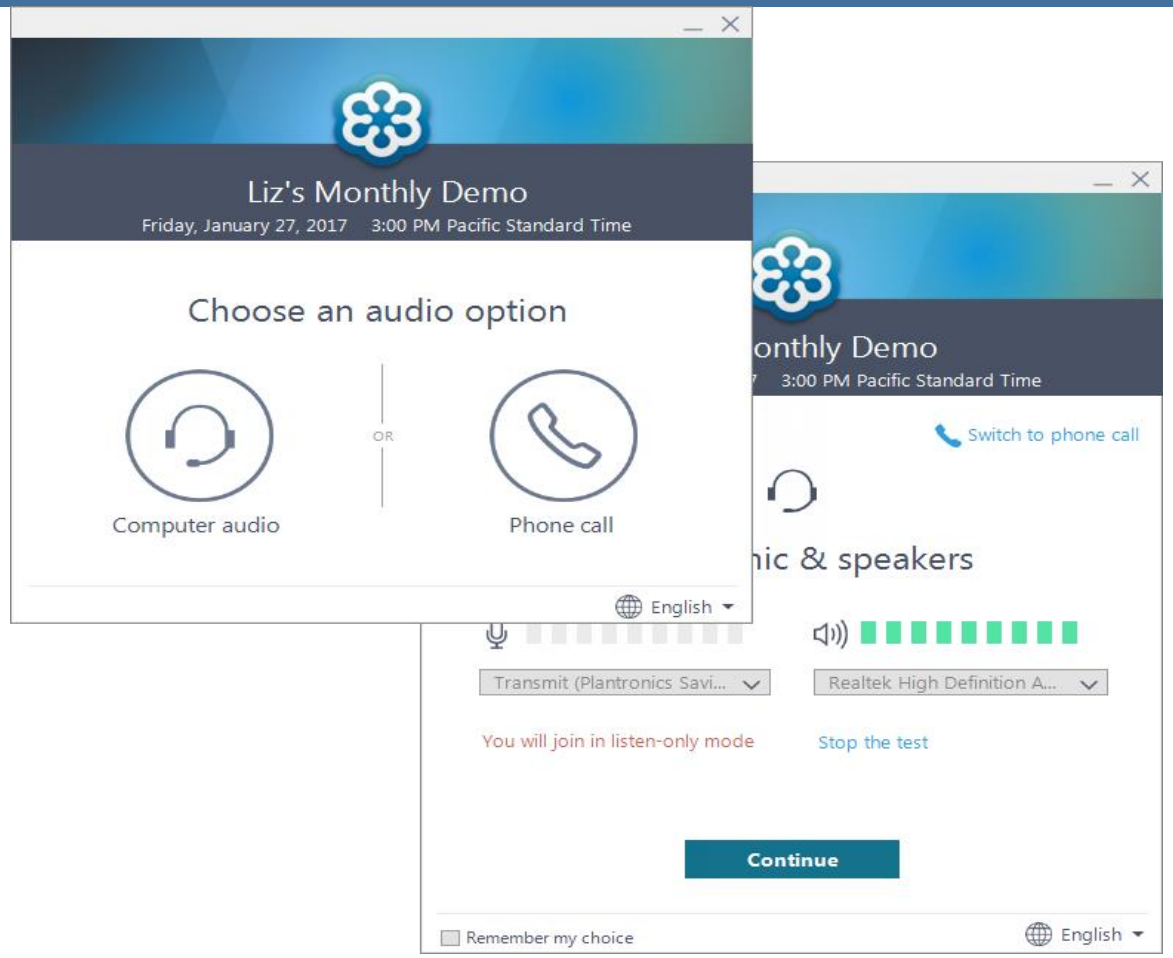
Clinical Practice Alert Update: Cervical Cancer Screening & Emergency Contraception

March 24, 2020

Presenters: Michael S. Policar, MD, MPH and Nicole Economou, MD

GoToWebinar Housekeeping: Set Up Audio

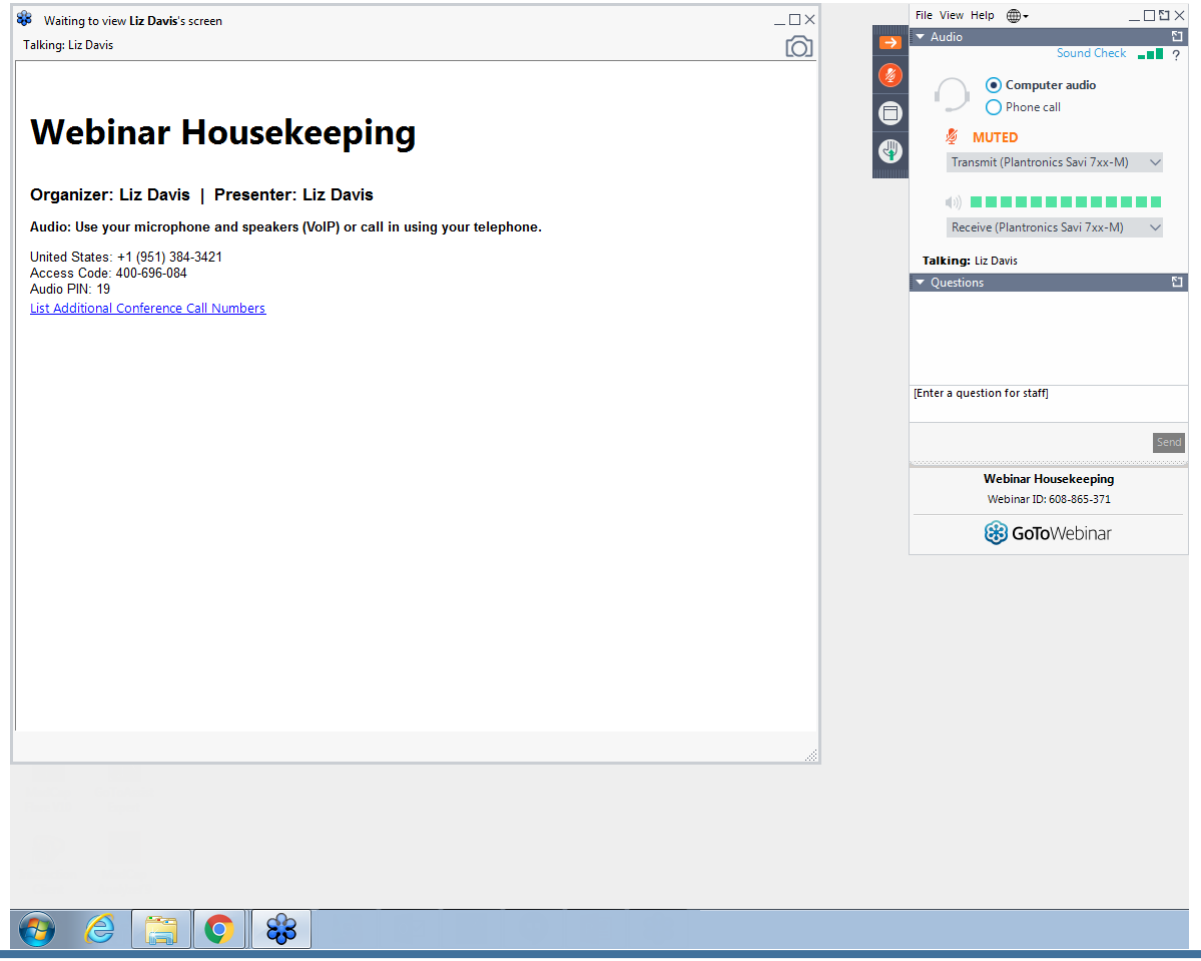


Your Participation

Once you've been launched into session, you will be prompted to set up your audio.

