# UPDATE ON WOMEN'S HEALTH ISSUES 2016

CAFP Symposium

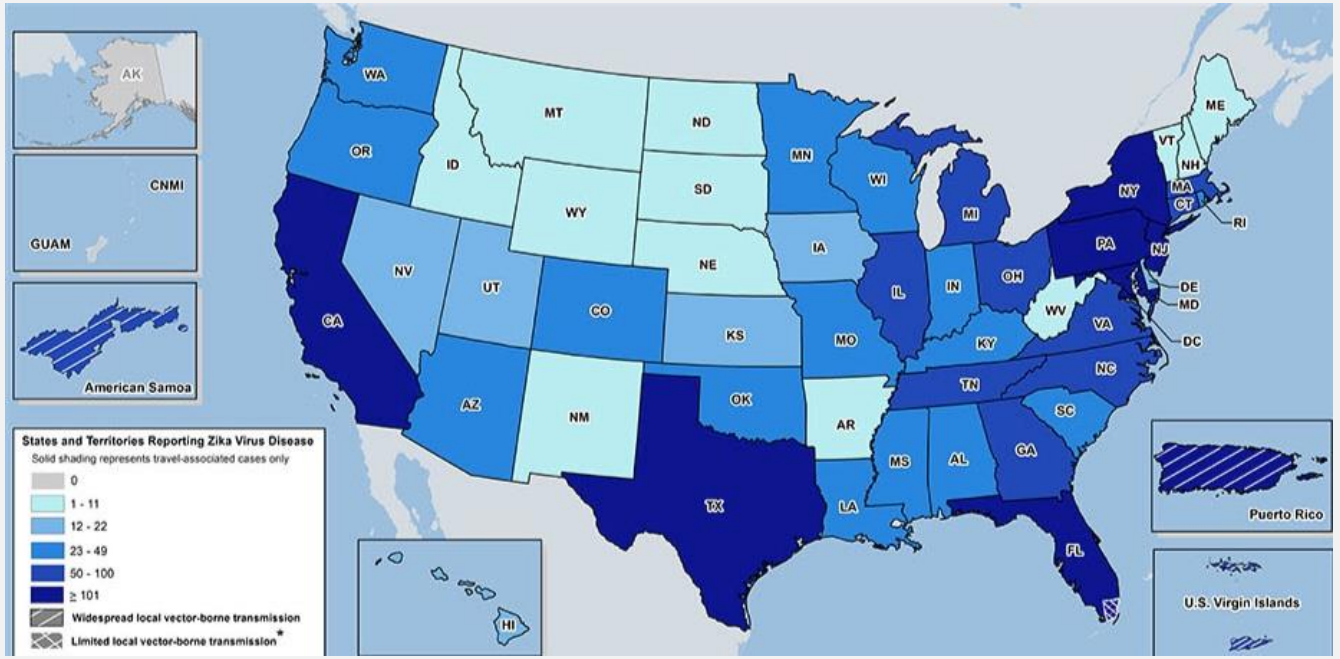
October 2016

# ZIKA VIRUS

# WHAT DO WE KNOW ABOUT ZIKA?

- Arthropod-borne flavivirus transmitted by mosquitoes
- Methods of transmission:
  - Bite of the Aedes species mosquito
  - Vertical (mother to fetus)
  - Sexual (primarily male-to-female)
  - Blood products
  - Organ transplant
- Majority (75-80%) of cases are asymptomatic

# ZIKA IN THE U.S.



# WHAT ARE THE SYMPTOMS OF ZIKA?

- Symptoms start 2-14 days after mosquito bite
- Acute onset low-grade fever, pruritic maculopapular rash, nonpurulent conjunctivitis, arthralgias (especially of hands and feet), malaise, headache
- Symptom duration – a few days to a week
- An association is noted with Guillian-Barre syndrome

Symptoms are similar to Dengue and Chikungunya (fever, arthralgias, malaise) but onset of these diseases following a bite is shorter (1 week or less)

# SPECIAL CONCERN FOR WOMEN

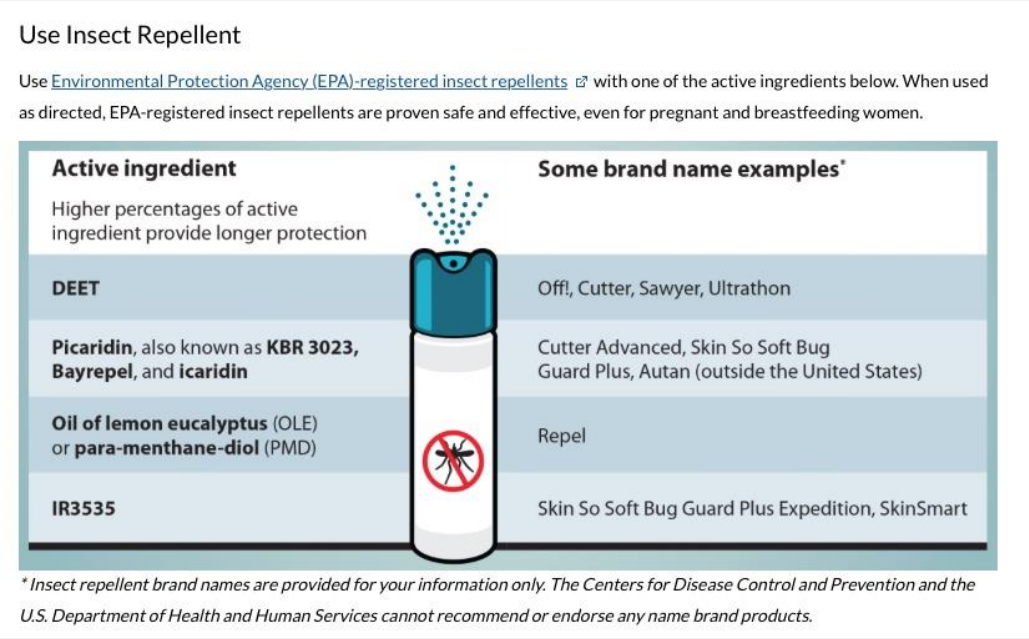
- Infection during pregnancy is linked to microcephaly, eye defects, hearing loss (6% of infants with microcephaly) and impaired growth.
- The risk is highest in the first trimester of pregnancy and appears to be less in the third trimester.
- Because Zika transmission is sexual as well as via mosquito,  counseling women on pregnancy and pregnancy plans is imperative.
- There is evidence that infants without abnormalities noted at birth may still have Zika-effects.

# ZIKA BEYOND MICROCEPHALY

- But as evidence mounts that the virus' strong affinity for neural stem cells may also cause subtler central nervous system damage, the medical community fears that the current tragedy may give way to an equally horrific second act that will play out over years as exposed children who seemed unscathed at birth exhibit serious neurological ills as they age. Expectations range from auditory and visual problems to cognitive delays and seizure disorders. (NEJM)
- Accordingly, the World Health Organization recently called for broadening the definition of Zika-related pathology beyond microcephaly, noting "Zika virus is an intensely neurotropic virus that particularly targets neural progenitor cells, but also—to a lesser extent—neuronal cells in all stages of maturity. … [I]t is possible that many thousands of infants will incur moderate to severe neurological disabilities."

# ADVISING PREGNANT WOMEN

- Avoid travel to areas with Zika infection
- If travel to a Zika area is necessary (or patient lives in a Zika area), counsel regarding preventing mosquito bites – repellents, long-sleeved shirts and long pants, environmental changes to minimize mosquito exposure
- Pregnant women who travel to Zika areas should be tested for the virus, regardless of whether they have symptoms.



Use Insect Repellent

Use Environmental Protection Agency (EPA)-registered insect repellents with one of the active ingredients below. When used as directed, EPA-registered insect repellents are proven safe and effective, even for pregnant and breastfeeding women.

| Active ingredient<br>Higher percentages of active ingredient provide longer protection | Some brand name examples* |
|---|---|
| **DEET** | Off!, Cutter, Sawyer, Ultrathon |
| **Picaridin**, also known as **KBR 3023, Bayrepel**, and **icaridin** | Cutter Advanced, Skin So Soft Bug Guard Plus, Autan (outside the United States) |
| **Oil of lemon eucalyptus** (OLE) or **para-menthane-diol** (PMD) | Repel |
| **IR3535** | Skin So Soft Bug Guard Plus Expedition, SkinSmart |



** Insect repellent brand names are provided for your information only. The Centers for Disease Control and Prevention and the U.S. Department of Health and Human Services cannot recommend or endorse any name brand products.*

# ADVISING WOMEN WHO ARE ATTEMPTING PREGNANCY

| Suggested timeframe to wait before trying to get pregnant | | |
|---|---|---|
| **Possible exposure via recent travel or sex without a condom with a man infected with Zika** | | |
| | **Women** | **Men** |
| **Zika symptoms** | Wait at least 8 weeks after symptoms start | Wait at least 6 months after symptoms start |
| **No Zika symptoms** | Wait at least 8 weeks after exposure | Wait at least 8 weeks after exposure.<br>Talk with your healthcare provider |
| **People living in areas with Zika** | | |
| | **Women** | **Men** |
| **Zika symptoms** | Wait at least 8 weeks after symptoms start | Wait at least 6 months after symptoms start |
| **No Zika symptoms** | Talk with doctor or healthcare provider | Talk with doctor or healthcare provider |

# SEROLOGIC TESTING

Serologic testing is NOT recommended for men or women who are attempting reproduction who have a possible exposure to Zika but no clinical illness. It is not known whether a positive serologic test result in an asymptomatic man would indicate possible presence of Zika in the semen, or if a negative serologic test would preclude the presence of virus in the semen.

