RCT
Potential PURL Review Form
PURL Jam Version
PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

B. Link to PDF of full article: https://www.ncbi.nlm.nih.gov/pubmed/?term=28029926
C. First date published study available to readers: 12/29/2016
D. PubMed ID: 28029926
E. Nominated By: Jim Stevermer
F. Institutional Affiliation of Nominator: University of Missouri
G. Date Nominated: 1/13/2017
H. Identified Through: TOC
I. PURLs Editor Reviewing Nominated Potential PURL: Corey Lyon
J. Nomination Decision Date: 1/18/2017
K. Potential PURL Review Form (PPRF) Type: RCT
L. Assigned Potential PURL Reviewer: Greg Castelli
M. Reviewer Affiliation: UPMC St. Margaret

A. Abstract: Abstract
Background Reduced intake of n-3 long-chain polyunsaturated fatty acids (LCPUFAs) may be a contributing factor to the increasing prevalence of wheezing disorders. We assessed the effect of supplementation with n-3 LCPUFAs in pregnant women on the risk of persistent wheeze and asthma in their offspring. Methods We randomly assigned 736 pregnant women at 24 weeks of gestation to receive 2.4 g of n-3 LCPUFA (fish oil) or placebo (olive oil) per day. Their children formed the Copenhagen Prospective Studies on Asthma in Childhood2010 (COPSAC2010) cohort and were followed prospectively with extensive clinical phenotyping. Neither the investigators nor the participants were aware of group assignments during follow-up for the first 3 years of the children's lives, after which there was a 2-year follow-up period during which only the investigators were unaware of group assignments. The primary end point was persistent wheeze or asthma, and the secondary end points included lower respiratory tract infections, asthma exacerbations, eczema, and allergic sensitization. Results A total of 695 children were included in the trial, and 95.5% completed the 3-year, double-blind follow-up period. The risk of persistent wheeze or asthma in the treatment group was 16.9%, versus 23.7% in the control group (hazard ratio, 0.69; 95% confidence interval [CI], 0.49 to 0.97; P=0.035), corresponding to a relative reduction of 30.7%. Prespecified subgroup analyses suggested that the effect was strongest in the children of women whose blood levels of eicosapentaenoic acid and docosahexaenoic acid were in the lowest third of the trial population at randomization: 17.5% versus 34.1% (hazard ratio, 0.46; 95% CI, 0.25 to 0.83; P=0.011). Analyses of secondary end points showed that supplementation with n-3 LCPUFA was associated with a reduced risk of
infections of the lower respiratory tract (31.7% vs. 39.1%; hazard ratio, 0.75; 95% CI, 0.58 to 0.98; P=0.033), but there was no statistically significant association between supplementation and asthma exacerbations, eczema, or allergic sensitization. Conclusions Supplementation with n-3 LCPUFA in the third trimester of pregnancy reduced the absolute risk of persistent wheeze or asthma and infections of the lower respiratory tract in offspring by approximately 7 percentage points, or one third. (Funded by the Lundbeck Foundation and others; ClinicalTrials.gov number, NCT00798226 ).

B. Pending PURL Review Date: 5/2/2017

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

A. Number of patients starting each arm of the study?
346 in the treatment group and 349 in placebo

B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)
In this single-center, double-blind, placebo-controlled, parallel-group trial, pregnant women between 22 and 26 weeks of gestation were recruited into the Copenhagen Prospective Studies on Asthma in Childhood 2010 (COPSAC 2010) pregnancy cohort.11 Women taking more than 600 IU of vitamin D per day and women with any endocrine, heart, or kidney disorder were excluded. The trial was approved by the local ethics committee and the Danish Data Protection Agency. Both parents of each child provided oral and written informed consent before enrollment.

