



## April 2015 Literature Alert

1.

J Pediatr. 2015 Mar;166(3):552-8.e1. doi: 10.1016/j.jpeds.2014.11.043. Epub 2015 Jan 6.

[Functional outcomes at age 7 years of moderate preterm and full term children born small for gestational age.](#)

Tanis JC, Van Braeckel KN, Kerstjens JM, Bocca-Tjeertes IF, Reijneveld SA, Bos AF.

### Abstract

#### OBJECTIVE:

To compare functional outcomes of 7-year-old (school-age) children born small for gestational age (SGA; ie, a birth weight z score  $\leq -1$  SD), with appropriate for gestational age (AGA) peers, born moderately preterm or full term.

#### STUDY DESIGN:

Data were collected as part of the Longitudinal Preterm Outcome Project study, a community-based, prospective cohort study of 336 AGA and 42 SGA born children (median gestational age 35 weeks, range 31-41). Of the SGA children, 32 were moderately preterm, 10 were full term; of the AGA, these numbers were 216 and 120, respectively. At 6.9 years, we assessed intelligence, verbal memory, attention, visuomotor integration, and motor skills and we collected the parent-reported executive functioning. We compared the outcomes of the SGA children with those of their AGA peers.

#### RESULTS:

The performance of SGA children was similar to that of their AGA peers, except for attention control which was abnormal more often in SGA children (OR 3.99, 95% CI 1.32-12.12). The IQ of SGA children was 3 points lower, but this difference failed to reach significance.

#### CONCLUSIONS:

At school age, children born SGA have a greater risk of abnormal test scores on attention control than children born AGA, independent of gestational age. Their motor

and many other cognitive functions are similar. The impact of these outcomes seems limited. Nevertheless, the consequences for school performance deserve attention.  
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PMID: 25575420 [PubMed - in process]

2.

**J Pediatr. 2015 Mar;166(3):582-6. doi: 10.1016/j.jpeds.2014.10.004. Epub 2014 Nov 12.**  
**[Universal maternal drug testing in a high-prevalence region of prescription opiate abuse.](#)**

Wexelblatt SL, Ward LP, Torok K, Tisdale E, Meinzen-Derr JK, Greenberg JM.

Abstract

**OBJECTIVE:**

To evaluate the efficacy of a universal maternal drug testing protocol for all mothers in a community hospital setting that experienced a 3-fold increase in neonatal abstinence syndrome (NAS) over the previous 5 years.

**STUDY DESIGN:**

We conducted a retrospective cohort study between May 2012 and November 2013 after the implementation of universal maternal urine drug testing. All subjects with positive urine tests were reviewed to identify a history or suspicion of drug use, insufficient prenatal care, placental abruption, sexually transmitted disease, or admission from a justice center, which would have prompted urine testing using our previous risk-based screening guidelines. We also reviewed the records of infants born to mothers with a positive toxicology for opioids to determine whether admission to the special care nursery was required.

**RESULTS:**

Out of the 2956 maternal specimens, 159 (5.4%) positive results were recorded. Of these, 96 were positive for opioids, representing 3.2% of all maternity admissions. Nineteen of the 96 (20%) opioid-positive urine tests were recorded in mothers without screening risk factors. Seven of these 19 infants (37%) required admission to the special care nursery for worsening signs of NAS, and 1 of these 7 required pharmacologic treatment.

**CONCLUSION:**

Universal maternal drug testing improves the identification of infants at risk for the development of NAS. Traditional screening methods underestimate in utero opioid exposure.

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PMID: 25454935 [PubMed - in process].

3.

Int J Gynaecol Obstet. 2015 Mar;128(3):236-40. doi: 10.1016/j.ijgo.2014.09.013. Epub 2014 Nov 8.

[Risk factors for adverse fetal outcomes among women with early- versus late-onset intrahepatic cholestasis of pregnancy.](#)

Jin J, Pan SL, Huang LP, Yu YH, Zhong M, Zhang GW.

Abstract

OBJECTIVE:

To determine risk factors for adverse fetal outcomes (AFOs) among women with intrahepatic cholestasis of pregnancy (ICP) on the basis of time of onset.