Testing of semen is NOT recommended since no test for the presence of infectious Zika has been validated.

In August 2016 the FDA advised testing of ALL donated blood and blood components for Zika. (Previously was only in areas of active Zika transmission.)

# WHAT WE KNOW

- Zika illness itself is not concerning and generally is mild, self-resolving and does not require treatment.
- Illness in children is usually mild, but physicians are urged to test if appropriate, monitor children for adverse effects and warn teens regarding pregnancy.
- The fact that Zika can cause significant birth defects, especially in the early trimesters makes it a major public health concern. Dengue and chikungunya do not cause birth defects like Zika.
- What makes things complicated and different than other mosquito-borne diseases that we are familiar with is that Zika is also transmitted sexually. This makes the potential for spread outside known Zika areas possible, even in the absence of mosquitoes.

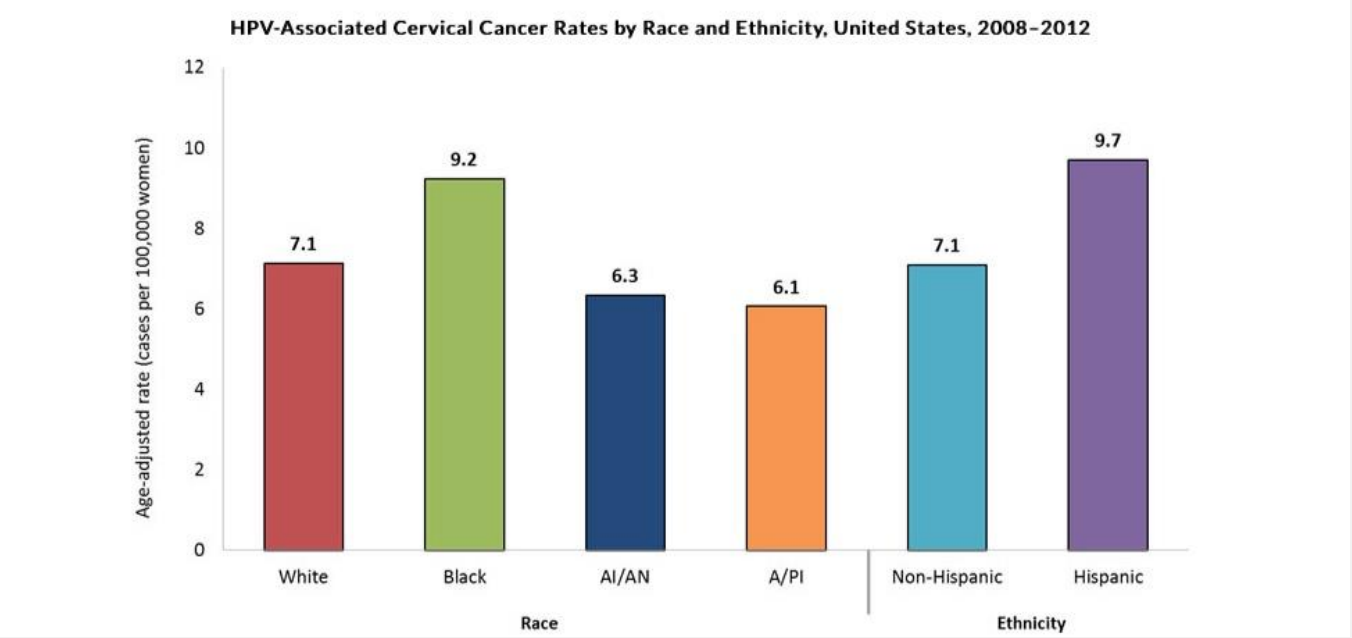
# WHAT WE DON'T KNOW

- NEJM reported a child whose mother contracted Zika at 26 weeks gestation. Infant's initial examination was normal but brain MRI showed multiple abnormalities. This infant was found to be viremic 67 days after birth. What does this mean in terms of prognosis and infectivity?
- What are the problems that we potentially can see in infants born to mothers who had Zika over and above the problems noted at birth? While microcephaly is less likely when the disease is contracted by the mother in the 3$^{rd}$ trimester, is the child still at risk for problems?
- What is the magnitude of the risk (if any) of infants born to mothers with asymptomatic infection?
- Will the current recommendations regarding reproduction going to be sufficient to protect future pregnancies?

# CERVICAL CANCER AND SCREENING

# WHAT ARE THE STATISTICS?

- In 2013 – 11, 955 women were diagnosed with cervical cancer
- In 2013 – 4,217 women died from cervical cancer



# CERVICAL CYTOLOGY – PAP SMEAR

- Introduced in the 1940s and accounts for the significant decline in cervical cancer in the developed world.
- Why are there still cases of a treatable cancer?
- Evolution of recommendations – Where are we now?
  - Pap smears starting at age 21 years
  - For women 21-29 years of age: cytology with reflex HPV every 3 years
  - For women 30-65 years: cytology with HPV co-testing every 5 years (preferred) or cytology every 3 years

# WHY DO HPV TESTING?

- It is now recognized that certain types of human papilloma virus (HPV) cause cervical cancer.
- Some types (6, 11, 40, 42, 43, 44, 54, 61, 72, 81) are considered to have low oncogenic potential.
- Some types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 82) are considered high-risk (oncogenic or cancer-related).
- Of the high-risk types, 16 and 18 account for one-quarter of low-grade lesions, a little more than half of high-grade lesions and 70% of cancers.

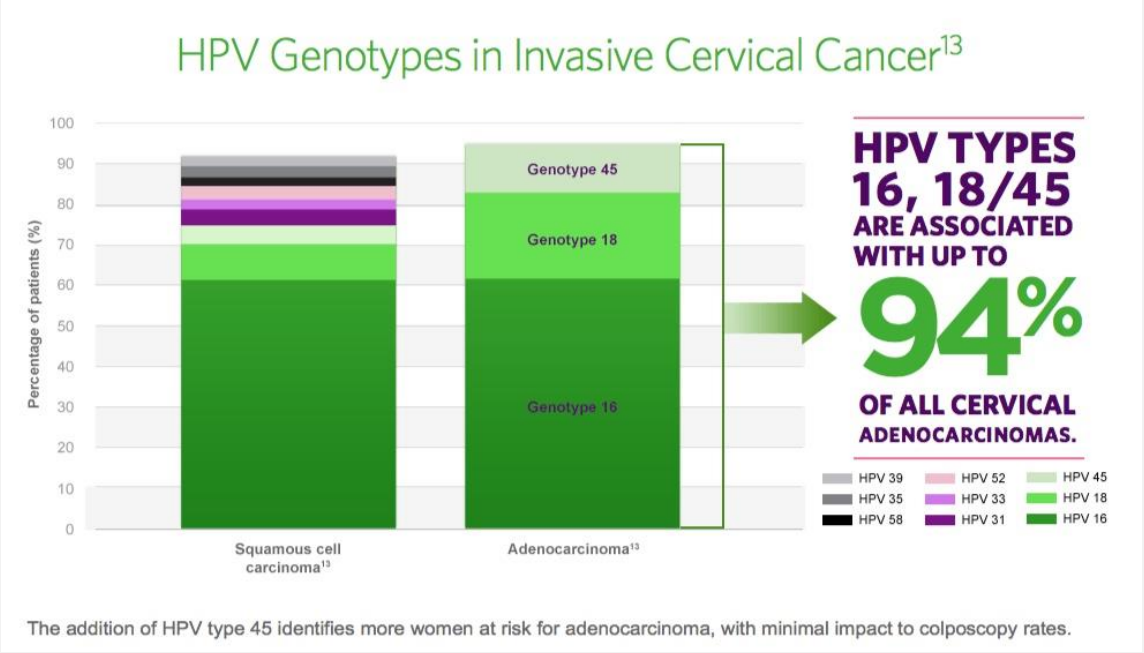
# WHAT IS NEW WITH HPV TESTING?

- In the past, reporting of HPV was limited to the presence or absence of high-risk HPV, but there was no differentiation separate identification of the subtypes most likely to cause cervical dysplasia and cancer.
- Tests are now available that can identify the presence of these particularly high-risk subtypes.
- Different tests use different detection strategies for identification of the high-risk subtypes – which gene they are testing for and whether they are testing for DNA or mRNA.

