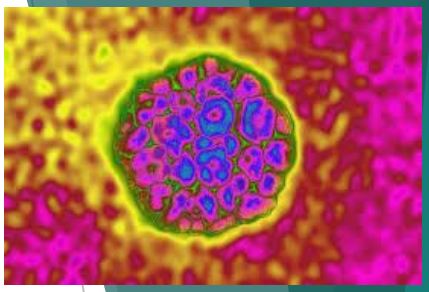


HPV tests



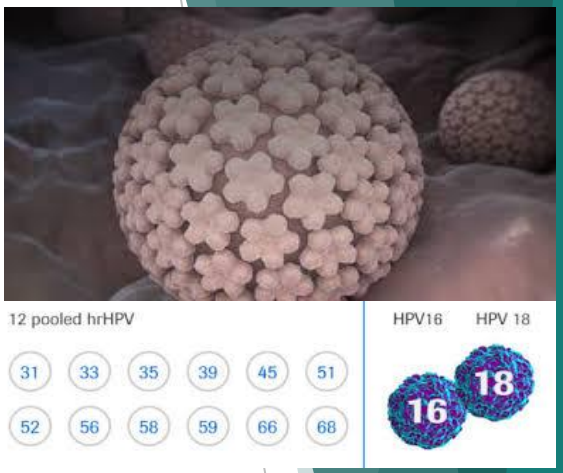
- Hundreds of HPV subtypes
- 14 cause cervical cancer
  - Some more likely than others
- Identify if a high risk HPV variant is present in the specimen
- Many are considering using HPV testing ALONE (without Pap smears)
  - Less expensive
  - More “scaleable”
  - More accurate than Pap alone

HPV tests



- Inexpensive
  - (are some less costly alternatives)
- Easy to perform by all level of providers, and
  - Preferably by the woman herself
- Point of care
  - Able to make a diagnosis in real time
    - Some tests under investigation have very quick turn around time
- Good accuracy
- High reproducibility

Screening tests for cervical precancer



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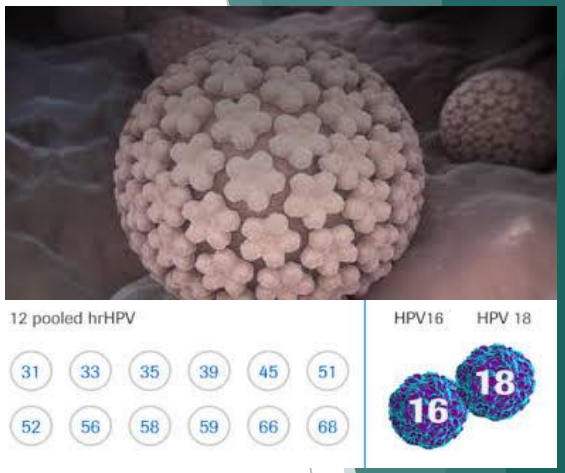
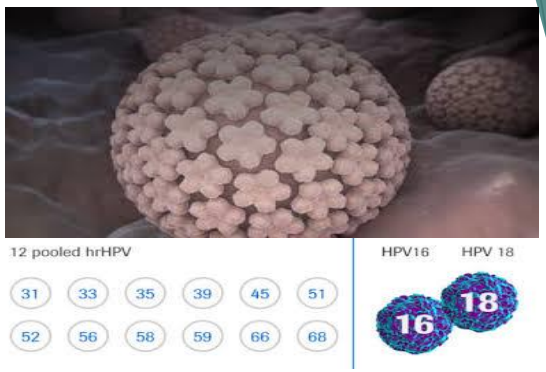
HPV Genotyping



- Hundreds of HPV subtypes
- 14 can cause cervical cancer
  - Some more than others
- Can test for SPECIFIC subtypes
  - Those that are most likely to cause cancer
  - Can triage the highest risk women for treatment

HPV Genotyping



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- Artificial Intelligence (AI) algorithm-driven image diagnosis

Artificial Intelligence (AI) algorithm-driven image diagnosis *experimental*

- Provider performs a speculum exam
- Uses an app on a smart phone
  - Applies acetic acid (white vinegar)
  - After one minute, takes a picture of the cervix
- The image is run through the AI algorithm
  - Diagnosis returned within seconds

Artificial Intelligence (AI) algorithm-driven image diagnosis

- Inexpensive (once equipment is purchased)
  - An app is being developed that can be downloaded onto any smart phone
- Easy to perform by all level of providers and
  - Preferably by the woman herself
- Point of care
  - Able to make a diagnosis in real time
- Good accuracy
- High reproducibility

This is an area of active investigation

Okay – so the woman has been screened and is POSITIVE.