METHODS:

In a retrospective analysis, data were obtained for all women with ICP admitted to two centers in Guangzhou, China, between February 1, 1993, and January 31, 2014. Patients were divided into group A (early-onset ICP) and group B (late-onset ICP), and were further divided on the basis of severity. The frequency of AFOs was assessed.

RESULTS:

Among 371 eligible women, 57 (15.4%) were in group A and 314 (84.6%) in group B. AFOs affected 20 (35.1%) women in group A and 67 (21.3%) in group B ( $P=0.024$ ), and 12 (54.5%) of 22 women in group A and 21 (29.6%) of 71 in group B with severe ICP ( $P=0.032$ ). Independent risk factors for AFO in group A were increased levels of serum bile acid ( $P=0.016$ ) and alkaline phosphatase ( $P=0.004$ ). Independent risk factors in group B were increased levels of alkaline phosphatase ( $P<0.001$ ) and gamma-glutamyl transpeptidase ( $P=0.001$ ).

CONCLUSION:

Early-onset ICP is associated with a higher frequency of AFO than is late-onset ICP, especially in severe disease. The risk factors differ between early-onset and late-onset ICP.

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PMID: 25468047 [PubMed - in process]

4.

JAMA Pediatr. 2015 Mar 30. doi: 10.1001/jamapediatrics.2015.74. [Epub ahead of print]

[Association of Adverse Pregnancy Outcomes With Glyburide vs Insulin in Women With Gestational Diabetes.](#)

Camelo Castillo W, Boggess K, Stürmer T, Brookhart MA, Benjamin DK Jr, Jonsson Funk M.

Abstract

**IMPORTANCE:**

Glyburide is thought to be safe for use during pregnancy for treatment of gestational diabetes mellitus (GDM). However, there are limited data on the effectiveness of glyburide when compared with insulin as used in a real-world setting.

**OBJECTIVE:**

To estimate the risk of adverse maternal and neonatal outcomes in women with GDM treated with glyburide compared with insulin.

**DESIGN, SETTING, AND PARTICIPANTS:**

Retrospective cohort study of a population-based cohort from a nationwide US employer-based insurance claims database from January 1, 2000, to December 31, 2011. We identified women with GDM and their newborns. We excluded those with type 1 or 2 diabetes and those younger than 15 years or older than 45 years.

**EXPOSURES:**

Treatment with glyburide or insulin during pregnancy within 150 days before delivery.

**MAIN OUTCOMES AND MEASURES:**

We used binomial regression to estimate risk ratios (RRs) and risk differences with 95% confidence intervals for the association of glyburide with diagnosis codes for obstetric trauma, cesarean delivery, birth injury, preterm birth, hypoglycemia, respiratory distress, jaundice, large for gestational age, and hospitalization in the neonatal intensive care unit. Inverse probability of treatment weights were used to adjust for maternal characteristics that differed between the treatment groups.

**RESULTS:**

Among 110 879 women with GDM, 9173 women (8.3%) were treated with glyburide (n = 4982) or insulin (n = 4191). After adjusting for differences at baseline, newborns of women treated with glyburide were at increased risk for neonatal intensive care unit admission (RR = 1.41; 95% CI, 1.23-1.62), respiratory distress (RR = 1.63; 95% CI, 1.23-2.15), hypoglycemia (RR = 1.40; 95% CI, 1.00-1.95), birth injury (RR = 1.35; 95% CI, 1.00-1.82), and large for gestational age (RR = 1.43; 95% CI, 1.16-1.76) compared with those treated with insulin; they were not at increased risk for obstetric trauma (RR = 0.92; 95% CI, 0.71-1.20), preterm birth (RR = 1.06; 95% CI, 0.93-1.21), or jaundice (RR = 0.96; 95% CI, 0.48-1.91). The risk of cesarean delivery was 3% lower in the glyburide group (adjusted RR = 0.97; 95% CI, 0.93-1.00). The risk difference associated with glyburide was 2.97% (95% CI, 1.82-4.12) for neonatal intensive care unit admission, 1.41% (95% CI, 0.61-2.20) for large for gestational age, and 1.11% (95% CI, 0.50-1.72) for respiratory distress.