# CO-TESTING WITH APTIMA HPV

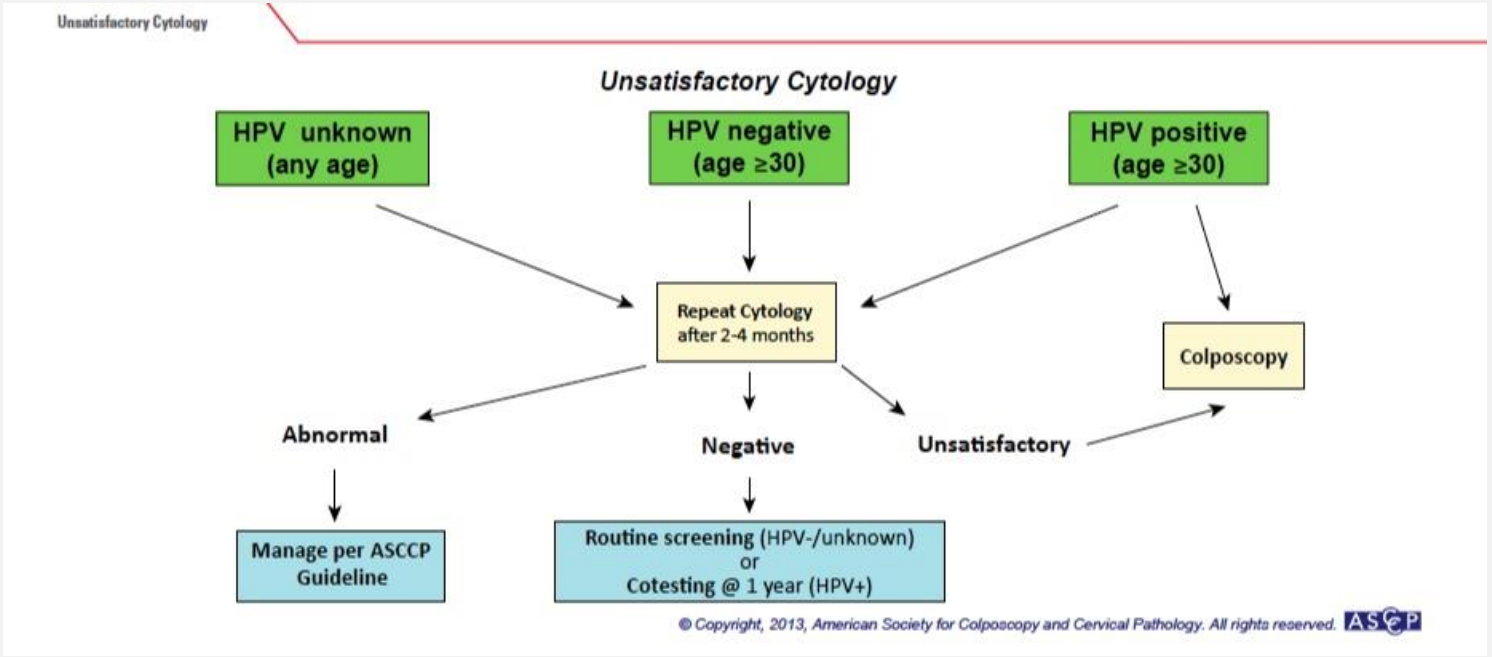
- The Aptima HPV test is made by the same company that does ThinPrep. Their previous HPV test was Cervista that used DNA and targeted E6/E7 oncogenes.
- Aptima tests for E6/E7 mRNA. Studies demonstrate similar sensitivity to DNA tests but with improved specificity (reduction in false-positive tests)
- mRNA levels increase with disease progression while DNA levels may decrease – potential false-negative tests
- Aptima tests for types 16, 18 and 45.
- The test is done as part of co-testing. Identification of 16, 18 and 45 will be reflex for younger women with ASCUS.
- Retrospective study demonstrates that using cytology and Aptima will decrease cancers missed by either test alone.

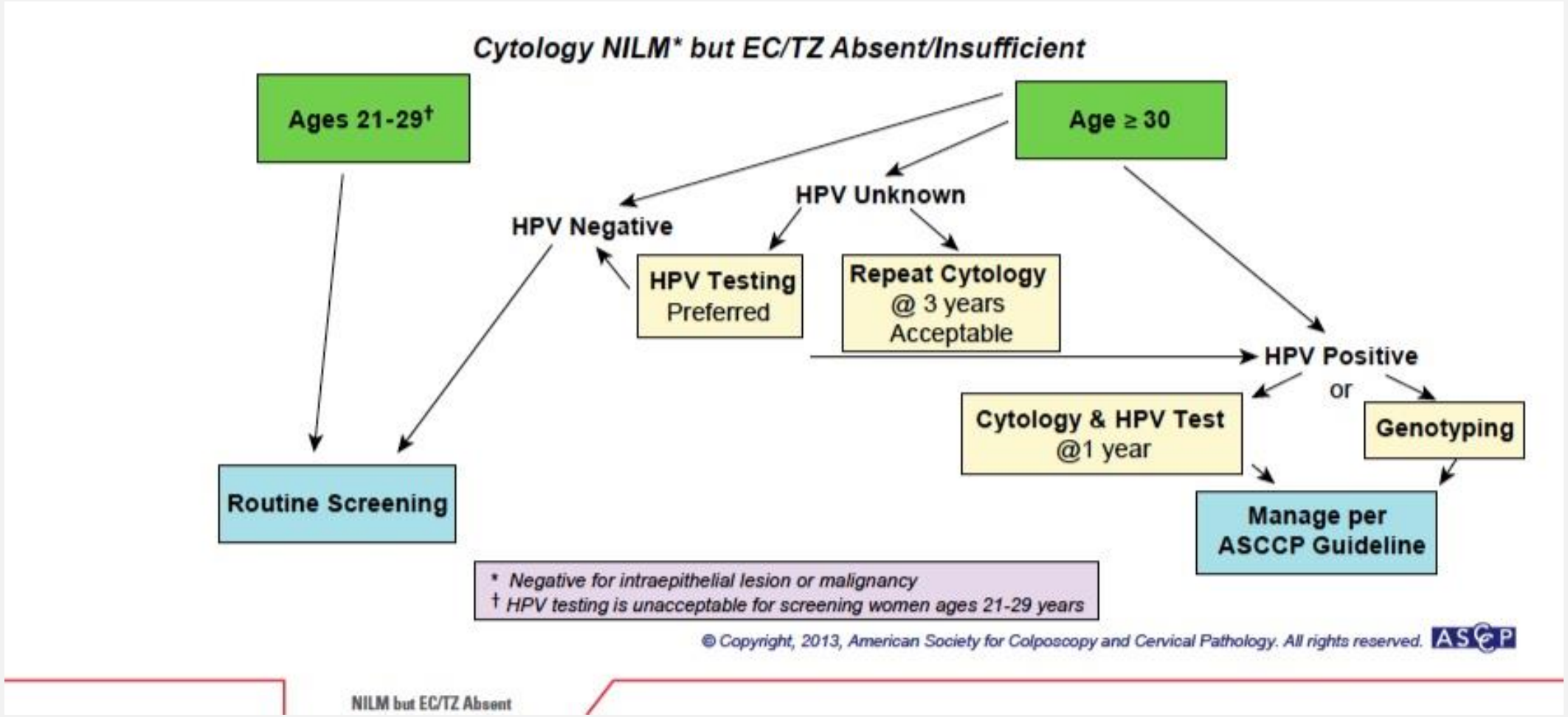
# IS THE ADDITION OF 45 IMPORTANT?




Squamous cell carcinoma accounts for 69% of cervical cancers.
Adenocarcinoma accounts for 25% of cervical cancer.

