ADVANCES IN WOMEN’S HEALTH: A CRITICAL REVIEW OF THE YEAR’S MOST IMPORTANT PAPERS

Judith Walsh, MD, MPH
Professor of Medicine
Division of General Internal Medicine
UCSF Women’s Health Center of Excellence

BACKGROUND
• Annual Update in Women’s Health for Society of General Internal Medicine
• Collaborators
  • Eleanor Schwartz, MD,MS, UC Davis
  • Kay Johnson, MD,MPH, University of Washington
  • Pelin Batur, MD, Cleveland Clinic

PLAN FOR TODAY…
• Review some of the most significant published advances in the Women's Health medical literature over the past year
  • Top articles
  • Key articles
  • Guidelines
• Assess the strength and scope of the evidence presented in the selected literature
• Apply this new information to our clinical practice
  • Take-home points

HOW WERE ARTICLES CHOSEN?
• Systematic review of 15 top journals in General Internal Medicine and Women’s Health from March 2015–February 2016
  Articles chosen had to fulfill criteria:
  • How new/innovative is this information?
  • Strength of the evidence?
  • How will it change my practice?
  • NOT covered elsewhere
TOPICS FOR TODAY

- Breast Cancer Prevention
- UTIs
- Vitamin D and Bone Health
- Cervical Cancer Screening
- Ovarian Cancer Screening and Prevention

BREAST CANCER PREVENTION

CASE

A 39 year old woman is very worried about her risk of breast cancer. Her mother and sister both had breast cancer; her sister tested negative for a known gene mutation. Using an online breast cancer risk calculator, you estimate her 5 year risk of breast cancer to be 3%.

Is she a candidate for chemoprophylaxis to decrease her breast cancer risk?

A. Yes
B. No
C. Maybe

BACKGROUND

- Four RCTs have shown that tamoxifen can reduce the risk of breast cancer in women at increased risk in the first 10 years of follow up
- Infrequently prescribed
- Limitations and surprising results of the first International Breast Cancer Intervention Study (IBIS) report
  - Increased deaths, though not statistically significant
THE NEWS

• Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial
  • Cuzick et al. Lancet Oncol 2015;16:67-75

• Objectives
  • Long-term follow-up after tamoxifen treatment to determine impact on occurrence and mortality of invasive breast cancer and DCIS

METHODS

• N=7154 women aged 35-70
• Blindly randomized to oral tamoxifen 20 mg daily vs placebo for 5 years
• Inclusion criteria
  • Aged 45-70: ≥2x risk
  • Aged 35-44: >2x risk
• Exclusions: h/o DVT, PE, desired pregnancy, h/o cancer

RESULTS

• Median follow up 16 years. 74% still masked to assignment
• Placebo group: 9.8% of women developed breast cancer
• Tamoxifen group: 7% of women
• Hazard ratio 0.71 (p<0.0001)
• HR is the same for the first ten years and 10+ years
• Women receiving HT had less benefit
• Hot flashes during active treatment
• DVTs OR 1.73 (increased during first 10 years only)
• Endometrial cancer during active treatment only (2.5 excess cases per thousand women)

CONCLUSIONS

• Tamoxifen x 5 years offers a very long period of protection, substantially improving the benefit-to-harm ratio
• NNT 22 to prevent one case of breast cancer in 20 years
• NNT 29 to prevent one case of estrogen receptor positive invasive breast cancer in 20 years
• No difference in breast cancer mortality (underpowered)
TAKE-HOME

- Women with extremely high risk (BRCA1 or BRCA2 gene mutations or other familial syndrome) should be counseled on prophylactic mastectomy
- USPSTF 2013 (B recommendation): For women at increased risk of breast cancer and low risk for adverse medication effects, clinicians should offer tamoxifen or raloxifene

CASE

A 39 year old woman is very worried about her risk of breast cancer. Her mother and sister both had breast cancer; her sister tested negative for a known gene mutation. Using an online breast cancer risk calculator, you estimate her 5 year risk of breast cancer to be 3%.

Is she a candidate for chemoprophylaxis to decrease her breast cancer risk?