C. Intervention(s) being investigated?
2.4 g per day of n−3 LCPUFA (55% EPA and 37% DHA) in triacylglycerol form (Incroomega TG33/22, Croda Health Care)

D. Comparison treatment(s), placebo, or nothing?
placebo (in the form of olive oil, containing 72% n−9 oleic acid and 12% n−6 linoleic acid [Pharma-Tech A/S]).

E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)
5 years from birth. Endpoint: Persistent wheeze or asthma

F. What outcome measures are used? List all that assess effectiveness.
Persistent wheeze or asthma (the primary end point) was diagnosed on the basis of a previously described quantitative diagnostic algorithm20,21 that included diary recordings of five episodes of troublesome lung symptoms within the preceding 6 months, each lasting for at least 3 consecutive days; symptoms typical of asthma; the rescue use of inhaled beta2-agonist; and response to a 3-month course of inhaled glucocorticoids followed by relapse after the end of treatment.20 Remission was defined as a period of 12 months without relapse. The diagnosis was termed “persistent wheeze” until a child reached 3 years of age and was termed “asthma” thereafter.
Infection of the lower respiratory tract was defined as a diagnosis of pneumonia or bronchiolitis on the basis of symptoms and clinical presentation (i.e., without confirmation by means of pathogen identification or radiologic or laboratory findings).\textsuperscript{22-24} Allergic sensitization was determined at 6 months and 18 months as a wheal larger than 2 mm in response to any skin-prick test (ALK-Abelló) or a specific IgE level of 0.35 kU per liter or higher against milk, egg, dog, or cat allergens (ImmunoCAP tests, Thermo Fisher Scientific).\textsuperscript{11} Allergic rhinoconjunctivitis was diagnosed longitudinally by COPSAC pediatricians on the basis of systematic interviews and was defined as allergic rhinitis, allergic conjunctivitis, or both. Lung function at 5 years of age was assessed by means of spirometry, specific airway resistance by means of whole-body plethysmography, and the lung-clearance index by means of multiple-breath washout.\textsuperscript{11} A diagnosis of eczema was based on the criteria defined by Hanifin and Rajka.\textsuperscript{25-27}

G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.

During the prespecified, double-blind follow-up period, which covered children from birth to between 3 and 5 years of age, 136 of 695 children (19.6%) received a diagnosis of persistent wheeze or asthma, and this condition was associated with reduced lung function by 5 years of age, with parental asthma, and with a genetic risk of asthma (Table S4 in the Supplementary Appendix). The risk of persistent wheeze or asthma was 16.9% in the treatment group and 23.7% in the control group (hazard ratio, 0.69; 95% confidence interval [CI], 0.49 to 0.97; \( P=0.035 \)), with a relative reduction in risk of 30.7% (Table 1). The effect estimate and significance level remained largely unchanged in adjusted analyses (i.e., with adjustment for twin status, sex, supplementation with a high dose of vitamin D\textsubscript{3}, and EPA and DHA level before randomization) (Table S5 in the Supplementary Appendix).

The preventive effect of supplementation appeared to be driven primarily by children of mothers who had low blood levels of EPA and DHA at randomization (the lowest third of the trial population), for whom the risk of persistent wheeze or asthma was 17.5% in the treatment group as compared with 34.1% in the control group (hazard ratio, 0.46; 95% CI, 0.25 to 0.83; \( P=0.011 \)), corresponding to a relative reduction of 54.1% (Table 1).

There was no statistically significant interaction between supplementation with n−3 LCPUFA and high-dose vitamin D\textsubscript{3} with regard to persistent wheeze (\( P=0.065 \)). However, exploratory analyses stratified according to randomization to receive high-dose vitamin D\textsubscript{3} suggested that the strongest effect of n−3 LCPUFA supplementation occurred in children of mothers who did not receive high-dose vitamin D\textsubscript{3} supplementation (Table S6 in the Supplementary Appendix).

The number needed to treat to prevent a case of persistent wheeze or asthma was 14.6 among the...
entire cohort and 5.6 among women in the lowest third with regard to EPA and DHA levels before the intervention. The safety profiles for n−3 LCPUFA supplementation and olive oil appeared to be similar (Table S7 in the Supplementary Appendix).