# HOW DO WE INCORPORATE HPV TESTING INTO MANAGEMENT OF ABNORMAL CERVICAL CYTOLOGY?




Cytology NILM* but EC/TZ Absent/Insufficient
Ages 21-29†
Age ≥ 30
HPV Unknown
HPV Negative
HPV Testing
Preferred
Repeat Cytology
@ 3 years
Acceptable
HPV Positive
or
Cytology & HPV Test
@1 year
Genotyping
Routine Screening
Manage per
ASCCP Guideline
* Negative for intraepithelial lesion or malignancy
† HPV testing is unacceptable for screening women ages 21-29 years
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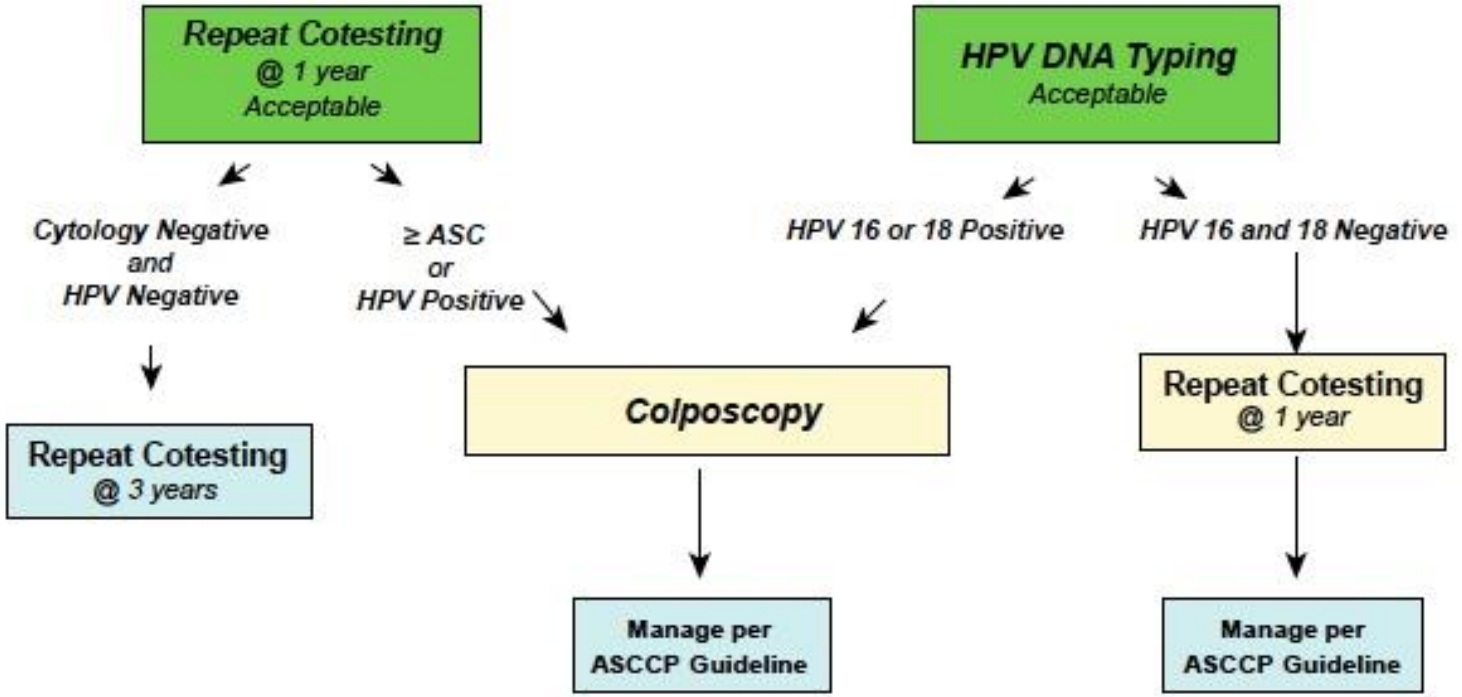
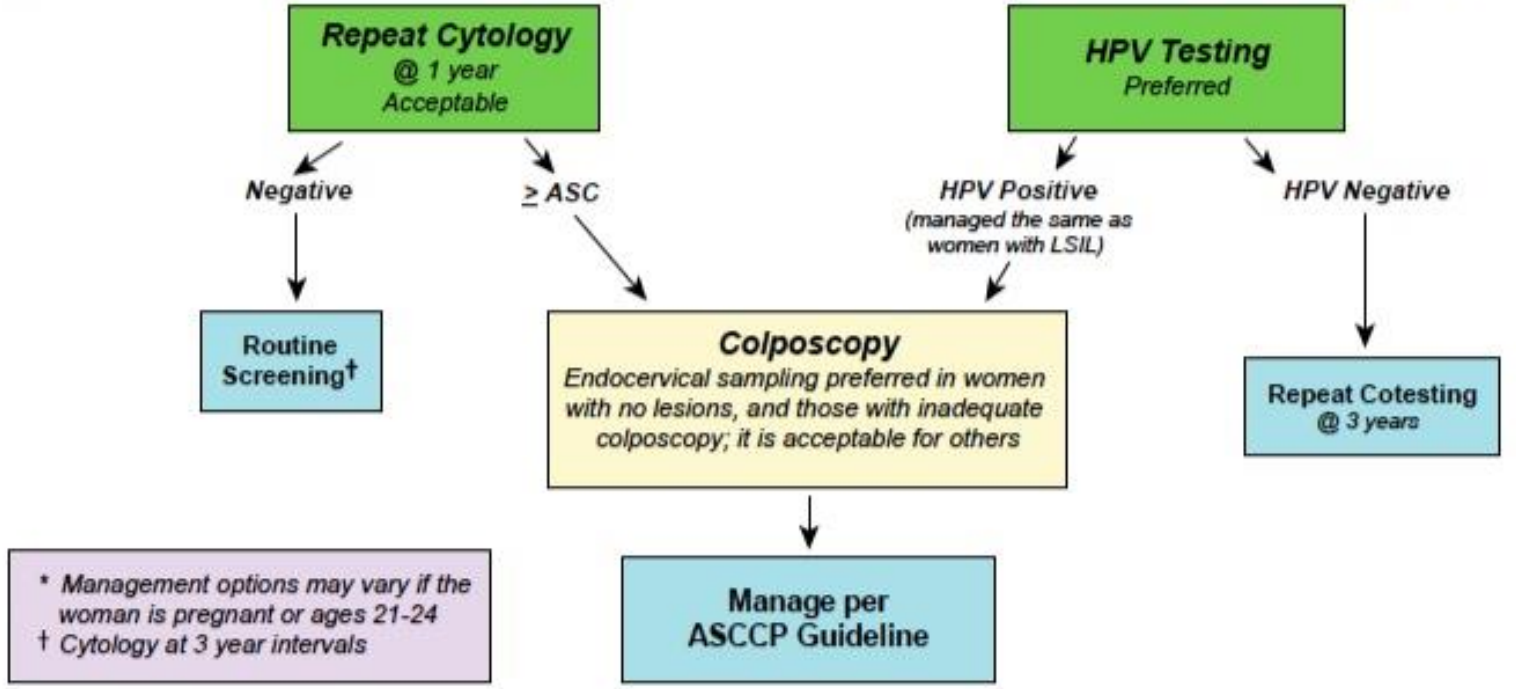
ASCCP

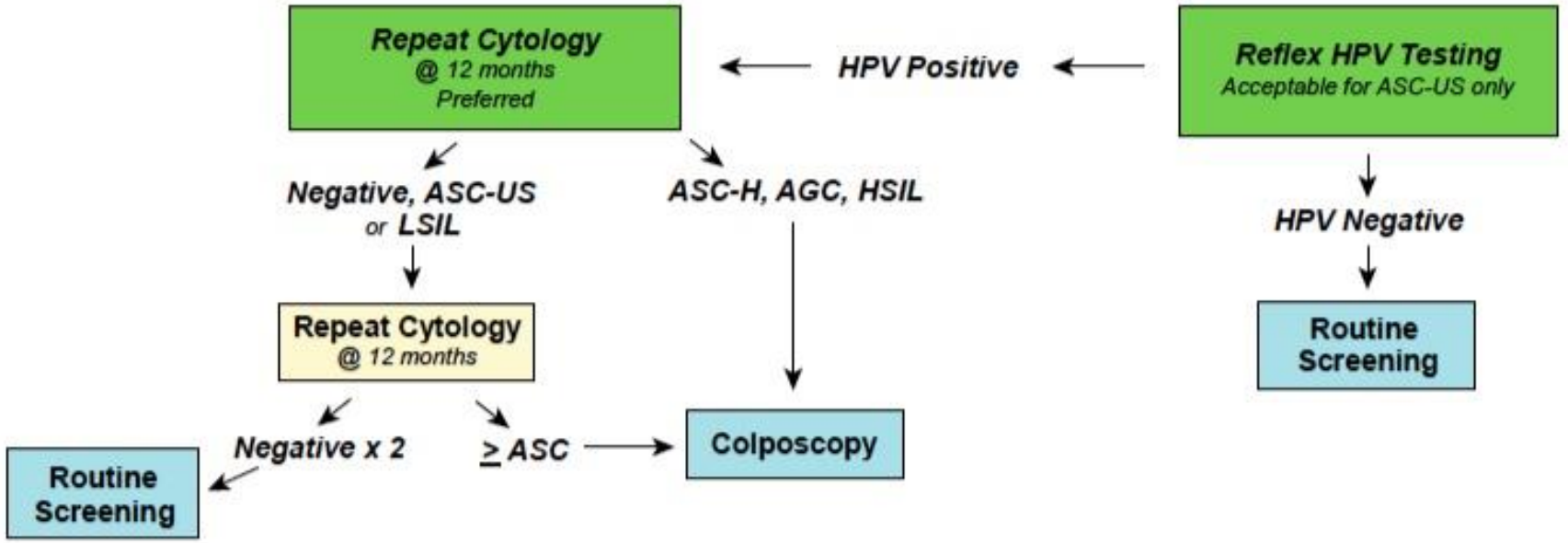
# Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive

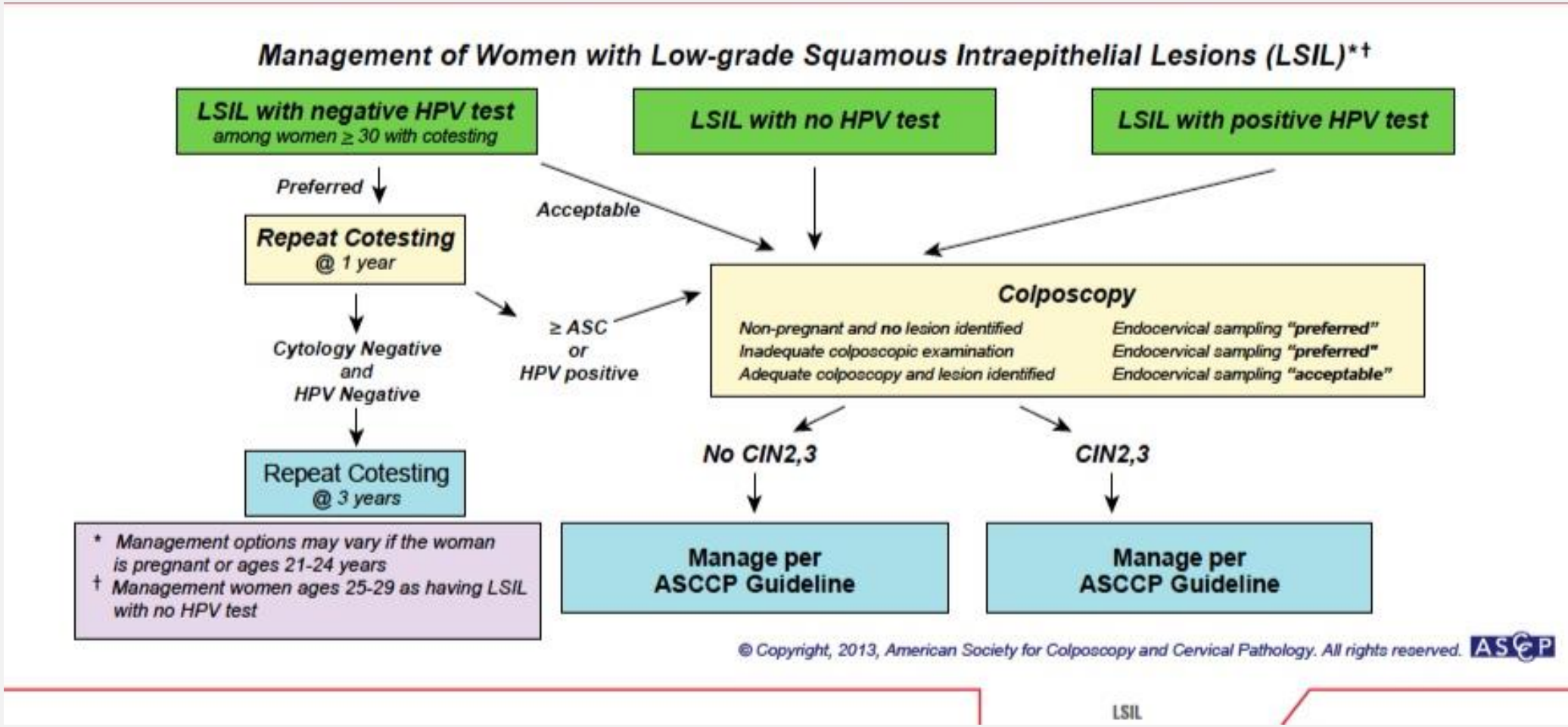


## Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology*



## Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)




Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)*†
LSIL with negative HPV test
among women ≥ 30 with cotesting
LSIL with no HPV test
LSIL with positive HPV test
Preferred
Acceptable
Repeat Cotesting
@ 1 year
Cytology Negative
and
HPV Negative
Repeat Cotesting
@ 3 years
≥ ASC
or
HPV positive
Colposcopy
Non-pregnant and no lesion identified
Inadequate colposcopic examination
Adequate colposcopy and lesion identified
Endocervical sampling "preferred"
Endocervical sampling "preferred"
Endocervical sampling "acceptable"
No CIN2,3
CIN2,3
Manage per
ASCCP Guideline
Manage per
ASCCP Guideline
* Management options may vary if the woman is pregnant or ages 21-24 years
† Management women ages 25-29 as having LSIL with no HPV test
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ASCCP

# WHAT ELSE IS NEW WITH HPV TESTING?

- Cobas HPV test (DNA-based detection) does differentiate 16 and 18 (along with 12 other types) and in 2014 was approved by the FDA as a stand-alone test (no cytology needed). It is also used for co-testing.
  - In 2015 the Society of Gynecologic Oncology (SGO) and the American Society for Colposcopy and Cervical Pathology (ASCCP) issued guidance regarding the use of primary HPV testing as screening for cervical cancer.
  - In 2016 the American College of Obstetricians and Gynecologists (ACOG) issued a practice bulletin supporting use of primary HPV testing

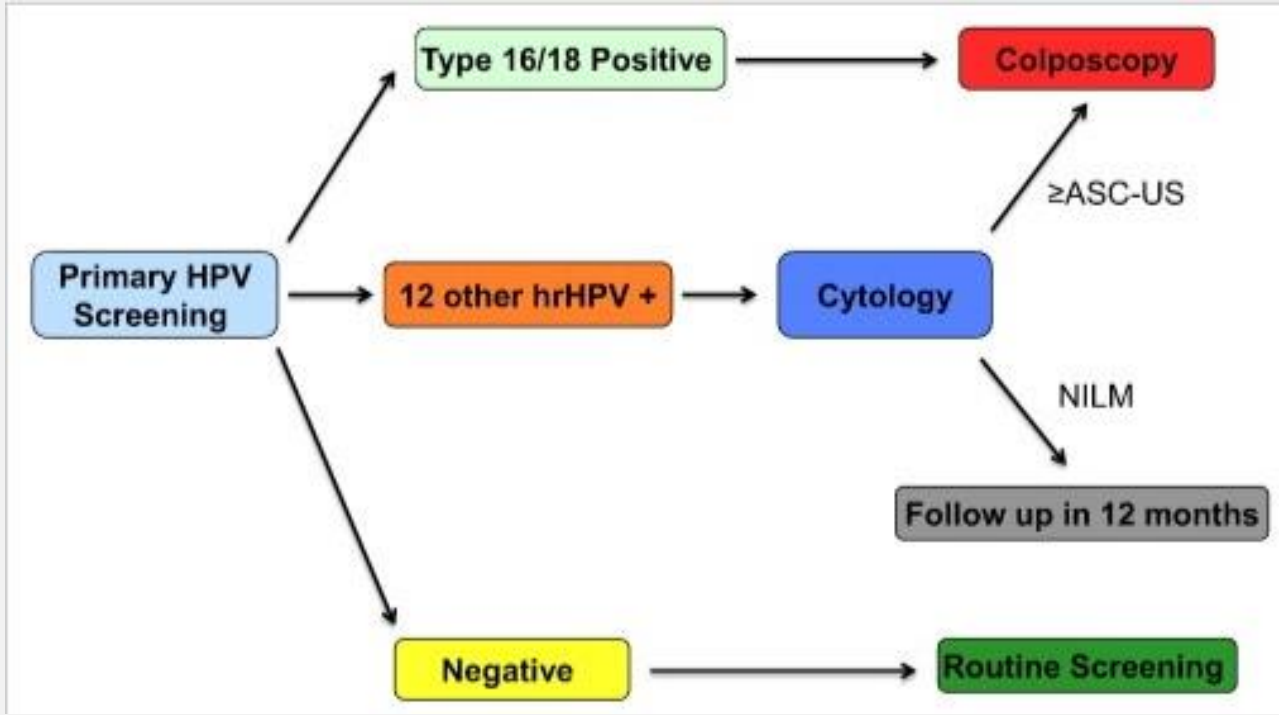
Currently test is performed on specimens obtained from the cervix at the time of a speculum examination (was originally either reflex or co-testing).

# WHAT IS THE EVIDENCE?

- In all studies, the risk of cervical intraepithelial neoplasia (CIN) 3 or greater at 3 years and 5 years, and cervical cancer at 3 years and 5 years, was significantly lower following a negative hrHPV test than after negative cytology (using current HPV testing recommendations).
- The conclusion is that hrHPV testing is as good or better than cytology and is an alternative to conventional cytologic testing.

# CURRENT GUIDANCE

- Primary HPV testing can be considered for women **starting at age 25 years**.
- Women with a negative primary HPV test result should not be retested again for at least 3 years. This is the same screening interval recommended under current guidelines for a normal cytology test result.
- An HPV test positive for HPV 16 or 18, two types associated with a higher risk of future disease, should be followed with colposcopy.
- A test that is positive for HPV types other than 16 or 18 should be followed with cytology testing.


Type 16/18 Positive
Colposcopy
≥ASC-US
Primary HPV Screening
12 other hrHPV +
Cytology
NILM
Follow up in 12 months
Negative
Routine Screening

# HOT OFF THE PRESS FROM ASCO

- Journal of Global Oncology – October 16, 2016
- Recommendations based on resource setting (basic, limited, enhanced, maximal)
- HPV testing recommended for all resource settings
  - Maximal – 25-65 years, every 5 years
  - Enhanced – 30-65 years, every 10 years if 2 consecutive negative tests at 5 year intervals
  - Limited – 30-49 years, ever 10 years
  - Basic – 30-49 years, 1-3 times per lifetime

# WHAT IS THE FUTURE OF CERVICAL CANCER SCREENING?

BMJ Open. 2016 Apr 25;6(4):e010660. doi: 10.1136/bmjopen-2015-010660.

**Clinical validation of hrHPV testing on vaginal and urine self-samples in primary cervical screening (cross-sectional results from the Papillomavirus Dumfries and Galloway-PaVDaG study).**

Stanczuk G[1], Baxter G[2], Currie H[3], Lawrence J[2], Cuschieri K[4], Wilson A[5], Arbyn M[6].

**RESULTS:** HrHPV prevalence was 14.7%, 16.6% and 11.6% in cervical, vaginal and urine samples, respectively. Sensitivity for detecting CIN2+ was 97.7% (95% to 100%), 94.6% (90.7% to 98.5%) and 63.1% (54.6% to 71.7%) for cervical, vaginal and urine hrHPV detection, respectively. The corresponding specificities were 87.3% (86.4% to 88.2%), 85.4% (84.4% to 86.3%) and 89.8% (89.0% to 90.7%). There was a 38% (24% to 57%) higher HPV detection rate in vaginal self-samples from women over 50 years compared with those ≤29 years. Relative sensitivity and specificity of hrHPV positivity for the detection of CIN2+ in vaginal versus cervical samples were 0.97 (0.94 to 1.00) and 0.98 (0.97 to 0.99); urine versus cervical comparisons were 0.53 (0.42 to 0.67) and 1.03 (1.02 to 1.04). The intralaboratory and interlaboratory agreement for hrHPV positivity in self-samples was high (κ values 0.98 (0.96 to 0.99) and 0.94 (0.92 to 0.97) for vaginal samples and 0.95 (0.93 to 0.98) and 0.90 (0.87 to 0.94) for urine samples).

**CONCLUSIONS:** The sensitivity of self-collected vaginal samples for the detection of CIN2+ was similar to that of cervical samples and justifies consideration of this sample for primary screening.