A. Yes
B. No
C. Maybe – refer to genetic counselor/high risk breast clinic

CASE

Nellie natural is here for her annual visit. She mentions mild UTI symptoms for 4 days. UA is + for LE and nitrites. She's not a fan of medications, tends to prefer “natural supplements”, and asks you if antibiotics are truly necessary. You tell her:

A. Antibiotics may lower her risk of pyelonephritis
B. She can try ibuprofen 400 tid instead of an antibiotic
C. More than 2/3 of typical UTIs resolve on their own
D. All of the above
THE NEWS

• Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial.
  • Objective:
    Can uncomplicated UTI be treated with ibuprofen to reduce antibiotic prescriptions without a significant increase in symptoms, recurrences, or complications?

METHODS

• Study Design:
  • Double blind randomized multicenter trial of 42 GPs in Germany
• Intervention:
  • 779 women, up to age 65, with suspected UTI randomized
    • Fosfomycin 3 g sachet x 1 day or
    • Ibuprofen 400 tid x 3 days
• Women scored their daily symptoms and activity impairment
• Safety data collected q 6mo, between 2012-2014
• Inclusion criteria:
  • Dysuria, frequency, urgency, +/- lower abdominal pain
• Exclusion criteria:
  • Fever, “flank” tenderness
  • Pregnancy, renal disease
  • UTI within 2 wks
  • Urinary catheterization
  • Contraindication to NSAIDs

RESULTS:

<table>
<thead>
<tr>
<th>Selected outcome</th>
<th>Ibuprofen (n=241)</th>
<th>Fosfomycin (n=243)</th>
<th>88.665% (58.8-74.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courses of antibiotic within 28d</td>
<td>81</td>
<td>277</td>
<td></td>
</tr>
<tr>
<td>Mean duration of symptoms</td>
<td>5.6 days</td>
<td>4.6 days</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>% Patients symptoms–free at day 7</td>
<td>70%</td>
<td>82%</td>
<td>P=0.004</td>
</tr>
<tr>
<td>% Patients with recurrence of UTI (d 15-28)</td>
<td>6%</td>
<td>11%</td>
<td>P=0.049</td>
</tr>
<tr>
<td>Number of patients with pyelonephritis</td>
<td>5</td>
<td>1</td>
<td>P=0.12</td>
</tr>
<tr>
<td>Number of patients with GI symptoms</td>
<td>6</td>
<td>15</td>
<td>NS</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• Women with mild to moderate symptoms may benefit
• Nonparticipants had higher symptom scores

Reminder:
Treatment of asymptomatic bacteruria not recommended. 2015 Cochrane review showed no benefit of antibiotics to prevent:
• symptomatic UTI
• complications
• death

TAKE-HOME

- Nellie can try ibuprofen for her UTI. She should be counseled to call if her symptoms persist, and to watch for possible pyelonephritis.
  - Two-thirds of UTIs resolved on their own
- Women who take ibuprofen are more likely to need additional antibiotic therapy, but still less likely to receive antibiotics overall.

VITAMIN D AND BONE HEALTH

CASE

Frances fragile is a 67 year old woman who has just come in to establish care with you. She has never had a DXA scan and you order one. You are on your way out the door when she asks whether or not you are going to check her vitamin D level. Her sister told her that she is supposed to have a level of 30 ng/ml. What do you say?

A. Of course. We should check Vitamin D levels in everyone
B. No. Just be sure you are taking a Vitamin D supplement of 800 IU a day.
C. We will check your Vitamin D level if your DXA scan shows osteoporosis.
D. I don't know. What do you want to do?

BACKGROUND

- Low Vitamin D levels contribute to osteoporosis
- The optimal Vitamin D level for skeletal health is debated
  - >30 ng/ml recommended by some
  - >20 ng/ml recommended by IOM
- Using a definition of Vitamin D deficiency of <30ng/ml, 75% of postmenopausal women would be deficient
- Determining the optimal level of 25 (OH) D for bone health and optimal calcium homeostasis is important
THE NEWS

- "Treatment of Vitamin D Insufficiency in Postmenopausal Women: A Randomized Controlled Trial"
- Objectives
  - To evaluate the impact of low dose and high dose cholecalciferol compared with placebo in postmenopausal women with Vitamin D deficiency on the following outcomes:
    - Changes in fractional calcium absorption,
    - Bone mineral density and muscle mass
    - Timed Up and Go tests and five sit to stand tests
    - Functional status and physical activity