What now?

SHE MUST HAVE ACCESS TO TREATMENT

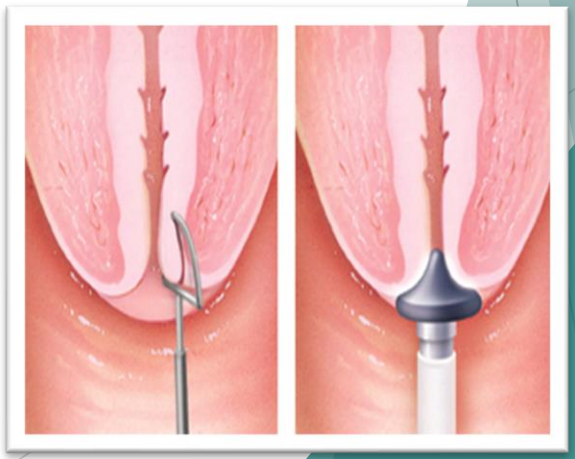
Treatment of cervical precancer can halt disease progression and SAVE LIVES

But how can women in low resource and/or remote settings gain access to these potentially life saving treatments?

Perfect treatments for cervical precancer:

A perfect cervical precancer treatment:

- Easy to perform by all level of providers
- Well tolerated by patient
- Few long-term complications
- Able to effectively treat disease
- Able to be performed in remote settings
  - Easy to transport
- Not reliant on consumables
  - including electricity
- Inexpensive

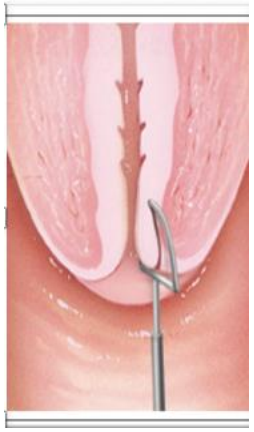


Treatments recommended by the WHO

Surgery

LEEP/Cold Knife Cone

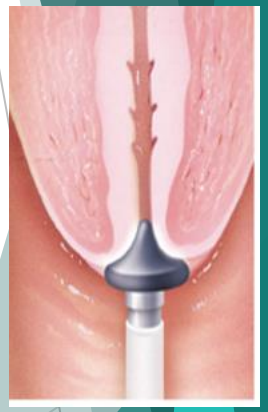
- Standard in high-resource regions/hospitals
- Requires highly-specialized training
- Can have serious complications
- Requires anesthesia
- More invasive



Ablation

Gas-based cryotherapy

- Standard in LMICs
- Freezes tissue
- Easy and simple application
- Rare serious complications
- Cure rates similar to LEEP



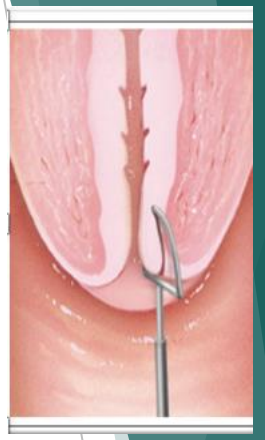
Thermal ablation

- Recently endorsed by the WHO
- Heats tissue
- Similar application to cryotherapy

LEEP/Cold Knife Cone

- LEEP = Loop Electro Excision Procedure
  - A highly trained provider inserts a speculum, numbs the cervix, and then uses an instrument with a thin wire loop attached to electricity to remove the affected area(s) of the cervix
- Cold Knife Cone
  - Same procedure but typically performed in an operating room and with a scalpel rather than an electric wire loop