# CARE OF HIV-POSITIVE WOMEN

# WHAT DO WE KNOW?

- Women account for 19% of HIV diagnoses, 25% of those living with HIV infection
- Acquisition is primarily by heterosexual contact (87%) and IV drug use (13%)
- Black women account for a disproportionately high percentage of cases.
- New HIV diagnoses have declined by 40% in women between 2005 and 2014
- AIDS diagnoses have tripled in women since 1985
  - 84% linked to HIV care in first 3 months (2013)
  - 55% are retained in care (2013)
  - 39% were receiving CART (end of 2012)
  - 30% achieved viral suppression

# WHAT CAN FAMILY PHYSICIANS DO?

Screening

- USPSTF recommendation to screen everyone 15 to 65 years of age
- Identify women at high risk and screen them

Prevention

- Consistent condom use

Encouraging good HIV care

- Refer to HIV specialist
- Encourage compliance with visits, medications and testing
- Know about medications – adverse effects, interactions, etc.
- Provide routine health maintenance

# GYNECOLOGIC PREVENTIVE CARE

- Cervical cancer screening – special recommendations for HIV-infected women
- Breast cancer screening – screening is the same as for uninfected women

# CERVICAL CANCER SCREENING

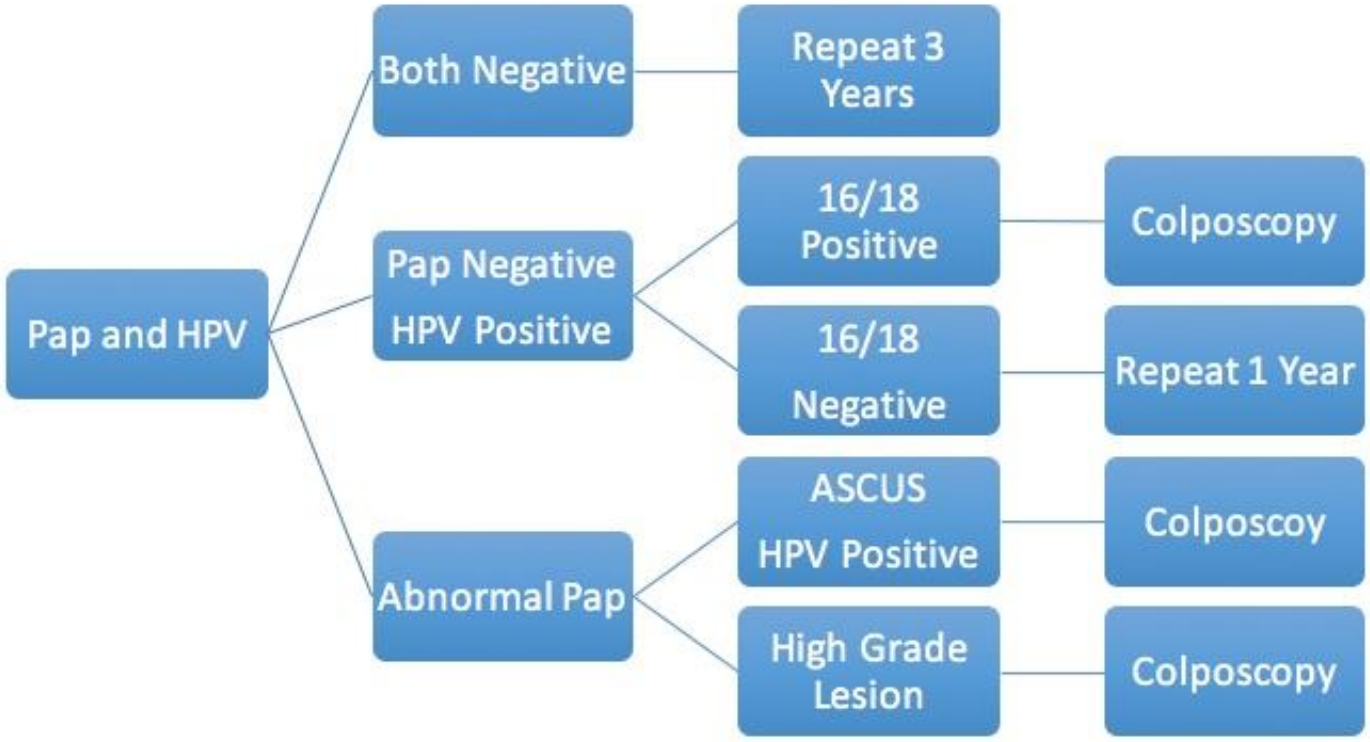
## Women <30 years of age

- Begin screening (Pap smear) **1 year after onset of sexual activity for women <21 years of age** (no later than age 21 years)
- **Screen at time of diagnosis for women 21-29 years of age**
- If screen is negative, repeat Pap smear in 1 year (some say 6 months)
- If 3 normal negative Pap smears, can increase interval to every 3 years
- If ASCUS – colposcopy if reflex HPV is positive or repeat Pap in 6-12 months
- Colposcopy for other abnormalities

# CERVICAL CANCER SCREENING

## Women >30 years of age

- **Screening should be continued indefinitely (lifetime)** with Pap smear alone or with HPV co-testing (ACOG preferred)
- If Pap smear alone – every 12 months (some recommend second test at 6 months) until 3 normal smears and then every 3 years.
- If Pap smear with co-testing –
  - Repeat in 3 years if both are negative
  - Pap negative but HPV positive
    - No HPV 16/18 – repeat co-testing in 1 year; if either test is positive 1 year later, refer for colposcopy
    - HPV 16/18 positive, refer for colposcopy
- If Pap is abnormal
  - ASCUS and positive HPV – refer for colposcopy
  - High grade lesions – refer for colposcopy


Pap and HPV
Both Negative
Repeat 3 Years
Pap Negative HPV Positive
16/18 Positive
Colposcopy
16/18 Negative
Repeat 1 Year
Abnormal Pap
ASCUS HPV Positive
Colposcoy
High Grade Lesion
Colposcopy

# POST-HYSTERECTOMY PATIENTS

- Vaginal Pap smears to screen for vaginal cancer are not necessary for women who had the hysterectomy for a benign reason.
- Pap smears of the vaginal cuff are recommended for women with a history of high-grade CIN, carcinoma in situ or invasive cervical cancer.

# CONTRACEPTION FOR HIV-INFECTED WOMEN

HIV-infected women

- Combined hormonal contraceptives, progesterone only pills, medroxyprogesterone injections and progesterone-only implants are CDC MEC category 1
- The copper IUD and progesterone IUDs are category 2 (initiation and continuation)

Women with AIDS

- Combined hormonal contraceptives, progesterone only pills, medroxyprogesterone injections and progesterone-only implants are CDC MEC category 1
- IUDs are category 3 for initiation and category 2 for continuation

Regardless of contraceptive method used, consistent condom use is recommended.

# BREAST CANCER SCREENING

# RECOMMENDATIONS – WHERE ARE WE NOW?

## American Cancer Society - 2015

- Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years (strong recommendation).
- Women aged 45 to 54 years should be screened annually (qualified recommendation).
- Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually (qualified recommendation).
- Women should have the opportunity to begin annual screening between the ages of 40 and 44 years (qualified recommendation).
- Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer (qualified recommendation).

# RECOMMENDATIONS – WHERE ARE WE NOW?

**American College of Obstetricians and Gynecologists - 2016**

- "ACOG continues to stand by our breast cancer screening recommendations, which provide for annual mammograms beginning at age 40. Evidence and experience have shown that early detection can lead to improved outcomes in women diagnosed with breast cancer."

# RECOMMENDATIONS – WHERE ARE WE NOW?

**USPSTF – 2016**

- The USPSTF recommends biennial screening mammography for women aged 50 to 74 years.
- The decision to start screening mammography in women prior to age 50 years should be an individual one.
- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women aged 75 years or older.

# WHY THE DIFFERENCES?

- USPSTF notes 50% increase in diagnosis of invasive plus noninvasive breast cancer since use of mammography – concern regarding over diagnosis. "Even with the conservative estimate of 1 in 8 breast cancer cases being overdiagnosed, for every woman who avoids a death from breast cancer through screening, 2 to 3 women will be treated."
- USPSTF also concerned with false-positive screening that results in further imaging and biopsies. Younger women are more likely to have a false-positive screening.
- The USPSTF found adequate evidence that mammography screening reduces breast cancer mortality in women aged 40 to 74 years. The number of breast cancer deaths averted increases with age; women aged 40 to 49 years benefit the least and women aged 60 to 69 years benefit the most.

# ADDING TO THE CONFUSION….

**Tailoring Breast Cancer Screening Intervals by Breast Density and Risk for Women Aged 50 Years or Older: Collaborative Modeling of Screening Outcomes**

Collaborative simulation modeling using national incidence, breast density, and screening