METHODS

- Single center randomized double blind controlled trial
- Participants:
  - 230 postmenopausal women without osteoporosis
  - 75 years or younger
  - Baseline Vitamin D levels 14-27 ng/dl
- Intervention:
  - 800 IU Vitamin D3 daily
  - 50,000 IU Vitamin D3 twice a month
  - Achieved and maintained Vitamin D levels ≥30 ng/dl
- Placebo
- Outcomes measured at 1 year

RESULTS

- Calcium absorption (change from baseline):
  - Increased by 1% in the high dose arm (10 mg/day)
  - Decreased by 2% in low dose arm (P=0.005 low vs high dose)
  - Decreased by 1.3% in placebo arm (P=0.03 placebo vs high dose)
- BMD or muscle mass scores:
  - No between arm differences in any comparisons
  - Timed Up and Go or five sit to stand tests
  - No between arm differences in any comparisons
- ALSO NO differences in:
  - number of falls
  - number of people who fell
  - functional status
  - physical activity

CONCLUSIONS

- Although high dose cholecalciferol therapy increased calcium absorption, there was no impact on bone density or other clinically important outcomes.
- Low and high dose cholecalciferol were equivalent to placebo with respect to effects on bone and muscle outcomes.
TAKE-HOME
• No evidence supports recommendations for maintaining serum 25 (OH) levels >30 ng/ml
• Back to Frances
  A. Of course. We should check Vitamin D levels in everyone
  B. No. Just be sure you are taking a Vitamin D supplement of 800 IU a day.
  C. We will check your Vitamin D level if your DXA scan shows osteoporosis.
  D. I don’t know. What do you want to do?

BACK TO FRANCES
• You tell Frances that there is no evidence that a Vitamin D level of >30 ng/ml is necessary for bone health, but she wants to know if there any other benefits to Vitamin D supplementation that she should know about.

VITAMIN D AND FUNCTIONAL DECLINE?
• RCT conducted in Switzerland
  • 200 men and women ≥70 with prior fall
  • Three groups received monthly treatment
    • 24,000 IU Vit D3
    • 60,000 IU Vit D3
    • 24,000 Vit D3 plus 300mcg calcifediol
  • Outcomes
    • Higher doses were more likely to result in 25-OH D ≥30 ng/ml
    • No impact on lower extremity function
    • More falls in the higher dose groups
  • Bischoff-Ferrari et al JAMA Int Med 2016

EXERCISE, VITAMIN D AND FALL PREVENTION
• Two year RCT of exercise and Vitamin D supplementation in Finland
• Four groups:
  • Vitamin D 800 IU without exercise
  • Vitamin D 800 IU with exercise
  • Placebo and exercise
  • Placebo and no exercise
• Outcomes: monthly reported falls, injurious falls, number of fallers and injured fallers
• Neither Vitamin D nor exercise reduced rate of falls
• Rate of injurious falls significantly decreased with strength/balance/exercise training
  • Uusi-Rasi K et al JAMA Int Med 2015
CASE: MS. FRAGILE, CONTINUED

- On further questioning, Ms. Fragile tells you that she has been taking calcium supplements for years because she is very concerned about osteoporosis. Recently, she has heard that calcium supplements might actually be bad for her and that she might be better off getting all her calcium from her diet.
- She wants to know what you recommend.

BACKGROUND

- Calcium supplementation has been widely recommended for bone health
- Clinical trials of calcium supplementation of 1000 mg/day have suggested an increase in cardiovascular events, kidney stones and GI symptoms
- Current recommendations often focus on telling patients to increase calcium intake through diet rather than supplements
  - Assumption that this increases calcium intake to recommended goals without the adverse effects of supplements

THE NEWS

- “Calcium intake and risk of fracture: systematic review”
  - Boland et al. BMJ, 2015
  - Objectives:
    - To evaluate the evidence underlying recommendations to increase calcium intake through diet or calcium supplements in order to prevent fracture