**CONCLUSIONS AND RELEVANCE:**

Newborns from privately insured mothers treated with glyburide were more likely to experience adverse outcomes than those from mothers treated with insulin. Given the widespread use of glyburide, further investigation of these differences in pregnancy outcomes is a public health priority.

PMID: 25822253 [PubMed - as supplied by publisher]

5.

**Am J Obstet Gynecol. 2015 Mar;212(3):332.e1-9. doi: 10.1016/j.ajog.2014.11.041.**

**Epub 2014 Dec 2.**

[Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion syndromes.](#)

Wapner RJ, Babiarz JE, Levy B, Stosic M, Zimmermann B, Sigurjonsson S, Wayham N, Ryan A, Banjevic M, Lacroute P, Hu J, Hall M2, Demko Z, Siddiqui A, Rabinowitz M, Gross SJ, Hill M, Benn P.

Abstract

OBJECTIVE:

The purpose of this study was to estimate the performance of a single-nucleotide polymorphism (SNP)-based noninvasive prenatal test for 5 microdeletion syndromes.

STUDY DESIGN:

Four hundred sixty-nine samples (358 plasma samples from pregnant women, 111 artificial plasma mixtures) were amplified with the use of a massively multiplexed polymerase chain reaction, sequenced, and analyzed with the use of the Next-generation Aneuploidy Test Using SNPs algorithm for the presence or absence of deletions of 22q11.2, 1p36, distal 5p, and the Prader-Willi/Angelman region.

RESULTS:

Detection rates were 97.8% for a 22q11.2 deletion (45/46) and 100% for Prader-Willi (15/15), Angelman (21/21), 1p36 deletion (1/1), and cri-du-chat syndromes (24/24). False-positive rates were 0.76% for 22q11.2 deletion syndrome (3/397) and 0.24% for cri-du-chat syndrome (1/419). No false positives occurred for Prader-Willi (0/428), Angelman (0/442), or 1p36 deletion syndromes (0/422).

CONCLUSION:

SNP-based noninvasive prenatal microdeletion screening is highly accurate. Because clinically relevant microdeletions and duplications occur in >1% of pregnancies, regardless of maternal age, noninvasive screening for the general pregnant population should be considered.

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PMID: 25479548 [PubMed - in process]

6.

**J Neonatal Perinatal Med. 2015 Mar 10. [Epub ahead of print]**

[Comparison of neonatal outcomes in macrosomic infants of diabetic and non-diabetic mothers.](#)

Opati P, Zheng R, Wang J, Xin Y, Zhao H, Bi D.

Abstract

**OBJECTIVE:**

To compare the neonatal outcomes in macrosomic term infants of diabetic mothers and non-diabetic mothers.

**METHODS:**

This is a retrospective survey of all live-born term singletons with a birth weight  $\geq 4000$  g, admitted at Tianjin Medical University General Hospital between 2010 and 2013. Data collected for the mothers included age, parity, gestational age, method of glycemic control and mode of delivery. Data for the infants included sex, birth weight, birth length, duration of hospital stay and laboratory tests. Outcomes were compared between infants of diabetic mothers (IDMs) and infants of non-diabetic mothers (Non-IDMs). All data were analyzed using Statistical Package for Social Sciences (SPSS) 17.0.

**RESULTS:**

One hundred and eleven infant-mother pairs met the inclusion criteria. Fifty-seven were IDMs while 54 were non-IDMs. Seven (12.28%) of the IDMs were delivered vaginally while 50 (87.72%) were delivered via Caesarian section (CS). Seventeen (31.48%) of the non-IDMs were delivered vaginally while 37 (68.51%) were delivered by CS. Respiratory distress was the most common morbidity affecting 52.6% of the IDMs and 40.7% of the non-IDMs. Hyperbilirubinemia was observed in 49.1% of the IDMs and 14.8% of the non-IDMs. Hypoglycemia affected 38.6% of the IDMs and 7.4% of the non-IDMs. Cardiac enzymes were higher in IDMs than in non-IDMs. On average, IDMs had a longer duration of hospital stay.

**CONCLUSION:**

Macrosomic IDMs in comparison to macrosomic non-IDMs are at an increased risk for adverse neonatal outcomes.