LEEP/Cold Knife Cone



- Easy to perform by all level of providers
- Well tolerated by patient
- Few long-term complications
- Able to effectively treat disease
- Able to be performed in remote settings
  - Easy to transport
- Not reliant on consumables
  - including electricity
- Inexpensive

Cryotherapy: Challenges in the field

- Tanks weigh 50-70 kg
- A 5-foot tank treats only 10-20 patients
- Gas: expensive, difficult to procure
- Tank maintenance, storage and transfer - expensive and potentially dangerous

Cryogen Gas Cryotherapy

- Easy to perform by all level of providers
- Well tolerated by patient
- Few long-term complications
- Able to effectively treat disease
- Able to be performed in remote settings
  - Easy to transport
- Not reliant on consumables
  - including electricity
- Inexpensive

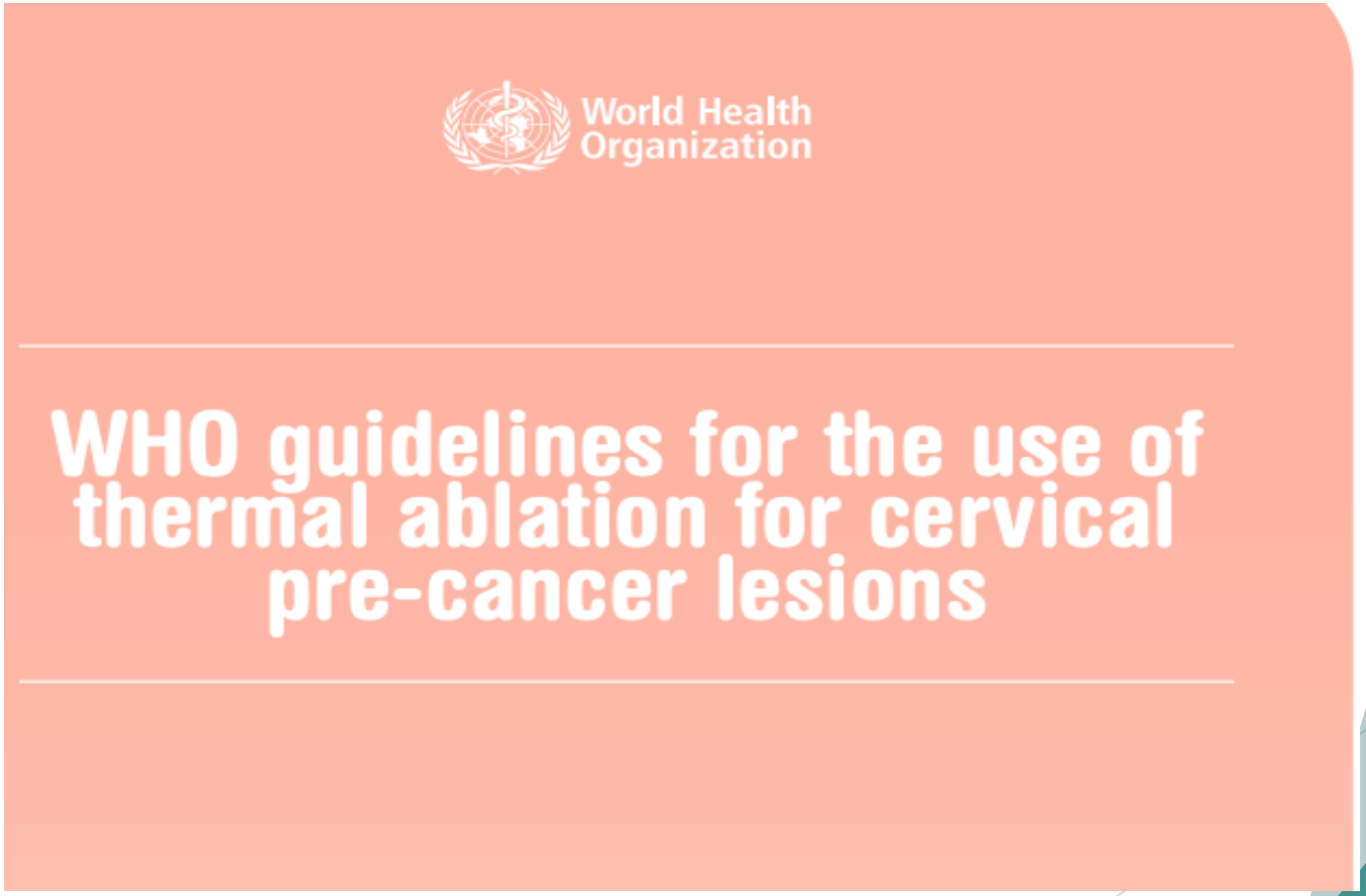
CryoPen® Cryotherapy

- Does NOT need cryogenic gas (CO2 or N2O)
  - Uses a state-of-art cooling technology
  - No cryogen gas procurement issues and/or expense
- Portable
  - weighs ~25 pounds
- Uses electricity and can be charged with a car battery
- Easy to use and clean
- Well tolerated by patients

CryoPen® Cryotherapy

- Easy to perform by all level of providers
- Well tolerated by patient
- Few long-term complications
- Able to effectively treat disease
- Able to be performed in remote settings
  - Easy to transport
- Not reliant on consumables
  - including electricity
- Inexpensive (once machine is bought)

WHO guidelines for thermal ablation (2019)



Thermal Ablation (aka cold coagulation, thermoablation, thermocoagulation)

- Desktop device used 1970s – present day
- Ablates tissue by using heat
  - superficial epithelium blisters, underlying stroma and glandular crypts are destroyed
- New modified devices available
- Meta analysis shows cure rates of 94%[1]
- Safe and effective, particularly promising for LMICs

WiSAP Portio Coagulator

1. Dolman, 2014. BJOG 121(8): 929-42

Handheld Thermal Ablation Devices

WiSAP C3

MedGyn

Liger