METHODS

- Systematic review
- RCTs in adults >50 at baseline with endpoint of fracture
- Cohort studies where most follow-up occurred in participants >50 years
- Studies where calcium was given with another treatment assuming treatment was given in both arms
- Included studies with calcium and Vitamin D co-administered
- Dietary calcium included milk, dairy, dietary intake from food and hydroxyapatite
- Meta-analyses with random effects and assessed for heterogeneity
RESULTS: DIETARY CALCIUM

- Two RCTS and 44 cohort studies assessed relationship between dietary calcium (n=37), milk (n=14), or dairy intake (n=8) and fracture outcomes
- Dietary calcium: most studies showed no association with fracture
  - 14/22 for total
  - 17/21 for hip
  - 7/8 for vertebral
  - 5/7 for forearm
- Milk and dairy intake: most studies showed no association with fracture
  - 25/28 milk
  - 11/13 dairy
- Too few trials to calculate summary estimate

RESULTS: CALCIUM SUPPLEMENTS

- 26 RCTS reported fracture outcomes
  - 14 calcium only
  - 8 Ca/D
- 20 trials used a dose of ≥1,000 mg of calcium
- Fracture reduction
  - Reduced risk of total fracture (RR 0.89; 95% C.I. 0.81-0.96)
  - Reduced risk of vertebral fracture (0.87; 95% C.I. 0.74-1.00)
- Funnel plot inspection suggested bias toward calcium supplements
- Studies with lowest risk of bias showed no effect on fracture

CONCLUSION

- Dietary calcium is not associated with fracture risk
- There is no clinical trial evidence that dietary calcium reduces fracture risk
- Some evidence that calcium supplementation reduces fracture risk but evidence is inconsistent

CALCIUM INTAKE AND BONE MINERAL DENSITY

- Meta-analysis of the impact of dietary or supplemental calcium on BMD
  - Tai et al BMJ 2015
- 59 eligible RCTs
  - 15 dietary calcium
  - 51 supplemental calcium
- Increasing calcium intake from dietary sources increased BMD
  - 0.6-1.0% at total hip and total body at one year
  - 0.7-1.8% at these sites at two years
- Calcium supplements increased BMD similarly
  - BMD increases similar for dietary and supplemental calcium and for Ca/D
  - Dietary and supplemental calcium lead to small nonprogressive increases in BMD-clinical significance is unclear
IMPACT FOR PRACTICE

- Dietary and supplemental calcium lead to small increases in BMD
- There is no clinical trial evidence that dietary calcium reduces fracture risk
  - Dietary studies have challenges
- The evidence for calcium supplements and fracture reduction is mixed
- There is no evidence that dietary calcium is more effective than supplemental calcium

CERVICAL CANCER SCREENING

Dramatic reduction in mortality with routine cervical cancer screening
- HPV is the causative agent in the majority of cases of cervical cancer
- Long latency period for development of cervical cancer
- Many lesions will regress on their own

QUESTION

Henrietta Peevey is a 35 year old woman who has always had normal pap smears. She has recently read about a “new and improved test” for cervical cancer which involves HPV instead of a conventional pap smear and she wants to know whether or not she should have it. What do you recommend?

A. Conventional cytology
B. HPV testing
C. Conventional cytology and HPV testing
D. Any of these are recommended options
“IN THE OLD DAYS”

- Annual Pap smear from now until forever
- Guidelines for screening less frequently have been in place for over 20 years

“IMPROVEMENTS” ON PAP TESTING

- Liquid Based Cytology
  - Initially touted as “better” than Pap tests
  - Similar test characteristics but allows for reflex HPV testing
- HPV testing
  - HPV types 16 and 18 major causative agents