- **To use your computer's mic and speakers:**
  1. Click Computer audio.
  2. Use the drop-down menus to select the desired audio devices.
  3. Click Continue.
- **To use your telephone to dial in:**
  1. Click Phone call.
  2. Use your telephone's keypad to dial the provided phone number and enter the codes when prompted.
  3. Click Continue.

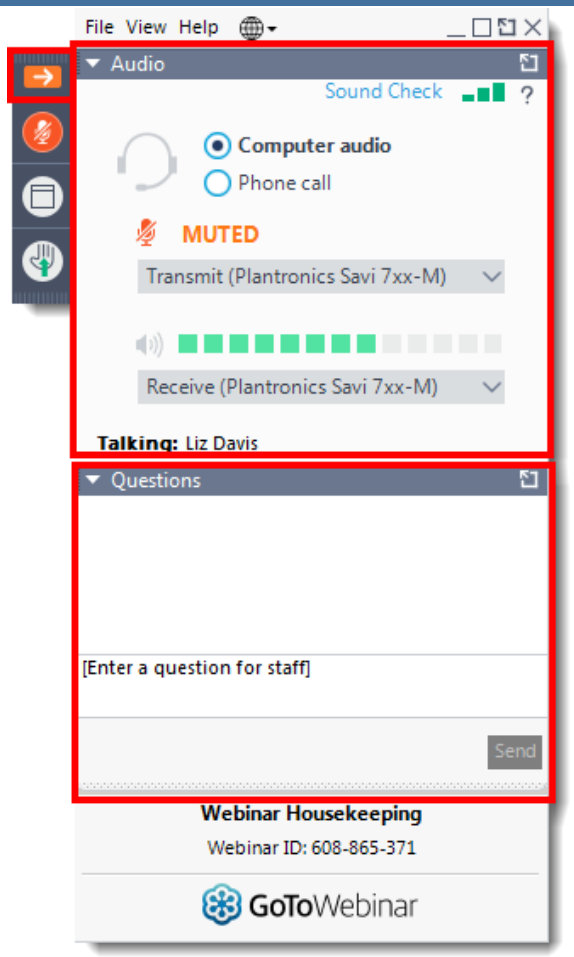
GoToWebinar Housekeeping: What Attendees See



Your Participation

- To the left is the GoToWebinar Viewer through which attendees see the presentation.
- To the right is the GoToWebinar control panel where attendees can raise their hand, ask questions and select audio mode.
- Note: The attendee control panel will collapse automatically when not in use by an Attendee. To keep it open, Attendees can click the “View” menu and uncheck “Auto-hide Control Panel”.

GoToWebinar Housekeeping: Attendee Participation



Your Participation

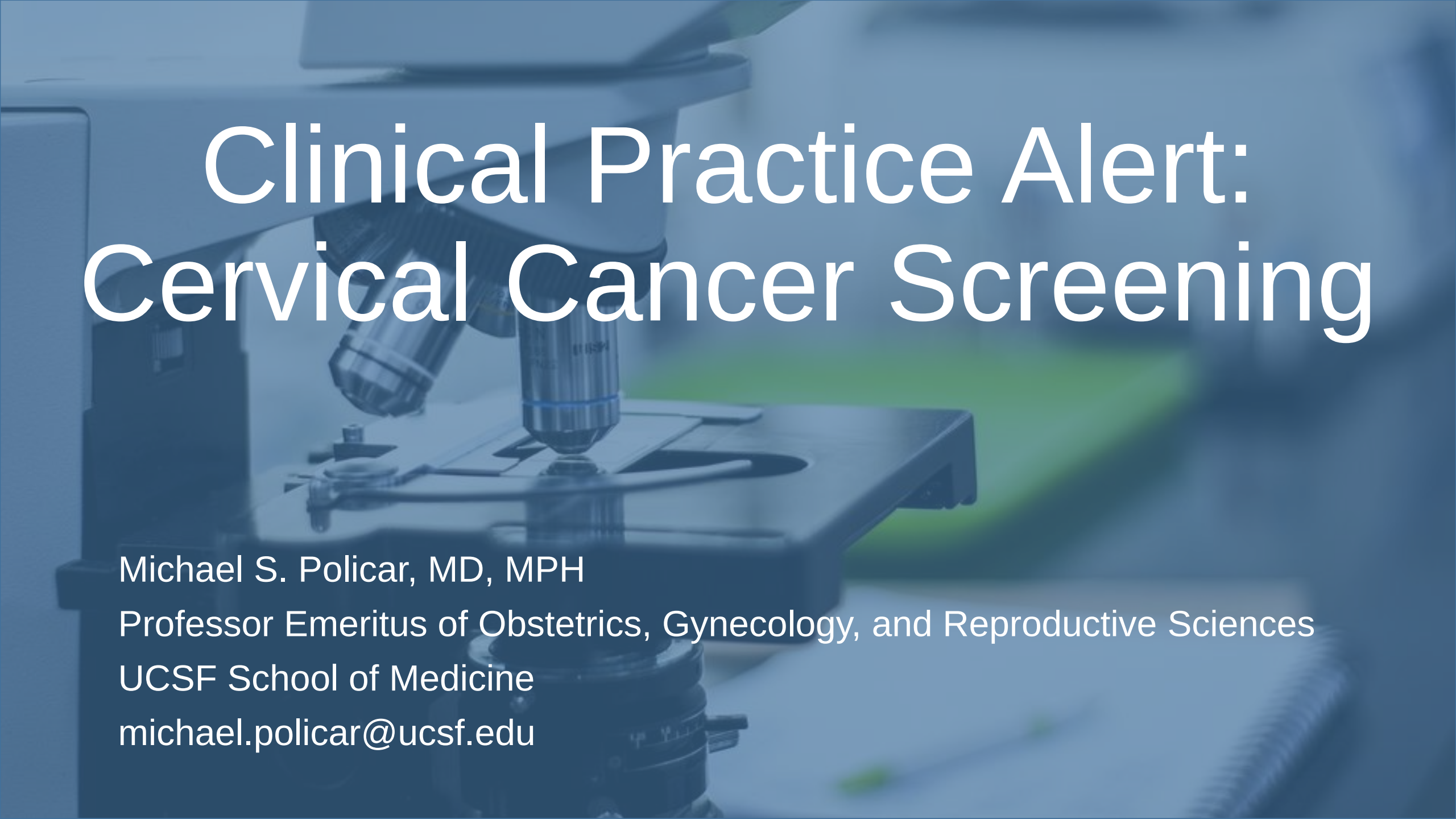
Open and close your control panel

Join audio:

- Choose **Mic & Speakers** to use VoIP
- Choose **Telephone** and dial using the information provided

Please submit questions and comments via the Questions panel

Note: Today's presentation is being recorded and will be provided through email at a later date along with the slides.