During the continued follow-up period for children from birth to the age of 5 years, there was a reduced risk of persistent wheeze or asthma among the children in the treatment group as compared with the control group (Table 1 and Fig. 1 and 2). A similar difference in risk between groups was also found when statistical analyses were conducted in March 2016 that covered the period from birth to the ages of 5 to 7 years (mean age, 6.0 years) (Table 1).

H. What are the adverse effects of intervention compared with no intervention?
No significant differences between groups.

I. The study addresses an appropriate and clearly focused question.
(select one) Adequately addressed
Comments: Yes, does maternal use of EPA/DHA supplementation reduce asthma risk in children?

J. Random allocation to comparison groups:
(select one) Adequately addressed
Comments: Participants were randomized, but allocation concealment not addressed.

K. Concealed allocation to comparison groups:
(select one) Poorly addressed
Comments: No.

L. Subjects and investigators kept “blind” to comparison group allocation:
(select one) Well covered
Comments: Yes, investigators were unaware of treatment group through the child’s 5th birthday.

M. Comparison groups are similar at the start of the trial:
(select one) Poorly addressed
Comments: This was located in the supplementary appendix and may not be accessed by all readers.

N. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential sources of bias. (select one) Not applicable
Comments: included in supplementary appendix, but no differences found.

O. Were all relevant outcomes measured in a standardized, valid, and reliable way?
(select one) Adequately addressed
Comments: Yes.

P. Are patient oriented outcomes included? If yes, what are they?
Yes, the diagnosis of pediatric asthma.

Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?
>90% follow up at 5 years in both groups. 71% of patients had 80% adherence rates.

**R.** Was there an intention-to-treat analysis? If not, could this bias the results? How?

No. This is unlikely to bias results. Only a small number of patients were lost to follow-up.

**S.** If a multi-site study, are results comparable for all sites?

N/a.

**T.** Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?

No, funding was provided by Copenhagen Prospective Studies on Asthma in Childhood

**U.** To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.

It seemed like the most benefit was realized by patients with low levels of EPA/DHA before randomization.

**V.** In what care settings might the finding apply, or not apply?

Primary care, OB settings.

**W.** To which clinicians or policy makers might the finding be relevant?

Primary care, OB, pediatricians.

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**SECTION 3: Review of Secondary Literature**
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

**Citation Instructions:**
For up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert date modified if given.} Accesses February 12, 2009. [whatever date PPRF reviewer did their search.]

For DynaMed, use the following style:

**A.** DynaMed excerpts
Supplementation of omega-3 fatty acids, fish oil, and/or high fish consumption:

- fish oil supplementation in pregnancy not recommended currently as strategy to prevent childhood asthma \(^2\)
- supplementation in pregnancy not generally recommended due to lack of evidence of efficacy; current evidence consists of 4 trials finding no reduction in asthma or wheeze and 1 trial finding reduction in subgroup of women with low baseline eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) blood levels
  - **omega-3 long-chain polyunsaturated fatty acid supplementation during pregnancy may not reduce risk of asthma or wheeze in children** (level 2 [mid-level] evidence)
    - based on Cochrane review limited by clinical heterogeneity
    - systematic review of 8 randomized trials comparing prenatal and/or postnatal omega-3 long-chain polyunsaturated fatty acid (PUFA) supplementation vs. placebo or no supplementation (control) in 3,366 women and 3,175 children
    - 5 trials evaluated prenatal supplementation and 4 had data for development of allergy or asthma
    - results limited by heterogeneity in omega-3 PUFA regimen, duration of follow-up, and baseline risk of allergy
    - for prenatal omega-3 PUFA supplementation, no significant difference in medically diagnosed or parent-reported asthma or wheeze
      - at 6 months with initiation of regular fish consumption at 20 weeks gestation (risk ratio [RR] 1.26, 95% CI 0.54-2.94) in 1 trial with 83 high-risk children
      - at 12 months with DHA 2.07 g plus EPA 1.03 g per day starting at 20 weeks gestation (RR 0.36, 95% CI 0.08-1.67) in 1 trial with 83 high-risk children
      - at 36 months with DHA 800 mg plus EPA 100 mg per day starting at < 21 weeks gestation (RR 0.92, 95% CI 0.71-1.18) in 1 trial with 688 high-risk children
      - at age 16 years with DHA 0.92 g plus EPA 1.28 g per day starting at 30 weeks gestation (RR 0.58, 95% CI 0.25-1.35) in 1 trial with 528 children
    - no significant differences in maternal safety, early childhood infections, and fever
  - **fish oil supplementation during pregnancy may reduce risk of persistent wheeze or asthma in children in first 5 years of life** (level 2 [mid-level] evidence)
    - based on randomized trial with confidence interval including differences that may not be clinically important
    - 736 pregnant women at 24 weeks gestation were randomized to fish oil (n−3 long-chain polyunsaturated fatty acids) 2.4 g vs. olive oil (placebo) orally once daily until 1 week after delivery and were followed for 5 years
    - women taking vitamin D > 600 units/day or who had any endocrine, heart, or kidney disorders were excluded
    - 6% dropped out or were lost to follow-up and were excluded from analyses
    - comparing fish oil vs. olive oil in children aged 5 years
      - persistent wheeze or asthma in 17.4% vs. 24.6% (hazard ratio 0.68, 95% CI 0.49-0.95)
      - lower respiratory tract infection in 38.8% vs. 45.5% (hazard ratio 0.77, 95% CI 0.61-0.99)
    - no significant differences in asthma exacerbations or eczema at 6 and 18 months
    - in prespecified subgroup analyses by baseline EPA and DHA blood levels
      - fish oil associated with decreased risk of persistent wheeze or asthma in children born to mothers with lowest (< 4.3%) EPA and DHA levels (p = 0.011)
      - no significant difference in risk of persistent wheeze or asthma in children born to mothers with EPA and DHA levels ≥ 4.3%
- postnatal supplementation of omega-3 fatty acids
  - **postnatal omega-3 long-chain polyunsaturated fatty acid supplementation may not reduce risk of asthma or wheeze in children** (level 2 [mid-level] evidence)
    - based on Cochrane review limited by clinical heterogeneity
    - systematic review of 8 randomized trials comparing prenatal and/or postnatal omega-3 long-chain polyunsaturated fatty acid (PUFA) supplementation vs. placebo or no supplementation (control) in 3,366 women and 3,175 children
    - 2 trials evaluated postnatal supplementation in women with term or preterm birth

Updated 2/2017
• results limited by heterogeneity in patient population and omega-3 PUFA regimen
• for postnatal omega-3 PUFA supplementation, no significant difference in medically diagnosed or parent-reported asthma or wheeze
  ▪ at > 36 months with DHA 900 mg plus EPA 195 mg per day starting at 5 days after initiation of enteral feeds and continued until expected date of delivery in 1 trial with 531 children born at < 33 weeks gestation
  ▪ at 2.5 years with omega-3 PUFA enriched muesli bars for 4 months postpartum in 1 trial with 65 children
• no significant differences in maternal safety, early childhood infections, and fever
• Reference - Cochrane Database Syst Rev 2015 Jul 22;(7):CD010085