PMID: 25758004

**7.**

**Prenat Diagn. 2015 Mar;35(3):244-8. doi: 10.1002/pd.4528. Epub 2015 Feb 2.**

[First-trimester combined screening for trisomy 21 in women with renal disease.](#)

Valentin M, Muller F, Beaujard MP, Dreux S, Czerkiewicz I, Meyer V, Leruez M, Ville Y, Salomon LJ.

**Abstract**

**OBJECTIVE:**

To evaluate the results of first-trimester combined screening for Down syndrome in women with chronic renal disease.

**METHOD:**

Fifty-five pregnant women with renal disease were compared with 110 patients matched for maternal age, maternal weight, smoking status, and gestational age.

Maternal renal function was assayed at the time of the combined screening, and renal insufficiency was defined by serum creatinine  $>90 \mu\text{mol/L}$  and renal clearance  $<80 \text{ mL/min}$ . We defined three groups: kidney disease and normal renal function (group 1), kidney disease and renal insufficiency (group 2), and a control group (group 3). The values of nuchal translucency, pregnancy-associated plasma protein A, human  $\beta$ -chorionic gonadotrophin (hCG $\beta$ ), and false-positive rates for Down syndrome screening were compared.

#### RESULTS:

There were 39 (71%) and 16 (29%) cases in groups 1 and 2, respectively. Nuchal translucency and multiple of the median (MoM) pregnancy-associated plasma protein A were similar in the three groups. However, MoM hCG $\beta$  levels were higher in group 2 than in groups 1 and 3 (5.37 vs 1.1 vs 0.98 MoM,  $p = 0.0001$ ). The resulting screen-positive rate was also higher in group 2 than in groups 1 and 3 (43.7% vs 10.2% vs 5.5%,  $p = 0.0001$ ).

#### CONCLUSION:

Trisomy 21 first-trimester screening using hCG $\beta$  is not suitable in the case of maternal renal failure. © 2014 John Wiley & Sons, Ltd.

PMID: 25395363 [PubMed - in process]

## 8.

**Prenat Diagn. 2015 Mar;35(3):254-7. doi: 10.1002/pd.4534. Epub 2014 Dec 29.**

**[Congenital talipes equinovarus: frequency of associated malformations not identified by prenatal ultrasound.](#)**

Toufaily MH, Westgate MN, Holmes LB.

#### Abstract

#### OBJECTIVES:

To establish the frequency of prenatally undetected associated malformations (identified at birth) in infants with apparent "isolated" club foot deformity.

#### METHODS:

A cohort study of all infants with unilateral or bilateral club foot deformity identified at birth among 311 480 infants surveyed between 1972 and 2012 at Brigham and Women's Hospital in Boston. Those with talipes equinovarus were divided into "isolated" and "complex", based on the findings in examination and by chromosome analysis.

#### RESULTS:

One hundred and forty-two infants had "isolated" talipes equinovarus (TEV), and 66 had the "complex" type. Six (4.2%) of the 142 infants with "isolated" TEV were found at birth to have associated malformations that had not been identified by imaging during pregnancy. These abnormalities included hip dislocation ( $n = 2$ ), bilateral post-axial polydactyly of the feet ( $n = 1$ ), penile chordee ( $n = 1$ ), and hypospadias ( $n = 2$ ).

#### CONCLUSION:

In this consecutive series of infants with isolated talipes equinovarus, 95.8% had no additional malformations identified by examination at birth. None of the additional findings were severe enough to affect the medical prognosis of the affected infant. © 2014 John Wiley & Sons, Ltd.

PMID: 25394569 [PubMed - in process]

9.

**BJOG. 2015 Mar;122(4):468-76. doi: 10.1111/1471-0528.12935. Epub 2014 Jul 3.**  
[Balancing the efficacy and safety of misoprostol: a meta-analysis comparing 25 versus 50 micrograms of intravaginal misoprostol for the induction of labour.](#)

McMaster K, Sanchez-Ramos L, Kaunitz AM.

Abstract

**BACKGROUND:**

The optimal dose of misoprostol for the induction of labour remains uncertain.

**OBJECTIVES:**

To compare the efficacy and safety of 25 versus 50 micrograms of intravaginal misoprostol tablets for the induction of labour and cervical ripening.