Clinical Practice Alert: Cervical Cancer Screening

Michael S. Policar, MD, MPH
Professor Emeritus of Obstetrics, Gynecology, and Reproductive Sciences
UCSF School of Medicine
michael.policar@ucsf.edu

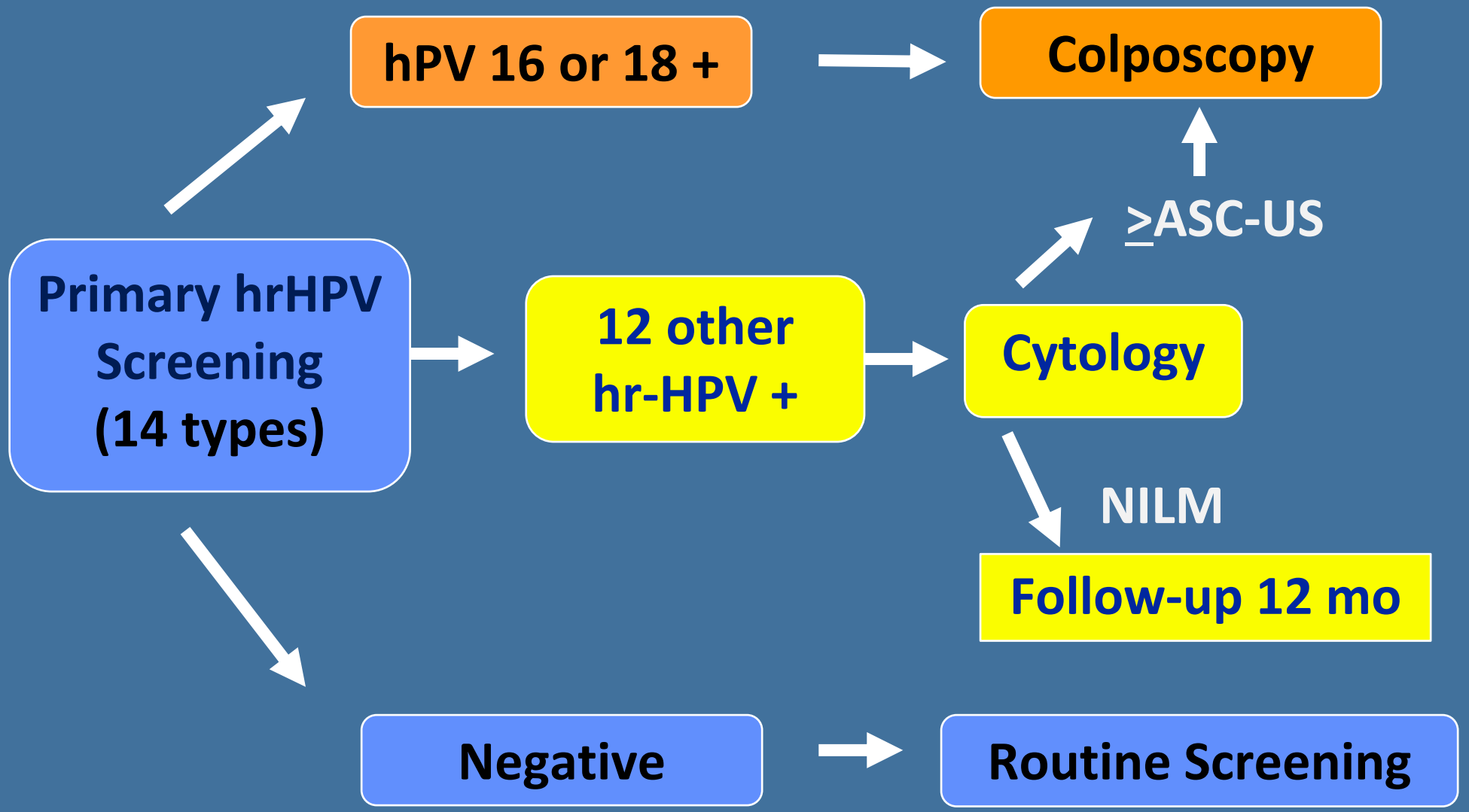
2016 Cervical Cancer Screening Guidelines

	<21 y.o.	21-29	30-65 y.o.	>65	Hyst, benign
USPSTF	[D]	Cytology every 3 y	Co-test: every 5 yr or Cytology: every 3 yr	None*	[D]
Triple A 2012	None	Cytology every 3 y	Co-test: every 5 yr or Cytology: every 3 yr	None*	None
ACOG 2016	"Avoid"	Cytology every 3 y	Co-test: every 5 yr or Cytology: every 3 yr	None*	None

Co-test: cervical cytology + hrHPV test
*** In adequately screened women (3 negative cytology results, or 2 negative co-tests, in prior 10 years, most recent within 5 years)**

How Is hrHPV-Alone Screening Different From Cytology Alone or Co-testing?

- In April 2014, the FDA approved the cobas® test for primary hrHPV-alone screening, based on the ATHENA trial
- hrHPV-alone detected 50% more CIN 3+ compared with cytology, but doubled the need for colposcopy



Wentzensen N, Schiffman M, et al. Triage of HPV positive women in cervical cancer screening. J Clin Virol. 2016

1º HPV Screening : Interim Guidance, 2015 (SGO, ASCCP, ACOG, ACS, others)

- **If hrHPV-alone screening**
  - Screening should not be initiated before 25 years of age
  - Screen *no sooner* than every 3 years
- **Advantages**
  - Better sensitivity than cytology alone
  - Less expensive than co-testing (since no cytology for most)
  - Highly adaptable to low-resource countries
- **Disadvantages**
  - Less specificity than cytology alone…more colposcopies

Huh WK. et al. Obstet Gynecol 2015;125:330–7

Cervical Cancer Screening
Final Recommendation

U.S. Preventive Services TASK FORCE

2018

[A] Three options for women 30-65 years of age….either

- Primary hrHPV (alone) every 5 years, OR
- Co-testing every 5 years, OR
- Cervical cytology alone every 3 years

[A] Women 21-29 years of age: cytology every 3 years

[D] Women < 21 years of age: do not screen

[D] Women ≥ 65, adequately screened in prior 10 yrs, no history of treatment or NED >20 years: do not screen

Recommends that females discuss options with clinician

2018 Cervical Cancer Screening Guidelines

	< 21 y.o.	21-29 y.o.	30-65 y.o.
USPSTF 2018	[D]	Cytology every 3 yrs	hrHPV-alone: every 5 yrs or Co-test: every 5 years or Cytology: every 3 yrs
Triple A 2012	None	Cytology every 3 yrs	Co-test: every 5 or Cytology: every 3 yrs
ACOG 2016	"Avoid"	Cytology every 3 yrs	Co-test: every 5 or Cytology: every 3 yrs

Co-test: cervical cytology plus high-risk HPV test (hrHPV)
Cytology: cervical cytology (Pap smear) alone

Implications: 2018 USPSTF Cervical Cancer Screening Recommendations

- ACOG, ACS & ASCCP haven't changed recommendations yet, but may do so
- Fewer cervical cytology tests, since 1º hrHPV-alone screening option added in women ≥ 30 years of age
- More colposcopies, as women ≥ 30 years of age move away from cytology alone and toward 1º HPV screening
- Health plans may consider limiting the use of co-tests to surveillance after abnormal cytology or treatment

Does Family PACT Ever Cover Screening More Often than Every 3 or 5 Years??

- Previously abnormal test result; in surveillance pathway
- Prior cryotherapy, LEEP, or cone biopsy
- “Insufficient specimen adequacy” or unsatisfactory for evaluation
- In utero exposure to diethylstilbestrol (DES)
- HIV infection, a major organ transplant with the use of an anti-rejection drug, or long-term corticosteroid use
- Newly enrolled in a practice and no documentation of recent result

Cervical Cancer Screening: HIV Positive

- If < 21 years of age
  - Cytology alone within 1 year of sexual activity, or
  - If sexually active, perform cytology now
  - Start no later than 21 years of age
    - If < 21 & ASC-US, repeat cytology in 6–12 m (no HPV)
- If < 30 y.o. and initial cytology is normal
  - Next cytology in 12 months
  - After three consecutive normal annual screenings, follow-up screening should be done every 3 years

Cervical Cancer Screening: HIV Positive

- If ≥ 30 years of age
  - Use cytology alone or co-testing
  - Cytology alone and 3 consecutive annual normal test results, or one negative co-test, follow-up screening every 3 years
- Cervical screening in HIV positive patients should not stop at 65 years of age…continue throughout lifetime

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: CDC, NIH, and IDSA. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.