Clinical considerations

- Retrospective evidence of efficacy (but not prospective randomized trials)
- Minimal side effects
  - Some patients report higher pain levels than with cryotherapy
- Power source: direct electrical vs. battery
  - Electrical: need to be near an outlet
  - Battery: portable, good for use in mobile clinics, 100 treatments before need to recharge

Cervix before and after thermal ablation

Thermal ablation (TA): Challenges in the field

- Not yet determined:
  - Efficacy
  - Temperature
  - Length of application time and technique
  - Patient acceptability
  - Provider acceptability
- BHI and others are doing research around the world to answer these questions

Goals of BHI Research

- **To develop patient-centered, comfortable, affordable and accessible screening and treatment options for women around the world, particularly those in low resource and remote settings.**
- **Vision: to live in a world where no woman dies of cervical cancer, an entirely preventable disease**


I JUST TRY TO FOCUS ON THE POSITIVE SIDE OF THINGS
BATTERY

QUESTIONS?

Other Considerations for Thermal Ablation

- Can perform biopsies before treatment (if needed)
- Potential to treat some lesions that extend beyond cryotherapy tip (avoiding referral for LEEP)
- Power source: direct electrical vs. battery
  - Electrical: need to be near an outlet
  - Battery: portable, good for use in mobile clinics, 100 treatments before need to recharge

WiSAP C3 Ablator

Thermal ablation probe tips

- Manufacturers offer a wide range of probe shapes and sizes
- Different probe tips are used at the clinician's discretion

Thermal Ablation: Need for Evidence-based recommendations

- BHI has ongoing NIH-sponsored randomized controlled trials comparing cure rates of high grade precancer using CO_2 cryotherapy (standard), CryoPen®, and thermal ablation
- Enrollment in El Salvador, Colombia and China
- Also studying most tolerated and highest efficacy TA techniques

UH3 Pain Measurements (Interim Data as of 12/2019):