**SEARCH STRATEGY:**

We performed electronic and manual searches to identify relevant randomised trials.

**SELECTION CRITERIA:**

The efficacy outcomes assessed were rates of vaginal delivery within 24 hours, delivery within one dose, and oxytocin augmentation, and interval to delivery. The safety outcomes assessed were incidences of tachysystole, hyperstimulation, caesarean delivery, cesarean delivery for non-reassuring fetal heart rate (FHR), operative vaginal delivery, abnormal 5-minute Apgar score, abnormal cord gas values, admission to a neonatal intensive care unit (NICU), and meconium passage.

**DATA COLLECTION AND ANALYSIS:**

Thirteen studies (1945 women) were included. Relative risk (RR) and 95% confidence intervals (CI) were calculated using fixed-effects and random-effects models.

**MAIN RESULTS:**

We found that 25 micrograms was less efficacious, with lower rates of delivery after one dose (RR 0.59; 95% CI 0.39-0.88) and vaginal delivery within 24 hours (RR 0.88; 95% CI 0.79-0.96), and with increased rates of oxytocin augmentation (RR 1.54, 95% CI 1.36-1.75). We noted an improved safety profile with 25 micrograms, however, with decreased rates of tachysystole (RR 0.46; 95% CI 0.35-0.61), hyperstimulation (RR 0.5; 95% CI 0.31-0.78), caesarean deliveries for non-reassuring FHR (RR 0.67; 95% CI 0.52-0.87), NICU admissions (RR 0.63; 95% CI 0.4-0.98), and meconium passage (RR 0.65; 95% CI 0.45-0.96).

**CONCLUSIONS:**



Although 50 micrograms of intravaginal misoprostol may be more efficacious, safety concerns make the 25-microgram dose preferable.

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PMID: 24989790 [PubMed - in process]

## 10.

**BJOG. 2015 Mar;122(4):478-90. doi: 10.1111/1471-0528.13202. Epub 2014 Nov 26.**  
[Effectiveness of folic acid supplementation in pregnancy on reducing the risk of small-for-gestational age neonates: a population study, systematic review and meta-analysis.](#)  
Hodgetts VA, Morris RK, Francis A, Gardosi J, Ismail KM.

### Abstract

#### OBJECTIVES:

To assess the effect of timing of folic acid (FA) supplementation during pregnancy on the risk of the neonate being small for gestational age (SGA).

#### DESIGN:

A population database study and a systematic review with meta-analysis including the results of this population study.

#### SETTING AND DATA SOURCES:

A UK regional database was used for the population study and an electronic literature search (from inception until August 2013) for the systematic review.

#### PARTICIPANTS AND INCLUDED STUDIES:

Singleton live births with no known congenital anomalies; 111,736 in population study and 188,796 in systematic review.

#### OUTCOME MEASURES, DATA EXTRACTION AND ANALYSIS:

The main outcome was SGA based on customised birthweight centile. Associations are presented as odds ratios (OR) and adjusted odds ratios (aOR), adjusted for maternal and pregnancy-related characteristics.

#### RESULTS:

Of 108,525 pregnancies with information about FA supplementation, 92,133 (84.9%) had taken FA during pregnancy. Time of commencement of supplementation was recorded in 39,416 pregnancies, of which FA was commenced before conception in 10,036, (25.5%) cases. Preconception commencement of FA supplementation was associated with reduced risk of SGA <10th centile (aOR 0.80, 95% CI 0.71-0.90,  $P < 0.01$ ) and SGA <5th centile (aOR 0.78, 95% CI 0.66-0.91,  $P < 0.01$ ). This result was reproduced when the data were pooled with other studies in the systematic review, showing a significant reduction in SGA (<5th centile) births with preconception commencement of FA (aOR 0.75, 95% CI 0.61-0.92,  $P < 0.006$ ). In contrast, postconception folate had no significant effect on SGA rates.

#### CONCLUSION:

Supplementation with FA significantly reduces the risk of SGA at birth but only if commenced preconceptionally independent of other risk factors.

SYSTEMATIC REVIEW REGISTRATION:

This systematic review was prospectively registered with PROSPERO number CRD42013004895.