Cervical Cancer Screening: Immunocompromise

- Females with immunecompromised may develop lesions more rapidly than those who are immunocompetent
  - Major organ transplant with an anti-rejection drug
  - Long-term corticosteroid use
  - *Not* immunobiologicals
- ASCCP recommends that these clients should be screened at the same intervals as HIV-positive females

Cervical Cancer Screening: Other Questions

Are screening intervals any shorter for females with multiple sexual partners?

- No...females with multiple sexual partners
  - Have an increased risk for acquiring HPV infection
  - More likely to develop a pre-invasive lesion or cancer
  - BUT they do not have faster time of progression if a lesion does develop

Cervical Cancer Screening: Other Questions

Do virginal females need to be screened?

- Virginal females of any age should be advised that their risk of cervical cancer is extremely low, but not zero
- Once counseled, either she may decline cervical cancer screening or opt to be screened routinely

If Abnormal Cytology or Positive hrHPV, Should Hormonal Contraception Be Limited Or Withheld?

- No evidence that hormonal contraceptives adversely affect diagnosis and treatment outcomes
- US-MEC Category 2 (Cu-IUD and POP are Category-1)
  - Placing Cu-IUD and LNg-IUD are Category 4 if awaiting treatment for cervical cancer
- Even more important to provide effective contraception, as pregnancy may delay or complicate treatment

Some of my Clients Insist on Annual Screening What Do I Tell Them?

- These intervals balance benefits and risks of screening; screening too often may be harmful
  - Over-screening results in an excess risk of false positive results, which can lead to unnecessary colposcopy and biopsies, with attendant anxiety and inconvenience

What About Performing a *Screening* Pelvic Exam at a Well Woman Visit?

- USPSTF recommends against routine screening for ovarian cancer in low risk women
- ACOG: women ≥ 21 should be offered a screening pelvic exam in the context of shared decision making
- Family PACT Standards do not recommend a screening pelvic exam at any age

How Should Follow-up Visits Be Coded?

- In addition to the ICD-10-CM codes for the client's method of contraception, follow-up encounters for hrHPV-alone or co-testing screening are reimbursable with the ICD-10-CM diagnosis codes listed in the PPBI (ben fam rel, pages 29-31)

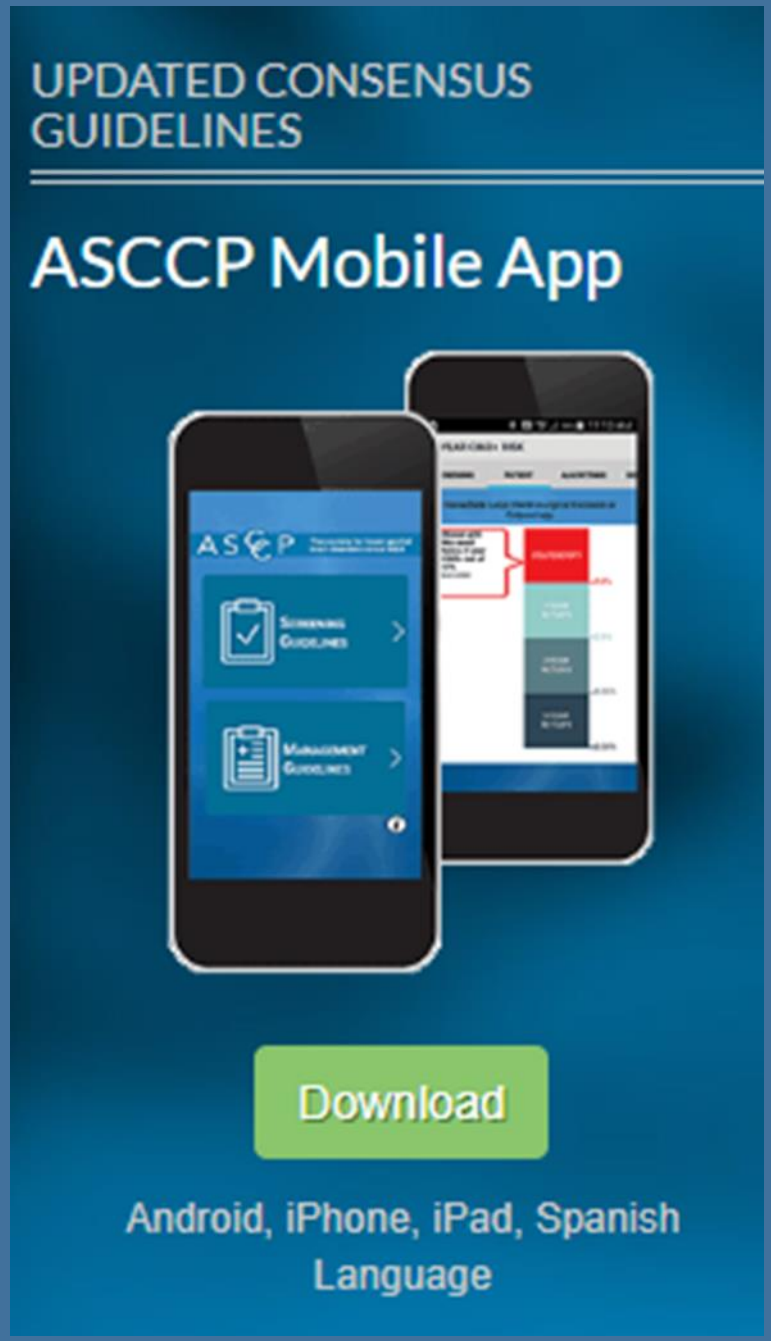
Code	ICD-10-CM Description
D06.9	Carcinoma in situ of cervix, unspecified
N87.0	Mild cervical dysplasia
N87.1	Moderate cervical dysplasia
R87.610	ASC-US
R87.611	ASC-H
R87.612	LSIL
R87.613	HSIL
R87.614	Cytologic evidence of malignancy on smear of cervix
R87.615	Unsatisfactory cytologic smear of cervix
R87.616	Satisfactory cervical smear but lacking transformation zone
R87.618	Other abnormal cytological findings on cervix uteri
R87.619	Unspecified abnormal cytological findings
R87.810	Cervical high risk HPV DNA test positive
Z87.410	Personal history of cervical dysplasia
Z01.42	Confirm findings of normal smear following initial abnormal smear

2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors

L. Stewart Massad, MD, Mark H. Einstein, MD, Warner K. Huh, MD, Hormuzd A. Katki, PhD, Walter K. Kinney, MD, Mark Schiffman, MD, Diane Solomon, MD, Nicolas Wentzensen, MD, and Herschel W. Lawson, MD, for the 2012 ASCCP Consensus Guidelines Conference

From Washington University School of Medicine, St. Louis, Missouri; Albert Einstein College of Medicine, New York, New York; University of Alabama School of Medicine, Birmingham, Alabama; Division of Cancer Epidemiology and Genetics and Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland; The Permanente Medical Group, Sacramento, California; and Emory University School of Medicine, Atlanta, Georgia

Journal of Lower Genital Tract Disease, Volume 17, Number 5, 2013, S1-S27



Cytology every 3 y from ages 25-65 y

Abnormal test result	Recommended next steps		Cytology Alone
ASC-US	Cytology in 1 y		
	or		
	hrHPV test	hrHPV+ →	Colposcopy
		hrHPV- →	Cytology in 3 y
LSIL or worse	Colposcopy		

Sawaya GF, JAMA 2019

hrHPV testing alone every 5 y from ages 30-65 y

Abnormal test result	Recommended next steps	hrHPV Alone		
hrHPV+	HPV-16/18 genotyping	HPV-16/18+ →	Colposcopy	
		HPV-16/18- →	Cytology	Abnormal → Colposcopy
				Normal → Retest in 1 y