		Baseline	Before treatment	During treatment	After treatment
China	N	506	379	379	305
	Range	0-3	0-6	0-8	0-6
	Mean (95% CI) SD	0.03 (0-0.5) 0.2	0.24 (0.2-0.3) 0.7	2.07 (1.9-2.3) 2.1	0.16 (0.1-0.2) 0.7
Colombia	N	59	55	57	28
	Range	0-8	0-8	0-10	0-6
	Mean (95% CI) SD	0.31 (0-0.6) 1.2	0.67 (0.3-1.1) 1.5	3.05 (2.3-3.8) 2.7	0.79 (0.2-1.4) 1.5
El Salvador	N	233	195	201	57
	Range	0-2	0-8	0-10	0-4
	Mean (95% CI) SD	0.03 (0-0.5) 0.2	1.45 (1.2-1.7) 1.7	4.15 (3.8-4.5) 2.5	0.4 (0.2-0.6) 0.9

Pain differs significantly at all time points, except baseline, with women in China reporting lower pain scores than women in ES and Colombia

UH3 Pain by treatment arm (Interim Data):

		Before speculum	Before treatment	During treatment	After treatment
CO_2 cryo	N	213	211	213	130
	Range	0-2	0-8	0-10	0-2
	Mean (95% CI) SD	0.02 (0-0.5) 0.19	.63 (0.5-0.8) 1.3	2.23 (1.9-2.5) 2.3	0.12 (0.04-0.2) 0.5
CryoPen	N	212	205	211	131
	Range	0-3	0-8	0-10	0-6
	Mean (95% CI) SD	0.5 (0-0.1) 0.3	0.7 (.5-.8) 1.3	2.6 (3.3-4.0) 2.5	0.3 (0.1-0.4) 1.0
Thermal	N	212	211	211	128
	Range	0-8	0-8	0-10	0-6
	Mean (95% CI) SD	0.07 (0-0.2) 0.6	0.68 (0.5-0.8) 1.2	3.6 (3.3-4.0) 2.5	0.29 (0.1-0.4) 0.9
Kruskal-Wallis Test	p-value	.5	.6	.0001	0.16

Thermal ablation patients reported the highest mean pain score across treatments

Side Effect: Vasovagal Reaction (Interim Data):

- In China during or immediately after treatment
  - 50% (191/386) subjects have experienced flushing, hotness, dizziness, nausea, shortness of breath and heart palpitations
    - CO2 Cryotherapy = 94
    - CryoPen® = 84
    - Thermal ablation = 13
  - In El Salvador and Colombia
    - 4 patients reported headache, nausea, or weakness immediately after treatment (noted anecdotally by project coordinators)
    - All cases resolved within a few minutes after patient lies down

Infections across sites and treatment groups (Interim Data):

	Baseline (treatment visit)	6-week post-treatment
Bacterial Vaginosis	337	281
Yeast	26	19
Gonorrhea	2	2
Chlamydia	13	8
Trichomoniasis	17	7

Several patients with suspected infections at baseline received antibiotic treatment as per standard of care at the site hospitals, which could explain the fewer overall infections at the follow-up visit

Side effects reported at 6 weeks, by treatment arm (Interim Data):

		CO_2	CryoPen	Thermal	p*
Cramping	Yes (%)	79 (40.7)	70 (36.7)	72 (37.1)	.7
Intensity	Mild (%)	57 (29.4)	54 (28.3)	58 (29.9)	
	Moderate (%)	16 (8.3)	12 (6.3)	12 (6.2)	
	Severe (%)	6 (3.1)	4 (2.1)	2 (1.0)	.8
Duration in days	Range	1-40	1-30	1-30	
	Mean (95%CI)	6.2 (4.3-8.0)	4.4 (3.1-5.7)	5.2 (3.7-6.6)	.4
	SD	8.1	5.4	6.3	
Watery Discharge	Yes (%)	189 (97.4)	186 (97.4)	190 (97.9)	.9
Intensity	Mild (%)	75 (38.7)	88 (46.1)	90 (46.4)	
	Moderate (%)	69 (35.6)	61 (31.9)	77 (39.7)	
	Severe (%)	45 (23.3)	37 (19.4)	23 (11.9)	.1
Duration in days	Range	3-40	3-50	1-45	
	Mean (95%CI)	19.8 (18.6-21.1)	16.0 (14.8-17.3)	19.3 (18.0-20.6)	.6
	SD	8.7	8.4	9.0	