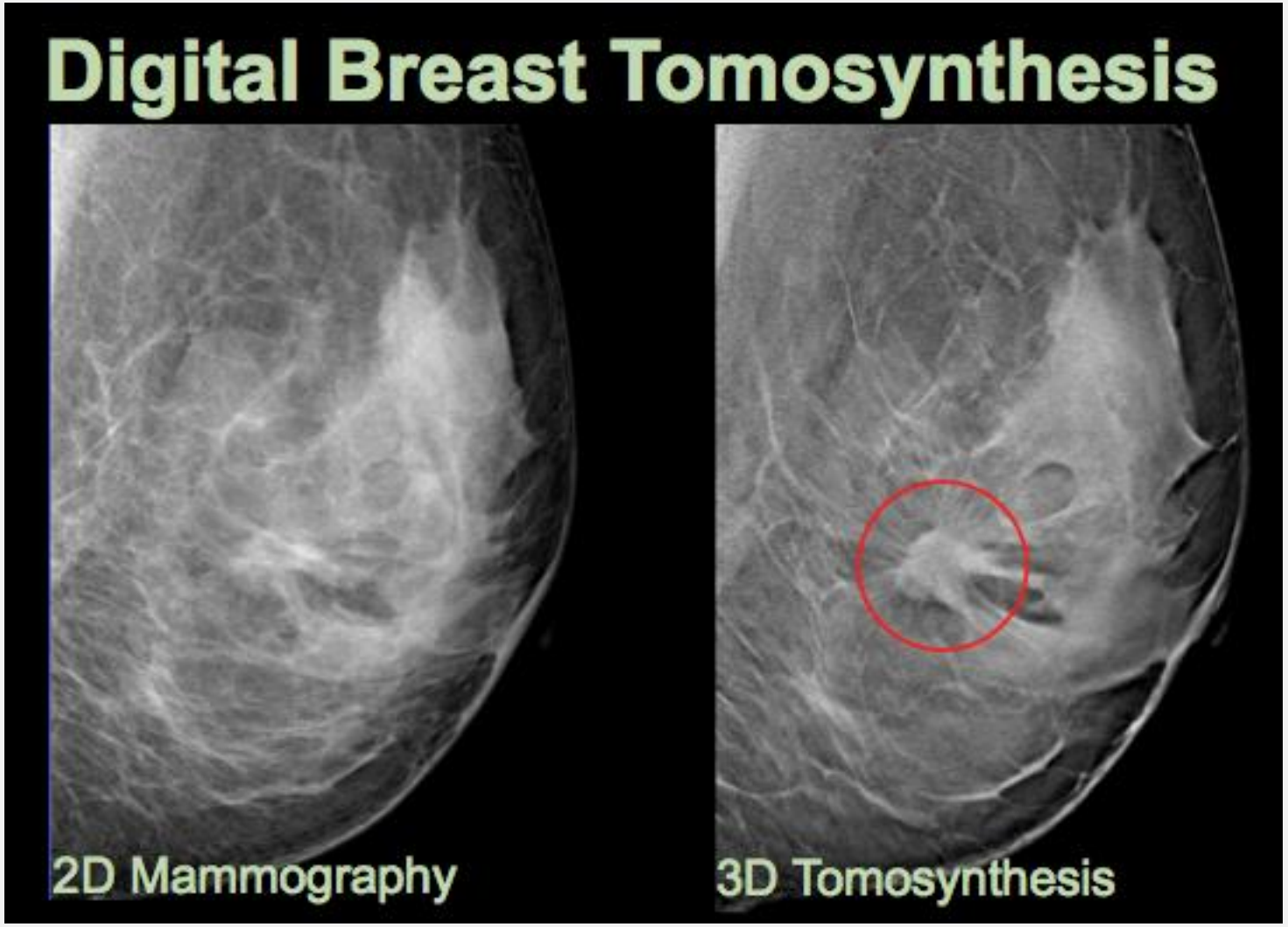
- **Results:** Screening benefits and overdiagnosis increase with breast density and RR. False-positive mammograms and benign results on biopsy decrease with increasing risk. Among women with fatty breasts or scattered fibroglandular density and an RR of 1.0 or 1.3, breast cancer deaths averted were similar for triennial versus biennial screening for both age groups (50 to 74 years, median of 3.4 to 5.1 vs. 4.1 to 6.5 deaths averted; 65 to 74 years, median of 1.5 to 2.1 vs. 1.8 to 2.6 deaths averted). Breast cancer deaths averted increased with annual versus biennial screening for women aged 50 to 74 years at all levels of breast density and an RR of 4.0, and those aged 65 to 74 years with heterogeneously or extremely dense breasts and an RR of 4.0. However, harms were almost 2-fold higher. Triennial screening for the average-risk subgroup and annual screening for the highest-risk subgroup cost less than $100 000 per QALY gained.

# WHAT DO WE DO?

- These organization recommendations are for average-risk women. It is crucial to do a complete evaluation of the patient to determine her risk status.
- Joint decision making with the patient.
- Must discuss potential benefits and weigh against potential risks.
- The decision is individual – a personal determination weighing the desire to potentially find an early cancer weighed against the possible harms that might occur as a result of screening.

# WHAT ABOUT 3D MAMMOGRAPHY? BREAST TOMOSYNTHESIS

- Digital tomosynthesis is a new kind of test that's trying to overcome some of the issues associated with traditional full-field traditional mammography – painful compression, overlapping tissue, 2D view.
- Tomosynthesis takes multiple X-ray pictures of each breast from many angles. The breast is positioned the same way it is in a conventional mammogram, but **only a little pressure is applied** — just enough to keep the breast in a stable position during the procedure. The X-ray tube moves in an arc around the breast while 11 images are taken during a 7-second examination. Then the information is sent to a computer, where it is assembled to produce clear, highly focused 3-dimensional images throughout the breast.


Digital Breast Tomosynthesis
2D Mammography
3D Tomosynthesis

# MORE ABOUT BREAST TOMOSYNTHESIS

- Was originally approved in combination with full-field mammography (2D) but in April 2016 there was approval for breast tomosynthesis (Siemans) as a stand alone test based on study that demonstrated increased rate of breast cancer detection with a 19% lower recall rate and a lower radiation dose than combined full-field and tomosynthesis.
- Current 95% of mammography units in the U.S. are full-field digital units.
- Some specialty facilities (e.g., Massachusetts General Hospital) routinely use a combination of full-field digital mammography and breast tomosynthesis.
- Based on current data, it may be that there will be a conversion to tomosynthesis from full-field digital mammography.

# USPSTF STATEMENT

- The USPSTF concludes that the current evidence is insufficient to assess the benefits and harms of digital breast tomosynthesis (DBT) as a primary screening method for breast cancer.

# WHAT ABOUT WOMEN WITH DENSE BREASTS?

- The American College of Radiology changed its reporting category for dense breasts in 2014. Previously was based on quantification of density by percentage.
  - The breasts are almost entirely fatty
  - There are scattered areas of fibroglandular density
  - The breasts are heterogeneously dense, which may obscure small masses
  - The breasts are extremely dense, which lowers the sensitivity of mammography.

Breast density not only decreases the sensitivity of mammography but is also a risk factor in itself for breast cancer.

Breast density if a subjective determination (observer-to-observer variability).

# WHAT ARE THE STATISTICS?

**Table 1.** BI-RADS Breast Density Categories, Demographics, Sensitivity of Cancer Detection, and Breast Cancer Risk ⇦

| BI-RADS Category | Description | Percentage of Population* | Sensitivity† (%) | Relative Risk of Breast Cancer‡ |
|---|---|---|---|---|
| 1 | Almost entirely fat | 10 | 88 | --- |
| 2 | Scattered fibroglandular densities | 43 | 82 | --- |
| 3 | Heterogeneously dense | 39 | 69 | 1.2 (compared with average breast density) |
| 4 | Extremely dense | 8 | 62 | 2.1 (compared with average breast density) |

Abbreviation: BI-RADS, Breast Imaging Reporting and Data System.

# LEGISLATION REGARDING NOTIFICATION OF DENSE BREASTS

# SUPPLEMENTAL SCREENING

- Ultrasound
  - Physician-performed
  - Technician performed
  - Automated
- Tomosynthesis (3D mammogram)
- MRI
- PET scan

# ULTRASOUND FOR SUPPLEMENTAL SCREENING

- Physician performed is not practical from a man-power standpoint.
- Technician-performed ultrasound is an option but there is no standardized training for technicians for scanning and documentation.
- Automated ultrasound is an option although not readily available. It also potentially produces thousands on images in a bilateral examination, thereby substantially increasing the interpretation time for the radiologist.
- Specificity is low, however.

"When performed by physicians, U/S produces consistent increased detection of an average of four cancers per 1,000 women screened. More than 85% of cancers detected only on screening U/S are invasive and node negative."

"For women with dense breasts given the choice of U/S or tomosynthesis, ultrasound shows more cancers."

# MRI FOR SUPPLEMENTAL SCREENING

- American Cancer Society recommends against MRI for women with lifetime breast cancer risk <15%.
- **There is insufficient evidence to recommend for or against breast MRI for women with moderately elevated risk (15-20%) risk such as women with dense breasts.**
- Women at high risk for breast cancer should have annual mammography with MRI.

# AMERICAN COLLEGE OF RADIOLOGY

**Variant 2: Intermediate-risk women: women with personal history of breast cancer, lobular neoplasia, atypical ductal hyperplasia, dense breasts, or 15% to 20% lifetime risk of breast cancer.**

| Radiologic Procedure | Rating | Comments | RRL* |
|---|---|---|---|
| Mammography screening | 9 | | ☢☢ |
| MRI breast without and with contrast | 7 | See statement regarding contrast in text under "Anticipated Exceptions." | O |
| US breast | 5 | | O |
| FDG-PEM | 2 | | ☢☢☢☢ |
| Tc-99m sestamibi BSGI | 2 | | ☢☢☢☢ |
| MRI breast without contrast | 1 | | O |
| Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate | | | *Relative Radiation Level |

"Supplemental screening with U/S for women with intermediate risk and dense breasts is an option. However, hand-held US screening by the radiologist has a high false-positive rate and is time-consuming. Therefore, this is likely not a cost-effective practice."

# TOMOSYNTHESIS FOR SUPPLEMENTAL SCREENING

- The Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts' interim analysis shows that ultrasound has better incremental BC detection than tomosynthesis in mammography-negative dense breasts at a similar FP-recall rate. However, future application of adjunct screening should consider that tomosynthesis detected more than 50% of the additional BCs in these women and could potentially be the primary screening modality.
- Methods that improve detection of node-negative invasive cancer should benefit women; a reduction in interval cancers has been shown for screening US, and a reduction in late-stage disease and improved metastasis-free survival has been shown for MRI. For tomosynthesis, the benefits are likely more modest. For women with dense breasts given the choice of US or tomosynthesis, US shows more cancers.

# USPSTF STATEMENT

- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adjunctive screening for breast cancer using breast ultrasonography, magnetic resonance imaging, DBT, or other methods in women identified to have dense breasts on an otherwise negative screening mammogram.

# THE DILEMMA OF SUPPLEMENTAL SCREENING

- The American College of Obstetricians and Gynecologists (the College) does not recommend routine use of alternative or adjunctive tests to screening mammography in women with dense breasts who are asymptomatic and have no additional *risk factors*. The College strongly supports additional research to identify more effective screening methods that will enhance meaningful improvements in cancer outcomes for women with dense breasts and minimize false-positive screening results. The College recommends that health care providers comply with state laws that may require disclosure to women of their breast density as recorded in a mammogram report.