Sawaya GF, JAMA 2019

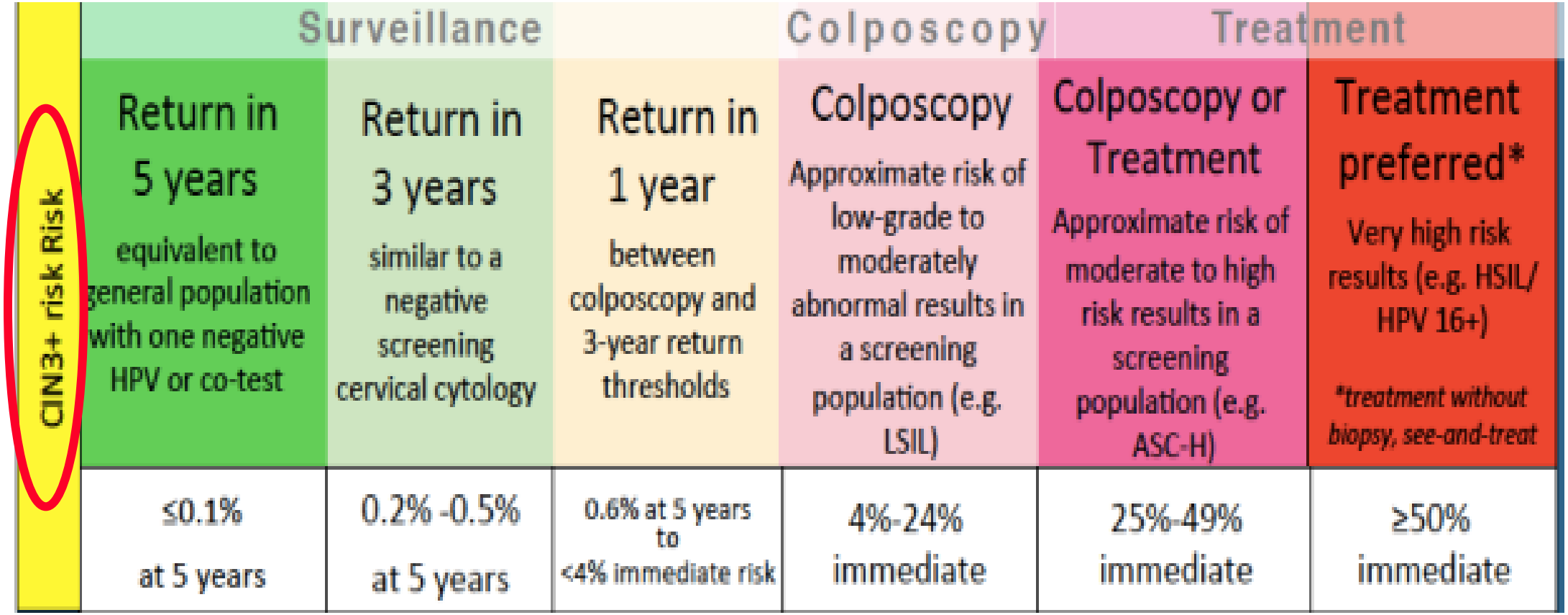
cytology and hrHPV testing every 5 y from ages 30-65 y

Abnormal test result	Recommended next steps	Co-Testing
ASC-US and hrHPV-	Cytology and hrHPV test in 3 y	
LSIL and hrHPV-	Cytology and hrHPV test in 1 y	
Normal cytology And hrHPV+	Cytology and hrHPV test in 1	
	or	
	HPV-16/18 genotyping	HPV-16/18+ → Colposcopy
		HPV-16/18- → Cytology and hrHPV test in 1 y
ASC-US and hrHPV+, LSIL and hrHPV+, ASC-H, HSIL or worse	Colposcopy	

Sawaya GF, JAMA 2019

2020 ASCCP Risk-Based Management Consensus Guidelines

- Focus on finding CIN 3
- Prior history critical re:“persistent HPV infection”
- Precision
- Simplicity



References

- ACOG Practice Bulletin No. 168 Cervical Cancer Screening and Prevention. Obstet Gynecol 2016 Oct;128(4):e112-130
- Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Obstet Gynecol 2015;125:330–7
- USPSTF Final Recommendation Cervical Cancer: Screening. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/cervical-cancer-screening2

References

- Wentzensen N, Schiffman M, et al. Triage of HPV positive women in cervical cancer screening. J Clin Virol. 2016 Mar; 76(Suppl 1): S49–S55.
- Sawaya GF, Smith-McCune K. Clinical Expert Series. Cervical Cancer Screening. Obstet Gynecol 2016;127:459–67.
- Conry JA, Brown H. Well-Woman Task Force: Components of the Well-Woman Visit. Obstet Gynecol 2015;126:697–701.
- USPSTF, Bibbins-Domingo K, Grossman DC, et al. Screening for Gynecologic Conditions with Pelvic Examination: US Preventive Services Task Force Recommendation Statement. JAMA 2017;317:947–953.

Clinical Practice Alert: Emergency Contraception

Nicole Economou, MD

Family Planning Fellow, UC San Diego

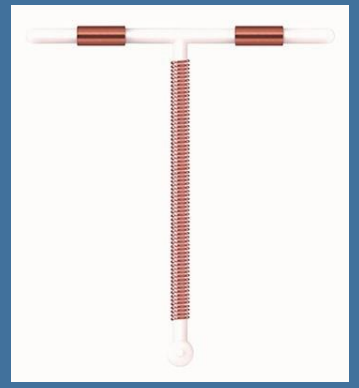
DISCLOSURES

- I have no financial disclosures.

OUTLINE

1) Emergency contraception methods
2) How patients can obtain EC
3) BMI and efficacy
4) Initiation of OCPs after EC
5) Common misconceptions

METHODS AND EFFICACY



HISTORY

- 1974: Yuzpe method described
- 1976: Non-hormonal (copper) IUD described for EC
- 1998: FDA approves Preven
- 1999: FDA approves Plan B
- 2009: FDA approves Plan B One Step and generic versions
- 2010: ella® (ulipristal acetate) approved

METHODS OF EMERGENCY CONTRACEPTION

Copper T-380A IUD

Oral EC (Pills)

- Levonorgestrel (LNG)
- Ulipristal acetate (UPA)

Paragard® IUD

- Paragard® approved by the FDA in 1984
  - Has been sold and used in the United States since 1988
- Can be used for EC up to 120 hours (5 days) after unprotected intercourse
- **High Efficacy**: Pregnancy Rate 0.1%
- Also provides long acting reversible contraception*
  - 94% multiparous women and 88% of nulliparous women maintained IUD for contraception

Wu S, Godfrey EM, Wojdyla D, Dong J, Cong J, Wang C, et al. Copper T380A intrauterine device for emergency contraception: a prospective, multicentre, cohort clinical trial. BJOG 2010;117:1205–10.