Most common side effect is watery discharge, followed by cramping

UH3 Goals

- **Compare the cure rates at one year of CIN2+** using
  - Standard Cryotherapy (3min freeze, 5 min thaw, 3 min freeze) vs
  - CryoPen (gasless cryotherapy) – single 5 min freeze vs
  - Thermal ablation – initial 40 sec application, followed by 20s applications to ablate entire Transformation Zone (TZ)

UH3 Goals, cont

- Evaluate:
  - Patient pain scores during thermal ablation treatment

Wong-Baker Faces

  - Side effects (6 wks after treatment)
    - Cramping, liquid discharge, malodorous discharge, bleeding

Recommend to a friend

- Reasons women gave for recommending treatment:
  - Fast, comfortable, not painful, non-invasive or not surgery, outpatient procedure
  - No complications, good follow-up care, belief that treatment was effective and improved health
    - Women who were unsure said they were waiting for the final biopsy results to decide

Stay tuned for the the next study. . .

- Another study with thermal ablation study is about to launch:
  - What is the most effective thermal ablation technique?
    - Currently, no standardized protocols for its use
    - Scant data on patient and provider acceptability, potential side effects, and the impact of different treatment protocols on quality of life

Side effects reported at 6 weeks, by treatment arm, cont (Interim Data):

		CO_2	CryoPen	Thermal	P*
Malodorous discharge	Yes (%)	69 (35.6)	56 (29.3)	50 (25.8)	.1
Intensity	Mild (%)	48 (24.7)	42 (22.0)	31 (16.0)	
	Moderate (%)	15 (7.7)	8 (4.2)	13 (6.7)	
	Severe (%)	6 (3.1)	6 (3.1)	6 (3.1)	.3
Duration in days	Range	1-30	1-30	1-30	
	Mean (95%CI)	9.3 (7.5-11.0)	8.9 (7.1-10.7)	9.4 (7.6-11.1)	.95
	SD	7.3	6.6	6.2	
Bleeding	Yes (%)	39 (20.1)	40 (20.9)	66 (34.0)	.002
Intensity	Mild (%)	33 (17.0)	35 (18.3)	54 (27.8)	
	Moderate (%)	3 (1.6)	2 (1.1)	10 (5.2)	
	Severe (%)	3 (1.6)	3 (1.6)	2 (1.0)	.008
Duration in days	Range	1-30	1-15	1-20	
	Mean (95%CI)	6.5 (3.7-9.2)	3.7 (2.8-4.7)	6.3 (5.1-7.6)	
	SD	8.4	3.0	5.0	.8

*Chi squares and ANOVA as appropriate

The only **statistically significant** differences across treatments are in bleeding frequency and intensity

Would you recommend this treatment to a friend?

	Was discomfort acceptable n (%)		Recommend to friend n (%)	
	6 wk. n=583	12 mo. n=184	6 wk. n=583	12 mo. n=184
Definitely yes	330 (57)	123	541 (93)	133 (72)
Probably yes	26 (4)	16	21 (4)	4 (2)
Probably not	2 (<1)	1	1 (<1)	0
Definitely not	0	0	3 (<1)	0
Unsure/don't know	1 (<1)	1	13 (2)	4 (2)
Missing	224 (38)	43 (77)	4 (<1)	43 (32)

[1]There is a large proportion of missing answers because some of these questions were added later.

Majority of women found discomfort acceptable and would recommend this treatment to a friend

UH3 Goals, cont

- **Evaluate side effects** 6 week post-procedure
  - Pelvic Exam and swabs at baseline and 6 week visit for:
    - BV/Yeast
    - Gonorrhea/Chlamydia
  - Patient questionnaire re:
    - Cramping, liquid discharge, malodorous discharge, bleeding

UH3 Enrollment

- **Enrollment** as of August, 2020: **n=764**
  - China = 487
  - El Salvador = 215
  - Colombia = 62
- **Treated**, **n=763**
- One year **follow-up** visits: **n=458**
  - China = 311
  - El Salvador = 123
  - Colombia = 24