○ neither omega-3 nor omega-6 oil supplementation associated with reduced risk of asthma or other allergy-related diseases (level 2 [mid-level] evidence)
  • based on systematic review with trial specific quality measures not reported
  • systematic review of 6 randomized trials evaluating use of omega-3 or omega-6 fatty acids vs. placebo in prevention of allergic disease in mostly high-risk children
  • supplements given to breastfeeding mothers or newborns included fish oil, canola and tuna-based oils, whey hydrolysate formula supplemented with gamma-linolenic acid, and borage oil
  • omega-3 oils not associated with significantly reduced risk of
    ▪ asthma (relative risk [RR] 0.81, 95% CI 0.53-1.25) in 4 trials with 1,078 patients
    ▪ eczema/atopic dermatitis (RR 1.1, 95% CI 0.78-1.54) in 3 trials with 664 patients
    ▪ allergic rhinitis (RR 0.8, 95% CI 0.34-1.89) in 2 trials with 599 patients
    ▪ food allergy (RR 0.51, 95% CI 0.1-2.55) in 2 trials with 148 patients
  • omega-6 oils not associated with significantly reduced risk of atopic eczema (risk reduction [RR] 0.8, 95% 0.56-1.16) in 2 trials with 259 patients
  • Reference - Allergy 2009 Jun;64(6):840

○ dietary omega-3 fatty acid supplementation in early life appears ineffective for prevention of atopy and asthma (level 2 [mid-level] evidence)
  • based on randomized trial with low follow-up rate
  • 616 pregnant women with family history of asthma were randomized to family intervention with daily tuna fish oil supplement plus omega-3-rich margarines and cooking oils vs. placebo supplements and cooking oils
  • 376 children (61%) completed assessment at 18 months
  • no differences in diagnosed asthma or atopy, but higher omega-3 fatty acid levels associated with reduced symptoms (wheeze, bronchodilator use, nocturnal coughing)
  • Reference - Pediatr Allergy Immunol 2004 Dec;15(6):517
  • observational follow-up of 516 children at 5 years found no significant differences in atopy or asthma, and no significant association between fatty acid exposure and respiratory symptoms (J Allergy Clin Immunol 2007 Jun;119(6):1438)

○ fish oil supplementation during first 6 months of life does not appear to prevent allergic disease in infants with familial allergy risk (level 2 [mid-level] evidence)
  • based on randomized trial with high loss to follow-up
  • 420 healthy term neonates with familial allergy risk (based on maternal skin prick test and history) randomized to fish oil (docosahexaenoic acid 280 mg plus eicosapentaenoic acid 110 mg) per day vs. olive oil for 6 months and evaluated for physician-diagnosed allergic disease at 12-month follow-up
  • 77% had follow-up at 12 months
  • allergic disease diagnosed in 37.8% in fish oil group vs. 39.5% in placebo group (not significant)
  • no significant differences between groups in
    ▪ prevalence of physician-diagnosed eczema, food allergy, or asthma
    ▪ sensitivity to egg, peanut, milk, dust mite, or cat on skin prick test
  • Reference - Pediatrics 2012 Oct;130(4):674 full-text

○ introduction of fish consumption at age 6-12 months may reduce risk of wheezing at age 48 months compared with earlier introduction or no fish consumption during first year of life (level 2 [mid-level] evidence)
  • based on secondary analysis of population-based prospective cohort study
  • 7,210 children evaluated for fish consumption in infancy, and wheezing and shortness of breath at age 36 and 48 months
  • introduction of fish at 6-12 months associated with decreased risk of wheezing at 48 months
    ▪ compared with no introduction of fish during the first year of life (odds ratio [OR] 0.64, 95% CI 0.43-0.94)
    ▪ compared with introduction of fish at 0-6 months (OR 0.65, 95% CI 0.43-0.93)
  • no association found between amount of fish servings and wheezing and shortness of breath at 36 and 48 months
  • Reference - Pediatrics 2012 Dec;130(6):1060 full-text

Updated 2/2017
C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)
Evidence for routine EPA/DHA supplementation to prevent childhood asthma is inconsistent and likely lacking.