ORAL LEVONORGESTREL (PLAN B)

- Most common EC in the US
  - Available OTC without age restriction
  - No contraindications to use
- Single oral 1.5mg dose
- Mechanism: inhibits the **LH surge** → prevents ovulation
  - Ineffective if surge as already occurred
- Labeled for use up to 72 hours after unprotected intercourse
  - *May* be effective up to 4-5 days though less
- Efficacy decreases with obesity (BMI >30)

ORAL LEVONORGESTREL (PLAN B)

- Pregnancy rate: 1.4% to 2.6%
- Plan B is contraindicated for pregnant women not because it incurs risk to the fetus but because it is INEFFECTIVE after implantation
  - No adverse effects on the fetus or pregnancy course in several studies

ULIPRISTAL ACETATE (ELLA ®)

- Single oral 30mg dose
- Mechanism: **antiprogestin**
  - Prevents ovulation by *delaying* follicular rupture before and after LH surge has started (but before it peaks)
- Labeled for use up to 120 hours (5 days) after unprotected intercourse
- Pregnancy rate: 0.9% - 1.8%
- Requires a prescription

Efficacy of ulipristal acetate for emergency contraception and its effect on the subsequent bleeding pattern when administered before or after ovulation. Li HW, Lo SS, Ng EH, Ho PC. Hum Reprod. 2016;31(6):1200. Epub 2016 Apr 6.
Interventions for emergency contraception. Shen J, Che Y, Showell E, Chen K, Cheng L Cochrane Database Syst Rev. 2019;1:CD001324. Epub 2019 Jan 20.
Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Glasier AF, Cameron ST, Fine PM, Logan SJ, Casale W, Van Horn J, Sogor L, Blithe DL, Scherrer B, Mathe H, Jaspart A, Ulmann A, Gainer E. Lancet. 2010;375(9714):555. Epub 2010 Jan 29.

ULIPRISTAL VERSUS LEVONORGESTREL

	Pregnancies (%)		p value
	Ulipristal	Levonorgestrel	
Crenin et al. (0-72 h)	0.9%	1.7%	0.135
Glasier et al. (0-120 h)	1.6%	2.6%	0.091
Meta-analysis (0-24 h)	0.9%	2.5%	0.035
Meta-analysis (0-72 h)	1.4%	2.2%	0.046
Meta-analysis (0-120h)	1.3%	2.2%	0.025

Crenin MD, Schlaff W, Archer DF et al. Progesterone receptor modulator for emergency contraception : a randomized controlled trial . Obstet Gynecol 2006; 108:1087-97.
Glasier AF, Cameron ST, Fine FM, et al. ulipristal acetate versus levonorgestrel regimen of emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet. 2010; 375:555-62.

ULIPRISTAL VERSUS LEVONORGESTREL

- Pregnancy rate if used within 72 hours
  - Within 24 hours: 2/3 risk (OR 0.35, CI 0.11-0.95)
  - Within 120 hours: 1/2 risk (OR 0.55, CI 0.32-0.93)

- Why is UPA more effective?
  - More effective than LNG in preventing ovulation of larger follicles

Glasier AF, Cameron ST, Fine FM, et al. ulipristal acetate versus levnorgestrel regimen of emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet. 2010; 375:555-62.

SUMMARY

Table 1. Available Methods of Emergency Contraception

Regimen	Formulation	Timing of Use After Unprotected Sexual Intercourse*	Access	FDA Labeled for Use as Emergency Contraception
Selective progesterone receptor modulator	1 tablet, containing 30 mg of ulipristal acetate	Up to 5 days	Requires a prescription	Yes
Progestin only	1 tablet, containing 1.5 mg of levonorgestrel	Up to 3 days	Available over the counter without age restriction	Yes
Progestin only	2 tablets, each containing 0.75 mg of levonorgestrel	Up to 3 days	Available over the counter to those 17 years and older with photo identification	Yes
Combined progestin-estrogen pills	A variety of formulations can be used	Up to 5 days	Requires a prescription	No
Copper IUD	N/A	Up to 5 days	Requires office visit and insertion by a clinician	No

ACOG Practice Bulletin #152

HOW DO I GET IT?

OBTAINING EC

- **Levonorgestrel EC**
  - Available over the counter!
  - No age restriction
  - Can be more costly OTC than with a prescription

- **UPA requires a prescription**
  - In CA, trained pharmacists can prescribe oral EC*
  - No age restriction

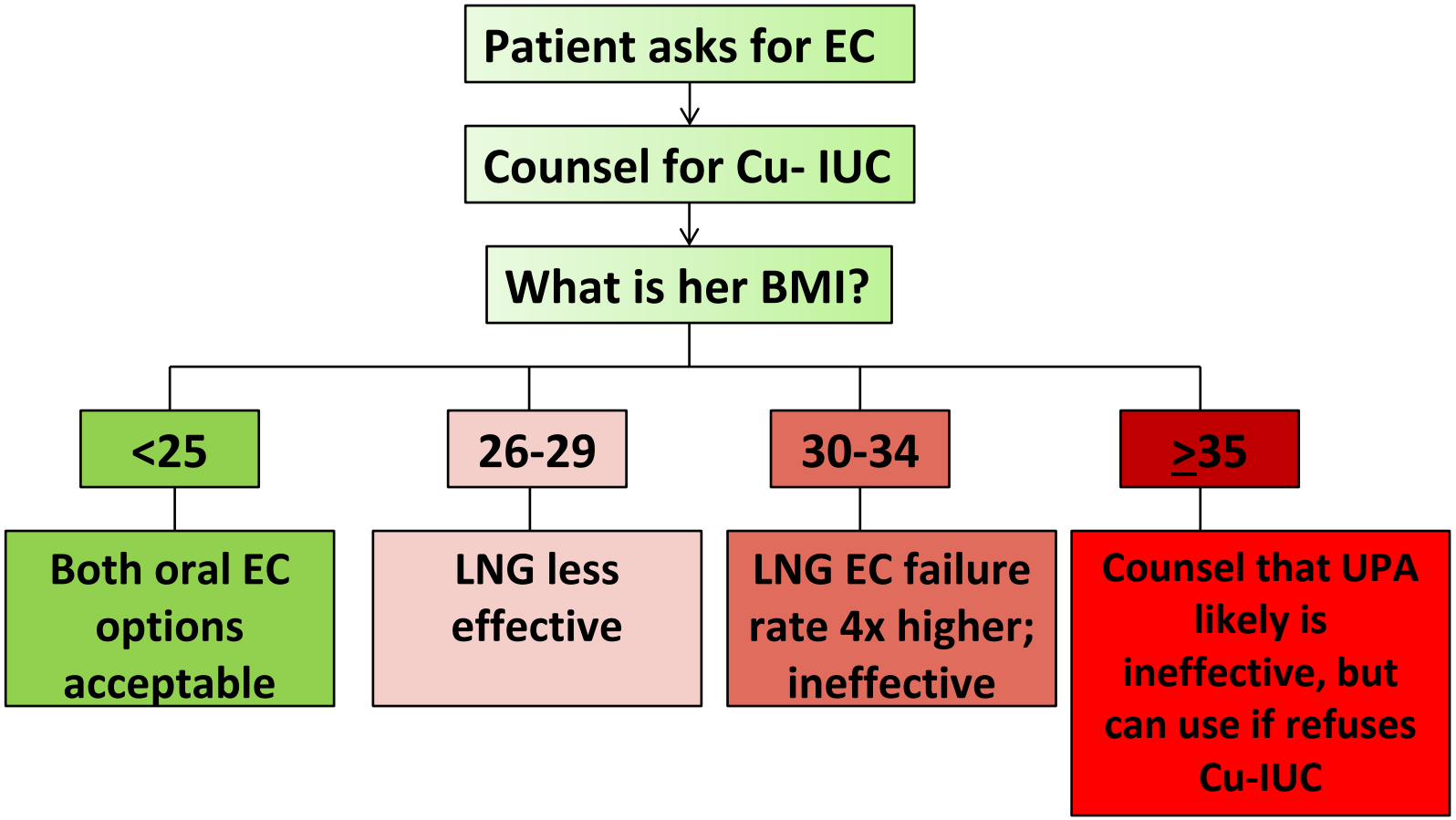
- **Copper IUD**
  - Requires insertion by trained clinician
  - Covered by FPACT if patient intends to use as long-term contraceptive method

BMI AND EFFICACY

BODY MASS INDEX (BMI)

- **Normal (18.5 – 24.9)**
  - UPA = LNG
- **Overweight (25 – 29.9)**
  - UPA > LNG
- **Obese (>30)**
  - UPA >>> LNG

Kapp, N., Abitbol, J. L., Mathé, H., Scherrer, B., Guillard, H., Gainer, E., & Ulmann, A. (2015). Effect of body weight and BMI on the efficacy of levonorgestrel emergency contraception. *Contraception*, *91*(2), 97–104.