# USING RISK TO DETERMINE WHETHER TO ORDER SUPPLEMENTAL SCREENING

Breast Cancer Surveillance Consortium studied 365,426 women

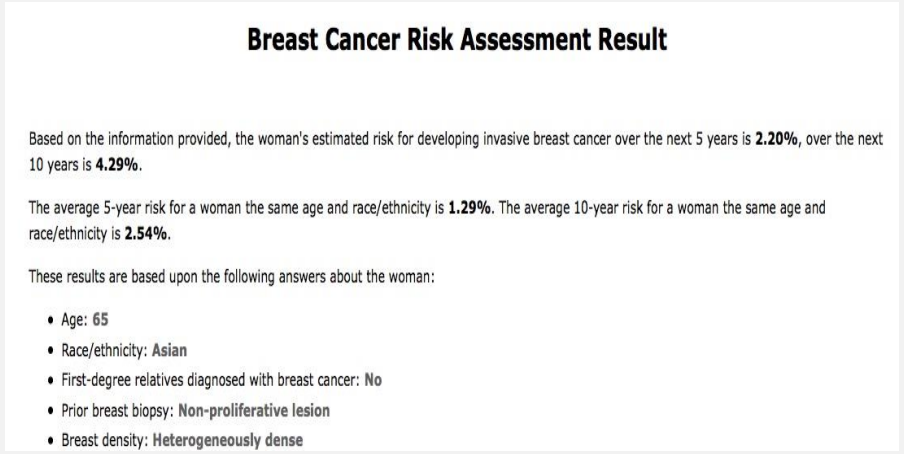
- Breast density should not be the sole criterion for deciding whether supplemental imaging is justified because not all women with dense breasts have high interval cancer rates. BCSC 5-year risk combined with BI-RADS breast density can identify women at high risk for interval cancer to inform patient-provider discussions about alternative screening strategies.
  - Age
  - Race/ethnicity
  - Family History (first-degree relative)
  - History of breast biopsy
  - BI-RADS breast density

# BCSC RESULTS

- Approximately 47 percent of women in the study had dense breasts. Among women with dense breasts, the risk of developing an interval cancer was greatest in those with extremely dense breasts (at least 75% of breast tissue is dense) and a 5-year risk of 1.67% or more and in those with heterogeneously dense breasts (more than half of the tissue in their breasts is dense) and a 5-year risk of 2.5% or more.
- Only 24% of women with dense breasts were at the high risk of an interval cancer based on the BCSC risk model and thus were the best candidates for discussion of additional or alternative screening,

# HOW DO WE USE THIS INFORMATION?

## BIOPSY



**Breast Cancer Risk Assessment Result**

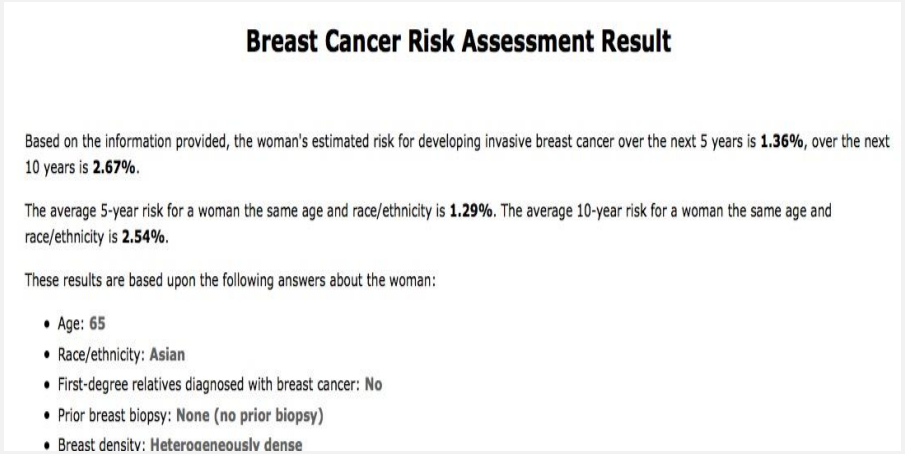
Based on the information provided, the woman's estimated risk for developing invasive breast cancer over the next 5 years is **2.20%**, over the next 10 years is **4.29%**.

The average 5-year risk for a woman the same age and race/ethnicity is **1.29%**. The average 10-year risk for a woman the same age and race/ethnicity is **2.54%**.

These results are based upon the following answers about the woman:

- Age: **65**
- Race/ethnicity: **Asian**
- First-degree relatives diagnosed with breast cancer: **No**
- Prior breast biopsy: **Non-proliferative lesion**
- Breast density: **Heterogeneously dense**

## NO BIOPSY



**Breast Cancer Risk Assessment Result**

Based on the information provided, the woman's estimated risk for developing invasive breast cancer over the next 5 years is **1.36%**, over the next 10 years is **2.67%**.

The average 5-year risk for a woman the same age and race/ethnicity is **1.29%**. The average 10-year risk for a woman the same age and race/ethnicity is **2.54%**.

These results are based upon the following answers about the woman:

- Age: **65**
- Race/ethnicity: **Asian**
- First-degree relatives diagnosed with breast cancer: **No**
- Prior breast biopsy: **None (no prior biopsy)**
- Breast density: **Heterogeneously dense**

# SOY AND WOMEN'S HEALTH

# SOY AND ISOFLAVONES

- Isoflavones are a group of phytoestrogens that includes genistein, daidzein and glycitein
- Weak estrogen effects but also can attach to estrogen receptors thus preventing stronger endogenous estrogen from having access to receptors

If isoflavones have estrogenic activity, do they increase the risk of developing breast cancer? Do they increase the risk of recurrence in women who have had breast cancer?

# PRIMARY BREAST CANCER

| Outcome | Type of study | Population | Comparison groups (highest vs lowest dietary intake of soy) | Result (95% confidence interval) |
|---|---|---|---|---|
| Primary breast cancer incidence | Systematic review with 7 prospective cohort studies[1] | Western and Asian women (N=~170,000) | Highest vs lowest dietary intake of soy isoflavone, soy foods/products, or measured isoflavone levels | No overall difference in risk |
| | 2 prospective cohort studies[2] | American and Dutch postmenopausal women (N=50,500) | Highest vs lowest soy isoflavone intake and soy supplementation vs no supplement | No overall difference in risk in either study |
| | 1 prospective cohort study[3] | Japanese women (N=30,454) | Highest vs lowest tertile, soy food intake | No overall difference in risk |
| | 2 prospective cohort studies[4] | Chinese women (N=1800) | Highest vs lowest soy food intake | No overall difference in risk |
| | 1 prospective cohort study[5] | American and Japanese women (N=178,000) | Highest vs lowest soy food intake (tofu and miso) | No overall difference in risk |

# WHAT ELSE DO WE KNOW?

- There are studies and meta-analyses that show that high soy intake in childhood and adolescence is associated with a lower risk of breast cancer. Studies are primarily in Asian women.
- Benefit of high, early soy intake is seen in post-menopausal women, with no difference in premenopausal women.
- Soy does not increase breast density.

# RECURRENT BREAST CANCER

| | | | | |
|---|---|---|---|---|
| Breast cancer recurrence and breast cancer-related mortality | Meta-analysis of 5 prospective cohort studies[6] | Chinese and American women with prior diagnosis of breast cancer (N=11,206) | **Soy protein intake**<br>>13 g/d vs <2 g/d<br>**Soy isoflavones**<br>>17 mg/d vs <7.6 mg/d | **Overall**<br>Highest vs lowest dietary soy intake (pooled)<br>Recurrence: HR=0.79 (0.72–0.87); mortality: HR=0.85 (0.77–0.93)<br>**Estrogen receptor positive**<br>Highest vs lowest soy intake<br>Recurrence: HR=0.81 (0.63–1.04); mortality: HR=0.72 (0.61–0.84)*<br>**Estrogen receptor negative**<br>Highest vs lowest<br>Recurrence: HR=0.64 (0.44–0.94);* mortality: HR=0.75 (0.64–0.88)* |

# PREGNANCY AND FUTURE HEALTH CONSIDERATIONS

# GESTATIONAL DIABETES

**Gestational diabetes – increased risk for developing diabetes later in life**

**Recommendations:**

- An oral glucose tolerance test (OGTT) is recommended at the 6- to 12-week postpartum visit
- Test women with GDM every 1-3 years if her 6- to 12-wk OGTT is normal
- The frequency of screening is based on the presence of risk factors: family history, pre-pregnancy BMI, or need for insulin or OAD medications during pregnancy
- Ongoing screening may be done with any glycemic test (A1C, fasting plasma glucose, OGTT) using nonpregnancy cut points

# CARDIOVASCULAR DISEASE RISK

- Preeclampsia has been associated with increased cardiovascular risk in later life. The AHA recommends that a history of preeclampsia be incorporated into the cardiovascular risk factor assessment for women.
- New large cohort study also found increased risk associated with gestational hypertension (accounted for 50.8% of all hypertensive disease of pregnancy).
  - Death from diabetes (adjusted HR, 2.8; 95% confidence interval, 2.2-3.6)
  - Ischemic heart disease (adjusted HR, 2.2; 95% CI, 1.9-2.6)
  - Stroke (adjusted HR, 1.9; 95% CI, 1.5-2.3)

# TAKE HOME MESSAGE

- Don’t forget to ask about pregnancy-related problems
- Test women with a history of gestational diabetes at the intervals suggested and encourage life style modifications. Early counseling is key.
- Pre-eclampsia is a cardiovascular disease risk factor. Gestational hypertension should be considered as a possible risk factor as well. These women should also have early counseling regarding lifestyle modification, as well as aggressive management of other risk factors (possibly consideration of statin therapy at a lower 10-year risk level).