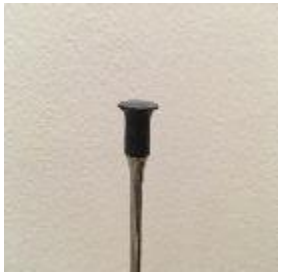
Summary of UH3 Interim Data

- Pain:
  - Significantly more pain during thermal ablation treatment vs. CO_2 cryotherapy or CryoPen®
  - Significant differences in pain across countries:
    - El Sal reported most pain during treatment, then Colombia, then China
- Side Effects:
  - Vasovagal reactions more common in China
  - No significant differences in infections across treatments
  - Watery discharge followed by cramping were the most commonly reported side effects
- Acceptability:
  - Majority of women would recommend these treatments to a friend

R01 Ablation study

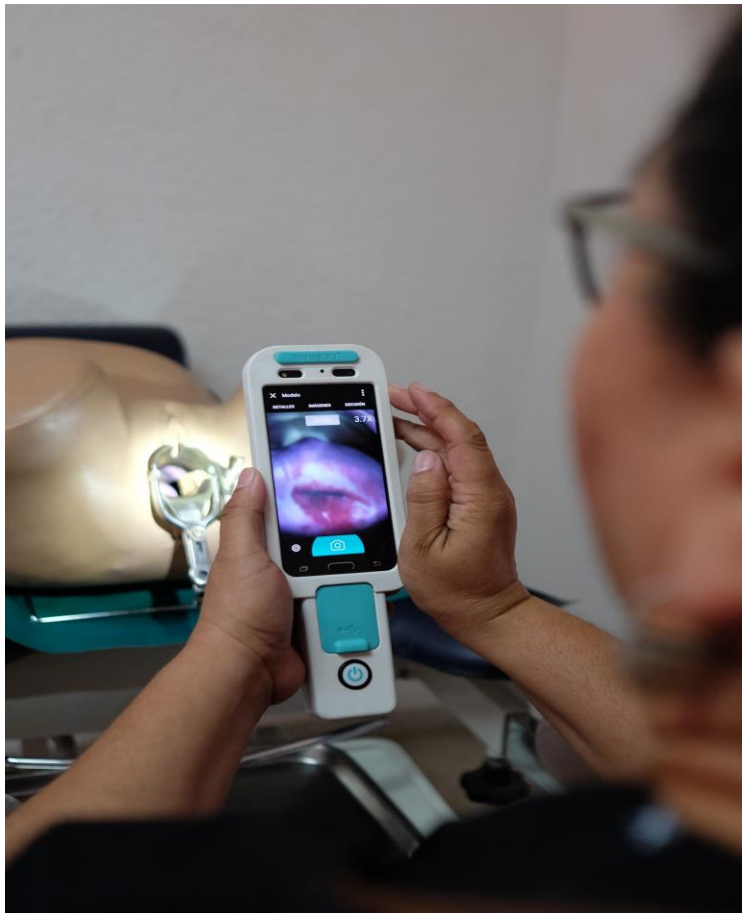
- El Salvador, China and Paraguay
- Patients eligible for enrollment N = 1,155
- Randomize women with CIN2+ to one of three treatment groups
  - CO2 Cryotherapy (3”-5”-3”)

  - 17mm conically-shaped probe with central nipple at 100ºC for 40sec application, vs
  - 10mm narrow nipple-shaped probe at 100ºC placed into the cervical os x 20 secs, followed by a 16mm flat probe at 100ºC for 20 secs applications until TZ is completely ablated