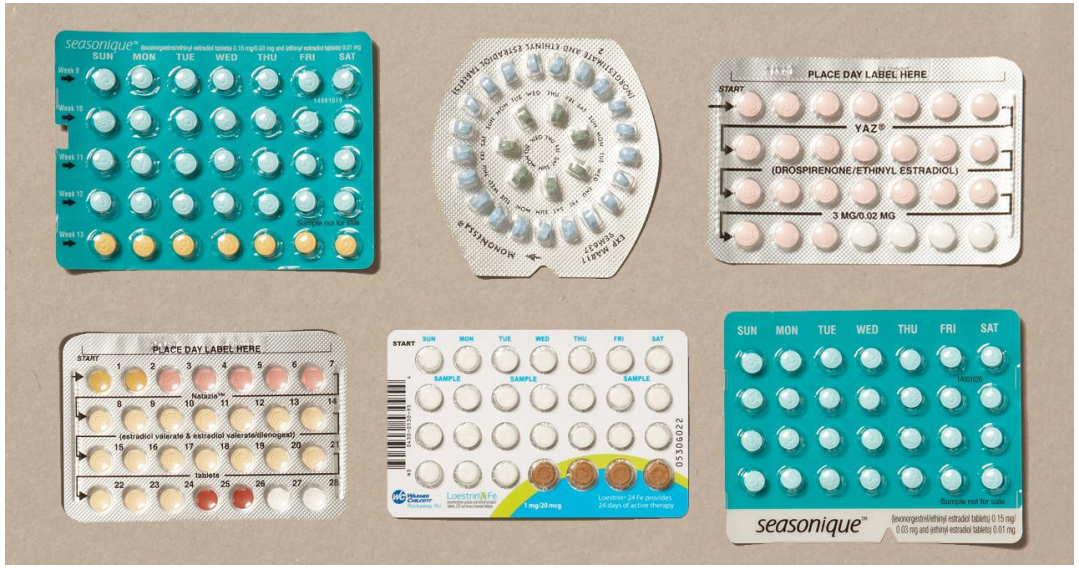


Rapkin RB, Creinin M, OBG Management 2011; 23(8): 16-24

WHEN TO START CONTRACEPTION?

LEVONORGESTREL EC

- Can resume or re-start any contraceptive method immediately
- Use barrier method for 7 days after start



ULIPRISTAL EC

"After using ella, if a woman wishes to use **hormonal contraception**, she should do **so no sooner than 5 days after the intake of ella**, and she should use a reliable barrier method until the next menstrual period."

FDA change to UPA label (March 2015)

EVIDENCE

- Prospective cohort study with 36 women
- Aim: to determine if COCs started shortly after UPA interferes with mechanism of action
- Participants received UPA for two cycles and followed for 7 days with transvaginal US, blood sampling for progesterone and LH
  - One cycle – daily COC started 2 days after UPA
- Results: In the cycle when COC was started – more women showed evidence of follicle rupture in less than 5 days ($p = 0.008$)
  - Includes women who experienced follicular rupture prior to initiating COCs
- Conclusion: Efficacy of UPA ***significantly reduced*** with early exposure to COCs

Edelman, et al. Combined oral contraceptive interference with the ability of ulipristal acetate to delay ovulation: A prospective cohort study. Contraception, Volume 98, Issue 6, 2018.

For women starting or continuing OCs, the Patch or the Ring:

For women who	Offer this ECP	For ongoing contraception	Days of backup required after ECP intake
Need EC because of missed pills, patch or ring	LNG	For pill users: Continue pill pack *or* start new pack if on last week of pills	7 days (2 days for POP)
Need EC because of missed pills, patch or ring	LNG	For patch/ring users: Start new patch or ring	7 days (2 days for POP)
Need EC because of missed pills, patch or ring	LNG	If missing pills is an ongoing concern, counsel on methods that are easier to use consistently and correctly	7 days (2 days for POP)
Want to start OCs, Patch or Ring	UPA	Provide method	7 days
Want to start OCs,	UPA	Counsel patient to set a reminder to	7 days

UNANSWERED QUESTIONS

1. Quickstarting other contraceptive methods?
   - LNG IUD, implant, Depo Provera?

2. How to weigh potential loss of UPA efficacy *vs* opportunity to start ongoing highly effective method?

MISCONCEPTIONS

MISCONCEPTION: EFFECTS ON PREGNANCY

- If pregnancy continues, Emergency Contraception does not effect the developing embryo

- Emergency Contraception does not increase rates of ectopic pregnancy

Bacic M, et al. Failure of large doses of ethinyl estradiol to interfere with early embryonic development in the human species. Am J Obstet Gynecol 1970: 107:53104.
Trussell J, Hedley A, Raymond E. Ectopic pregnancy following use of progestrin-only ECPs. J Fam Plann Reprod Health Care 2003;29:240
Cleand K, et al. Ectopic Pregnancy and emergency contraceptive pills: a systematic review. Obstet Gynecolol, 2010;115(6):1263.

MISCONCEPTION MECHANISM OF ACTION

- People confuse Plan B with mifepristone
- According to the NIH, FDA and ACOG
  - Pregnancy begins after a fertilized egg implants in the lining of the uterus.
- Oral EC: primary mechanism of action is to inhibit or delay ovulation
  - Ulipristal 30mg dose was titrated for inhibition of ovulation and is likely too low to inhibit implantation.
- Copper IUD: can prevent implantation, but does NOT disrupt it

MISCONCEPTIONS: ELIGIBILITY/SAFETY

- WHO Medical Eligibility Criteria for Contraceptive Use & the USMEC
  - No condition in which the risks of emergency contraception outweighs the benefits
- Women with contraindication to COCs should be still offered oral EC!
- Women who are breastfeeding may safely use LNG or UPA*
  - *Breastfeeding not recommended for 24 hours after UPA
  - MEC Cat 1

World Health Organization. Medical eligibility criteria for contraceptive use. 4th edition. Geneva: World Health Organization; 2008.