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PMID: 25424556 [PubMed - in process]

11.

**Obstet Gynecol. 2015 Mar;125(3):621-7. doi: 10.1097/AOG.0000000000000667.**

[Factors associated with second-trimester pregnancy loss in women with normal uterine anatomy undergoing in vitro fertilization.](#)

Hawkins Bressler L, Correia KF, Srouji SS, Hornstein MD, Missmer SA.

Abstract

OBJECTIVE:

To evaluate factors associated with second-trimester pregnancy loss in patients with normal uterine anatomy who conceived through in vitro fertilization.

METHODS:

Women aged 21-44 years with ongoing in vitro fertilization pregnancy (at least one fetus with fetal heart tones at 12 weeks of gestation) at an academic hospital from 2001 to 2012 were eligible for inclusion in this retrospective cohort. Comprehensive uterine evaluation permitted inclusion of only women with anatomically normal uterine cavities. Maternal and clinical characteristics associated with spontaneous second-trimester pregnancy loss (between 12 1/7 and 23 6/7 weeks of gestation) were assessed. Multivariable logistic regression generated adjusted odds ratios (ORs), 95% confidence intervals (CIs), and Wald two-sided P values.

RESULTS:

Among ongoing second-trimester pregnancies, 60 (2.1%) ended in spontaneous pregnancy loss and 2,841 (97.9%) ended in live birth. Multiple gestations (twins or more) conferred greater odds of pregnancy loss (adjusted OR 1.93, CI 1.15-3.24, P=.01) and were more prevalent among losses (48.3%) than live births (34.1%). Uterine leiomyomas were present in 16.7% of losses and 4.7% of live births and were associated with a nearly fourfold increased odds of second-trimester pregnancy loss (adjusted OR 3.82, CI 1.85-7.89, P<.001). Women with obese body mass index ([BMI] 30 or higher) at cycle start experienced twofold greater odds of pregnancy loss compared with normal-weight women (adjusted OR 2.38, CI 1.05-5.65, P=.04). There were eight obese women (32%) among losses and 209 obese women (16.5%) among live births. In vitro fertilization treatment parameters were not associated with odds of second-trimester loss nor were maternal age, ethnicity, or history of recurrent pregnancy loss.

CONCLUSION:

Odds of second-trimester spontaneous pregnancy loss among in vitro fertilization conceived pregnancies were greater with multiple gestations, leiomyomas, and obese maternal BMI.

LEVEL OF EVIDENCE: II.

PMID: 25730225 [PubMed - in process]

## 12.

**Pediatrics. 2015 Mar;135(3):e672-7. doi: 10.1542/peds.2014-1542. Epub 2015 Feb 9.**  
[Medical augmentation of labor and the risk of ADHD in offspring: a population-based study.](#) Henriksen L, Wu CS, Secher NJ, Obel C, Juhl M.

### Abstract

#### BACKGROUND AND OBJECTIVE:

Oxytocin for labor augmentation is widely used in obstetric care in Western countries. Two recent, smaller studies found opposing results regarding the association between prenatal exposure to oxytocin for labor augmentation and attention-deficit/hyperactivity disorder (ADHD). In Denmark, oxytocin is the medication used for nearly all medical augmentations of labor, and we examined the association between medical augmentation of labor and ADHD in a large cohort study based on national register data.

#### METHODS:

All singletons born after spontaneous onset of labor in Denmark between 2000 and 2008 (N = 546 146) were included in the study. Data from the Danish Medical Birth Registry on medical augmentation of labor (yes/no) were used to identify exposed children. ADHD was defined based on the diagnostic codes of International Classification of Diseases, 10th Revision, for hyperkinetic disorder and information on dispensed ADHD medication. A multivariate proportional hazards regression model was used to test the association.

#### RESULTS:

Among 546 146 deliveries, 26% included medical augmentation of labor, and 0.9% of the children were identified as having ADHD (n = 4617). We found no association between augmentation of labor and ADHD in the offspring (hazard ratio: 1.05 [95% confidence interval: 0.98-1.13]).

#### CONCLUSIONS:

Our study does not support an association between medical augmentation of labor and ADHD in the child.

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PMID: 25667242 [PubMed - in process]