CERVICAL CANCER SCREENING GUIDELINES

<table>
<thead>
<tr>
<th>USPSTF 2012</th>
<th>ACS/American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Joint Guidelines 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear every 3 years in women aged 21-65</td>
<td>Pap smear every 3 years in women aged 21-65 Pap plus HPV testing is the preferred method Pap every 3 years is acceptable</td>
</tr>
<tr>
<td>For women aged 30-65 who want to lengthen the screening interval, screen with a combination of cervical cytology and HPV testing every 5 years</td>
<td>For women aged 30-65 Pap plus HPV testing is the preferred method Pap every 3 years is acceptable</td>
</tr>
<tr>
<td>Discontinue in women over the age of 65 in whom smears have been consistently normal</td>
<td>Discontinue in women over the age of 65 in whom smears have been consistently normal Continue to screen women diagnosed with cervical pre-cancer</td>
</tr>
<tr>
<td>No HPV screening in women younger than 30</td>
<td>No HPV testing in women less than age 30 unless needed after an abnormal test result</td>
</tr>
<tr>
<td>No screening in women who have had a hysterectomy</td>
<td>No screening in women who have had a hysterectomy and have no history of cervical cancer or pre-cancer</td>
</tr>
</tbody>
</table>

HPV PRIMARY SCREENING?

- ATHENA trial evaluated HPV test as primary screen for cervical cancer in women ≥25 years old
- HPV alone detected more cases of CIN3+ but required more colposcopies
- Promising but not currently recommended as a primary screening test
  - ATHENA, 2015
THE NEWS

Use of Primary High-Risk Human Papillomavirus Testing for Cervical Cancer Screening: Interim Clinical Guidelines

- Sponsored by the Society of Gynecologic Oncology and ASCCP
- Representatives also from ACOG, ACS, ASC, CAP, ASCP

INTERIM GUIDELINES

- Primary hrHPV screening
  - Can be considered as an alternative to current U.S. cytology-based cervical cancer screening methods
  - Should occur *no sooner* than every 3 years
  - Should not be initiated before 25 years of age
  - Panel had concerns about harms
    *Progression to cancer is uncommon, and detection of most of the disease found in the 25-29 year age group can be safely deferred until age 30 and older.*
  - Based on limited evidence, this triage approach appears reasonable:

Recommended primary HPV screening algorithm

SCREENING GUIDELINES

- These interim guidelines have not been broadly adopted
  - USPSTF, ACS guidelines remain unchanged
- ACOG 2016
  - For women aged 30 and over, co-testing is the preferred screening strategy
  - Primary cytology is an option
  - Primary HPV testing can be considered for women ≥25 while acknowledging that cytology alone or co-testing "remain the options specifically recommended in most major society guidelines"
Henrietta Peevey is a 35-year-old woman who has always had normal pap smears. She has recently read about a "new and improved test" for cervical cancer which involves HPV instead of a conventional pap smear and she wants to know whether or not she should have it. What do you recommend?

A. Conventional cytology  
B. HPV testing  
C. Conventional cytology and HPV testing  
D. Any of these are recommended options  
   • However HPV alone is not broadly endorsed

HENRIETTA

• You perform Henrietta’s Pap with HPV co-testing. She recalls that in the past you have done a bimanual examination in order to "check her ovaries." She wants to know why you did not do that today.

SCREENING PELVIC EXAMINATION?

• A part of preventive health care for women for many years  
• Not needed for contraception or STD screening  
• What is the goal of a screening pelvic examination?

PELVIC EXAM AT THE WELL-WOMAN VISIT  
ACOG COMMITTEE OPINION 534;  
AUGUST 2012

• Women younger than 21 years  
  • Pelvic exam only when indicated by medical history  
  • Screen for GC, chlamydia with vaginal swab or urine  
• Women aged 21 years or older  
  • ACOG recommends an annual pelvic examination”  
    • No evidence supports or refutes routine exam if low risk  
    • If asymptomatic, pelvic exam should be a "shared decision”  
    • Individual risk factors, patient expectations, and medico-legal concerns may influence these decisions  
    • If TAH-BSO, decision “left to the patient” if asymptomatic
SCREENING PELVIC EXAMINATION: ACP EVIDENCE REPORT

- Review of 52 studies
- No evidence supporting the use of pelvic examination in asymptomatic average risk women
  - May cause pain, discomfort, fear, anxiety and embarrassment in about 30% of young women

ROUTINE PELVIC EXAMINATION?