MISCONCEPTION: REPEAT USE

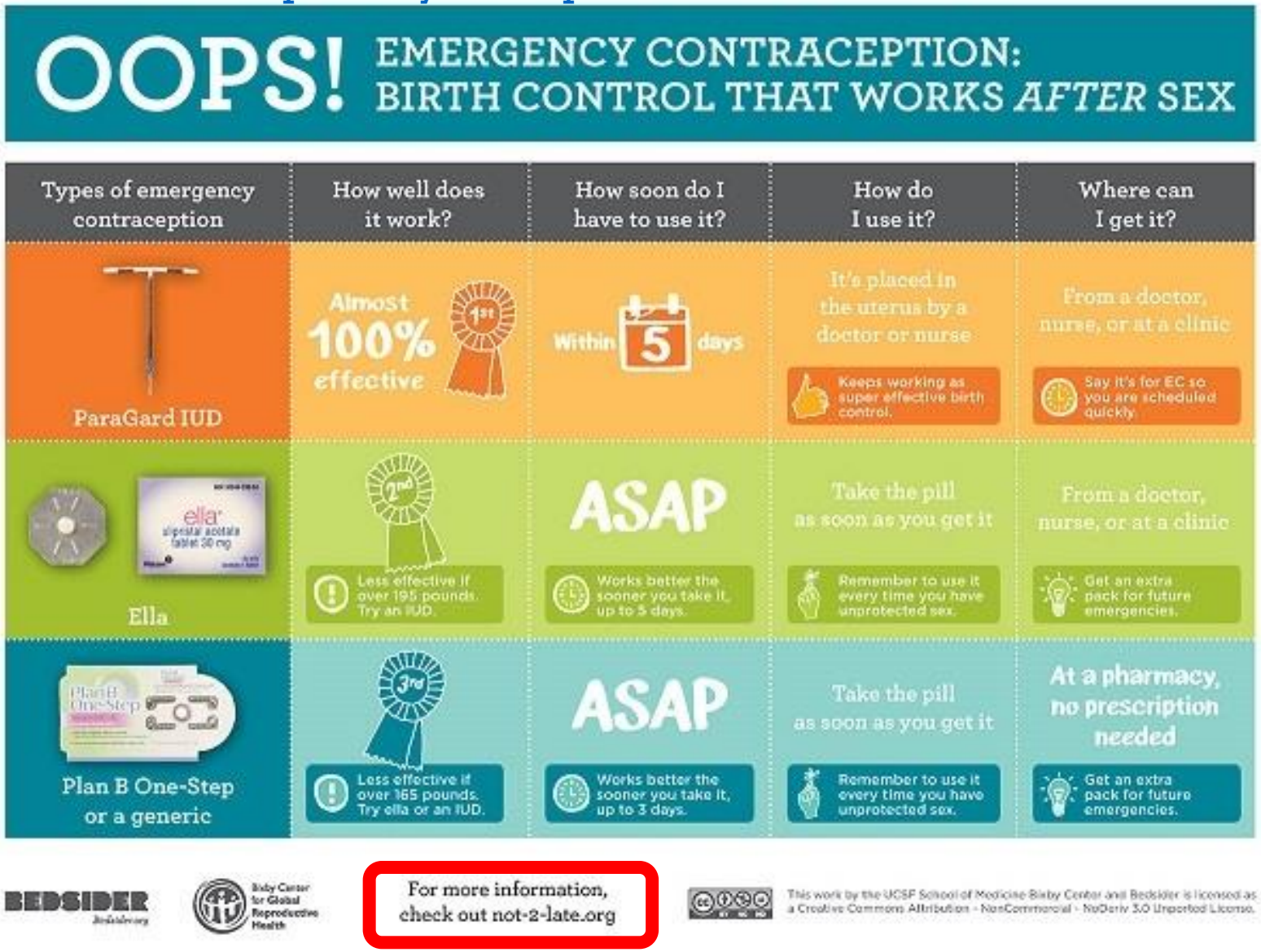
- Repeat use is uncommon but safe
- According to 2006-2008 National Survey of Family Growth
  - 61% of emergency contraception users had only used it once
- US MEC: Repeated EC use is Category 1 for all methods
- WHO guidelines on EC
  - “Although frequent use of EC pills is not recommended, repeat use poses no health risks and [health risks] should never be cited as a reason for denying women access to treatment.”

Kavanaugh ML, Williams SL, Schwarz EB. Emergency contraception use and counseling after changes in United States prescription status. Fertility and Sterility April 2011.
World Health Organization (WHO). Emergency Contraception A guide for service delivery. Geneva WHO ;1998.

RESOURCES

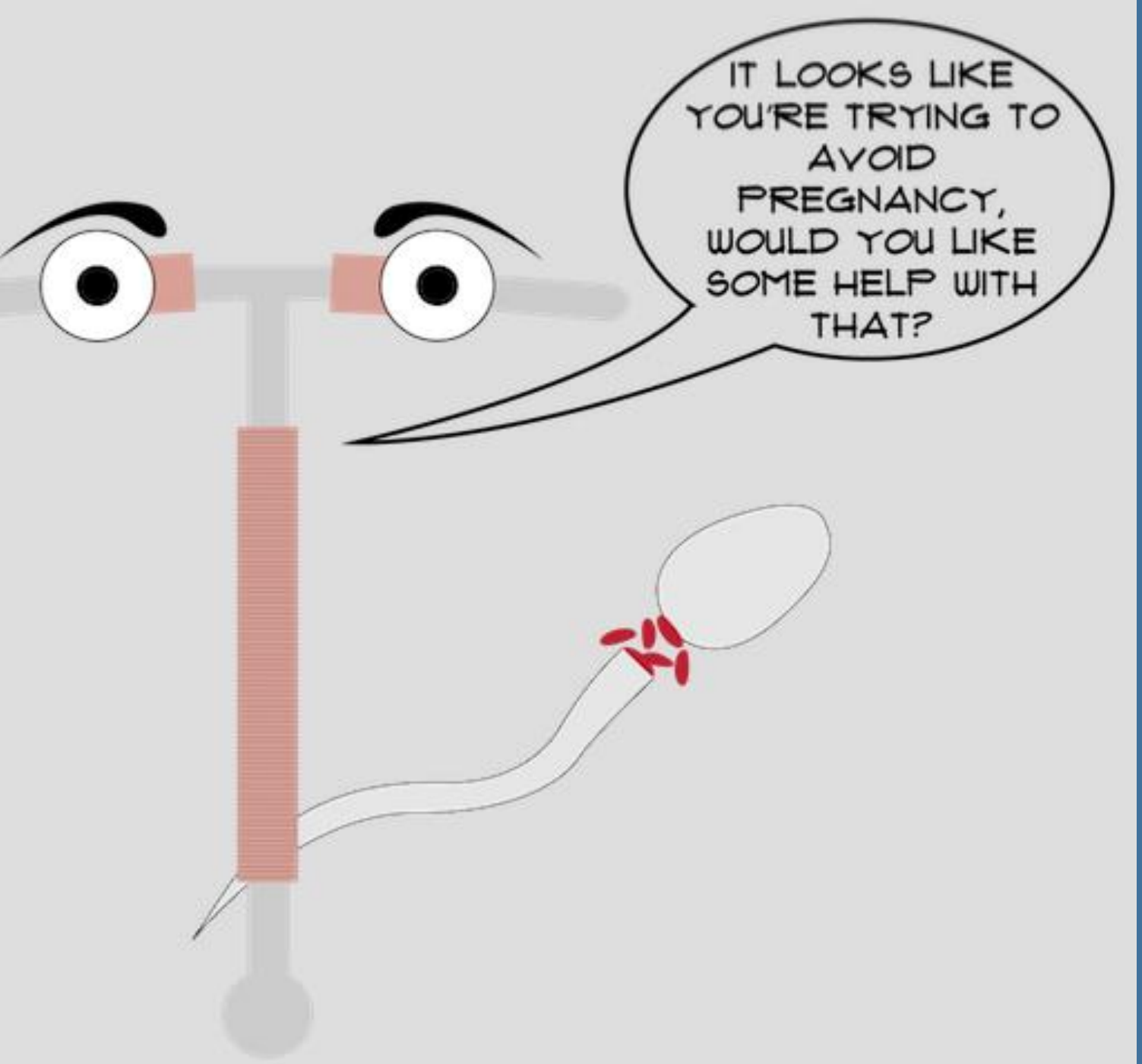
NOT-2-LATE.COM

https://beyondthepill.ucsf.edu/tools-materials



SUMMARY

- EC is time sensitive!
- Copper IUD is the most effective method of EC!
- For oral EC -
  - Up to **72 hours** after UPI: UPA and LNG have similar efficacy
  - **72 – 120 hours** after UPI: UPA (much) more effective than LNG
- BMI affects efficacy of oral EC



THANK YOU!

nieconomou@health.ucsd.edu