Objectives of R01

- Compare CIN2+ **cure rates** 12-months post-treatment for CO2-based cryotherapy and both single versus multiple tips thermal ablation strategies
- Assess provider and patient **acceptability** of each treatment
- Systematically evaluate the **side effects** of cryotherapy and thermal ablation (i.e. infection, pain, bleeding, discharge, and stenosis)
- Assess **satisfaction** with treatment at six weeks post-treatment, and to investigate quality of life and hope for the future pre-treatment and at 12 months post-treatment
- Perform a **cost-effectiveness** analysis of the three treatment arms and post-treatment surveillance procedures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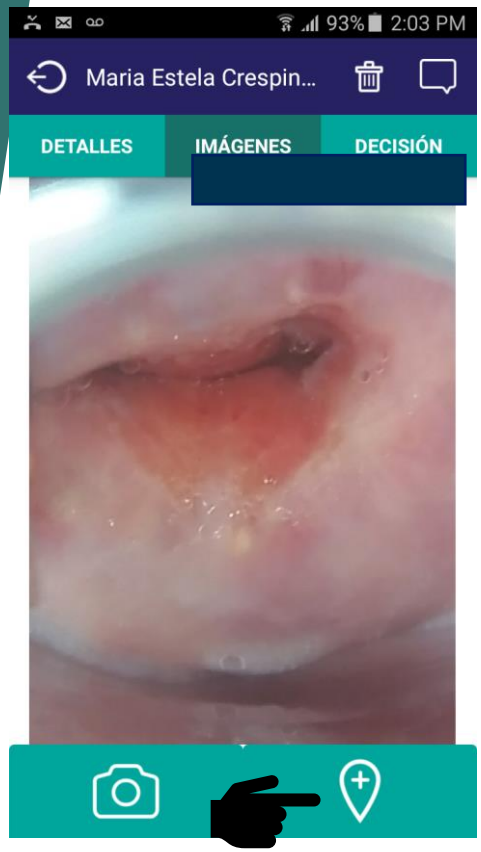
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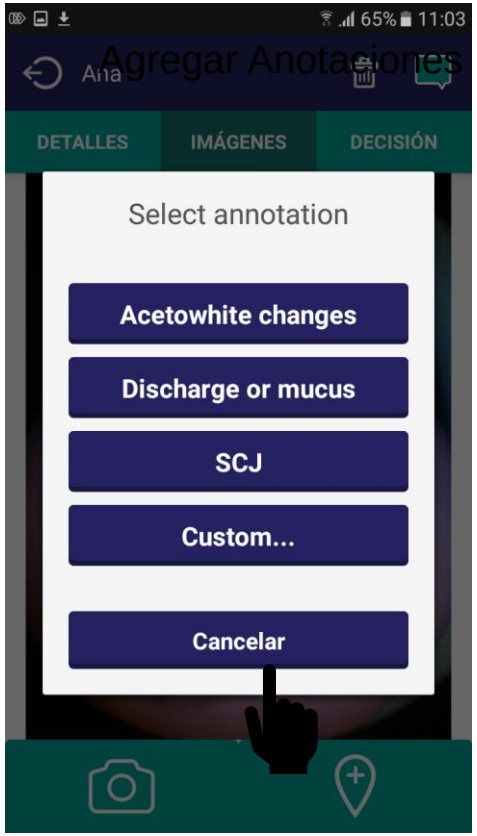
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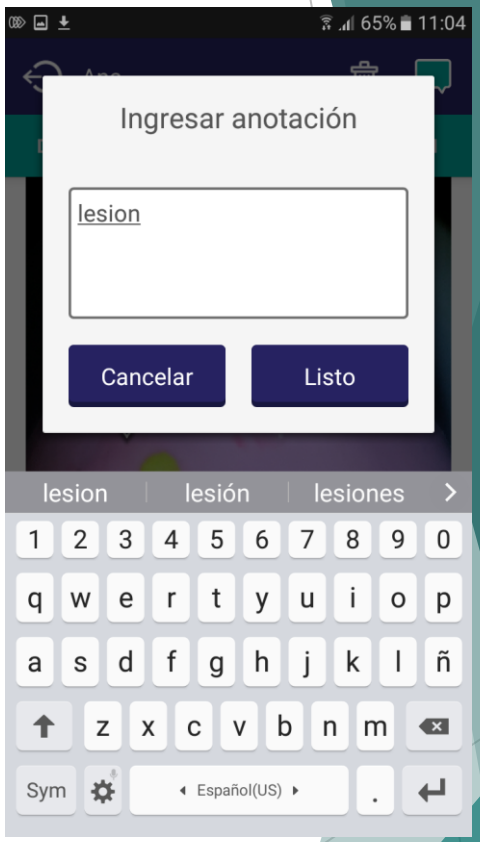
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