D. UpToDate excerpts

Atopic and allergic disease, asthma – The 2016 Evidence Report/Technology Assessment by the Agency for Healthcare Research and Quality analysis of randomized trials (discussed above) concluded that maternal n-3 PUFA supplementation during pregnancy did not reduce the incidence of asthma or other respiratory illnesses (OR 0.95, 95% CI 0.77-1.16; three trials, n = 1261 women), atopic dermatitis/eczema, or food/dust allergies in offspring [53]. Doses included 400 mg DHA daily, 3.7 g fish oil daily (56 percent DHA and 28 percent eicosapentaenoic acid [EPA]), and salmon twice weekly (each portion contains 1.16 g DHA and 0.57 g EPA).

Subsequent to this analysis, a double-blind placebo-controlled randomized trial (n = 736 women) of third-trimester supplementation with n-3 PUFA (2.4 g daily, 55 percent EPA and 37 percent DHA) reported that the intervention resulted in a 7 percent absolute reduction in the risk of persistent wheeze or asthma in offspring followed to age three to five years (16.9 versus 23.7 percent, hazard ratio 0.69, 95% CI 0.49-0.97) [55]. The reduction was driven by the impact of maternal treatment in women with EPA and DHA blood levels in the lowest third at baseline or with a FADS genotype associated with low EPA and DHA blood levels (low baseline EPA+DHA: persistent wheeze or asthma in offspring 17.5 versus 34.1 percent, hazard ratio 0.46, 95% CI 0.25-0.83). The estimated EPA+DHA intake of these women was below 321 mg/day before the intervention. There was also a reduction in risk of lower respiratory tract infections, but no difference in rates of asthma exacerbations, eczema, or allergic sensitization between groups. The supplement was well-tolerated, pregnancy outcomes were similar for both groups, and no adverse effects were described in the report.

Although high-dose maternal n-3 PUFA supplementation was effective for preventing asthma in offspring in this trial, it was not clear that offspring of women without very low blood levels of n-3 PUFA significantly benefit or whether benefits persist into the school-age years. Subsequent trials should address whether similar effects will be observed in other populations, whether the beneficial effects persist, and whether lower n-3 PUFA doses are effective (it would be essentially impossible to achieve a comparable n-3 PUFA dose from fish consumption as the dose was 20-fold higher than the average intake from fish consumption in the United States). In addition, an updated meta-analysis should be performed that includes the findings of this trial.


F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
There is no clear evidence that maternal fish intake or n-3 PUFA supplementation reduce the frequency of disorders with an inflammatory component, such as spontaneous preterm birth or asthma, allergic disease, or atopic disease in offspring.

Updated 2/2017
G. Other excerpts (USPSTF; other guidelines; etc.)

H. Citations for other excerpts

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

A. Validity: How well does the study minimize sources of internal bias and maximize internal validity? 2

B. If A was coded 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

C. Relevance: Are the results of study generalizable to and relevant to the health care needs of patients cared for by “full scope” family physicians? 3

D. If C was coded 4, 5, 6, or 7, please provide an explanation.

While it may be most beneficial for women with low DHA/EPA levels, there was statistical significance for the entire patient population.

E. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? 4 (uncertain)

F. If E was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

This would require either drawing EPA/DHA levels for pregnant women and utilizing fish oil for only those with low levels or starting supplementation on every pregnant patient. Both are above the usual care we provide and the cost to the healthcare system to prevent asthma/wheeze should be considered.

G. Applicability to a Family Medical Care Setting:
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or
referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? 3

H. If G was coded as a 4, 5, 6, or 7, please explain.

I. **Immediacy of Implementation:**
   Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? 3

J. If I was coded 4, 5, 6, or 7 please explain why.

K. **Clinically meaningful outcomes or patient oriented outcomes:**
   Are the outcomes measured in the study clinically meaningful or patient oriented? 2

L. If K was coded 4, 5, 6, or 7 please explain why.

M. In your opinion, is this a pending PURL? 3
   1. Valid: Strong internal scientific validity; the findings appear to be true.
   2. Relevant: Relevant to the practice of family medicine.
   3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
   4. Applicability in medical setting.
   5. Immediacy of implementation

N. Comments on your response for question M.