- Diagnostic accuracy for detecting ovarian cancer or BV is low
- Rarely detects non-cervical cancer or other treatable conditions
- ACP recommends against performing screening pelvic examination in asymptomatic, non-pregnant adult women

USPSTF DRAFT RECOMMENDATIONS

- Draft evidence review for screening for gynecological conditions with the pelvic examination
- No studies assessing effectiveness of pelvic examination in reducing all cause mortality, cancer and disease specific morbidity and mortality or improving QOL
- Evaluated diagnostic accuracy and potential harms for ovarian cancer, bacterial vaginosis, trichomoniasis and genital herpes
  - Limited evidence to guide practice in asymptomatic primary care populations

- USPSTF Draft Recommendations, 2016

DOES HENRIETTA NEED A PELVIC EXAM?

- Clinicians who choose to perform pelvic examinations in asymptomatic women should be aware that there is uncertain benefit and there is the potential to cause harm through a positive test result and subsequent testing
CASE

Ana Lee comes to clinic requesting screening for ovarian cancer.

A friend recently forwarded her an email which reads: "Please tell all your female friends and relatives to insist on a CA-125 blood test every year as part of their annual exam. This is an inexpensive and simple blood test. Don't take 'No' for an answer. If I had known then what I know now, we would have caught my cancer much earlier before it was Stage 3!"

CLINICAL QUESTION

Do you order:
A. A serum CA-125
B. A transvaginal ultrasound
C. Testing for BrCA1
D. More teal ribbons
E. None of the above

BACKGROUND

- Ovarian cancer is most deadly of female reproductive cancers
- Each year, 22,000 US women diagnosed with ovarian cancer
- In 2011, the Prostate Lung Colorectal Ovarian (PLCO) Cancer Screening trial, reported no benefit of screening over 78,000 women followed for over a decade...
  - Was the study underpowered?
  - Would a "risk of ovarian cancer algorithm" that considered longitudinal changes in CA-125 be more useful??
THE NEWS

- “Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKTOCS): a randomized controlled trial”

- Objectives
  - To assess the impact of annual screening for ovarian cancer using transvaginal ultrasound with and without serum Ca-125 levels interpreted using a “risk of ovarian cancer algorithm” on:
    - Ovarian cancer mortality
    - Death due to ovarian or primary peritoneal cancer
    - Complications due to screening and false positives

METHODS

- 202,638 postmenopausal women aged 50–74
  - 27 primary care trusts in England, Wales, Ireland
  - No history of oophorectomy, ovarian cancer or other active cancer
- Randomized trial
  - 50% no screening
  - 25% annual transvaginal ultrasound
  - 25% annual transvaginal ultrasound + CA-125
    - Interpreted using the patented “Risk of Ovarian Cancer Algorithm”
- Outcomes committee was masked,
- Participants and their clinicians were not blinded
- Followed for 10-12 years (median 11.1 years)

RESULTS

- Ovarian cancer mortality? No difference
- Ovarian or primary peritoneal cancer mortality? No

<table>
<thead>
<tr>
<th>Per 100,000 woman years</th>
<th>Ovarian CA Incidence</th>
<th>False positive surgeries</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Screening</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>Annual US</td>
<td>57</td>
<td>500</td>
</tr>
<tr>
<td>Annual US +CA-125</td>
<td>62</td>
<td>140</td>
</tr>
</tbody>
</table>

IF excluded prevalent cases AND deaths in first 7 years…

Maybe?? But NNT>2000 for 10 years
BACK TO ANA LE

Do you order:
(a) A serum CA-125
(b) A transvaginal ultrasound
(c) Testing for BrCA1
(d) More teal ribbons
(e) None of the above

CONCLUSIONS

- Still no good way to screen for ovarian cancer
- Focus on Prevention
  - Anything that suppresses ovulation
    - Hormonal contraception
    - Pregnancy & Lactation

TAKE-HOME

- Consider tamoxifen or raloxifene in high risk women
- Two thirds of UTIS will resolve without treatment
- No evidence to support maintaining a Vitamin D level ≥ 30 mcg/dl
- No clear evidence that dietary calcium is “better than” supplemental calcium
- The primary recommended cervical cancer screening strategies are cytology alone or co-testing
- Clinicians who perform routine pelvic examination should be aware of the current evidence
- No evidence for using transvaginal US or CA-125 to screen for ovarian cancer

QUESTIONS?