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Study protocol

Tests for predicting complications of pre-eclampsia: A protocol for systematic reviews

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Abstract

Background: Pre-eclampsia is associated with several complications. Early prediction of complications and timely management is needed for clinical care of these patients to avert fetal and maternal mortality and morbidity. There is a need to identify best testing strategies in pre eclampsia to identify the women at increased risk of complications. We aim to determine the accuracy of various tests to predict complications of pre-eclampsia by systematic quantitative reviews.

Method: We performed extensive search in MEDLINE (1951–2004), EMBASE (1974–2004) and also will also include manual searches of bibliographies of primary and review articles. An initial search has revealed 19500 citations. Two reviewers will independently select studies and extract data on study characteristics, quality and accuracy. Accuracy data will be used to construct 2 × 2 tables. Data synthesis will involve assessment for heterogeneity and appropriately pooling of results to produce summary Receiver Operating Characteristics (ROC) curve and summary likelihood ratios.

Discussion: This review will generate predictive information and integrate that with therapeutic effectiveness to determine the absolute benefit and harm of available therapy in reducing complications in women with pre-eclampsia.

Background

Hypertension is a common medical complication of pregnancy, affecting about 6–8% of all pregnancies[1]. Hypertensive disorders in pregnancy consist of a group of disorders that include pre-eclampsia, latent or chronic essential hypertension, a variety of renal diseases, and transient (gestational) hypertension. The definitions used to distinguish these disorders differ, leading to uncertainty about their prevalence, natural history and response to treatment. Pre eclampsia is associated with several complications[2] and remains one of the largest single cause of maternal and fetal mortality and morbid-

ity[3,4]. They have been reported to account for 14% of direct maternal deaths and 18% of fetal or infant deaths[3,4].

Once the diagnosis of pre-eclampsia is established, timely management is of the essence to avoid or minimise mortality and morbidity. Clinical prediction of disease complications using a combination of patients' characteristics, symptoms, physical signs and investigations all of which we consider tests, forms the basis of clinical care in these situations[5]. Therefore, there is a need for guidance regarding the best testing strategies with which to predict the development of complications in pre-eclampsia. As well as allowing clinicians to avoid unnecessary interventions in low risk groups, this would allow high-risk groups to benefit from monitoring of disease severity, use of anti-hypertensive therapy, administration of anticonvulsants, and antenatal corticosteroids[6,7].

Methods
A systematic quantitative overview of studies of complications of pre-eclampsia will be conducted to obtain summary estimates of accuracy of all available tests.

The proposed methodology is in line with the guidance of the NHS Centre for Reviews and Dissemination[8] and that of the Cochrane Methods Working Group on Screening and Diagnostic tests[9]. The investigation will be carried out in the following recommended steps: (i) Question formulation, (ii) Study selection and identification, (iii) Study quality assessment, (iv) Data extraction and (v) Data synthesis. Our strategy for each of these steps will be based on a prospective protocol, which is outlined below:

Question formulation
The tests to be considered by the review are specified in the form of structured questions in Table 1. We have generated a priority list based on importance to clinical practice using a modified Delphi survey.[10] An exhaustive list of the tests and outcomes in the prediction of pre eclampsia were sent to experts in the field. Each one of the issues were rated according to their importance to clinical practice and ranked accordingly. The review will focus on the prioritised tests obtained from the survey.

Study identification and selection
We have a thorough search protocol by which literature is identified via general bibliographic databases including MEDLINE and EMBASE. Specialist computer databases like DARE (Database Of Abstracts of Reviews of Effectiveness), MEDION (a database of diagnostic test reviews set up by Dutch and Belgian researchers), the Cochrane Library and relevant specialist registers of the Cochrane Collaboration, particularly the Pregnancy and Child Birth group are searched. Individual experts and those with an interest in this field will be contacted to uncover grey literature. SciSearch will be used to identify frequently cited

Table 1: Structured questions for systematic review of test accuracy studies

Question Components		Tests for predicting complications of pre eclampsia
Population		Pregnant women with pre eclampsia
Tests		
	History	Parity; Race; Maternal age; Previous severe pre eclampsia/Eclampsia; Family history of pre eclampsia/eclampsia; Obesity; Weight gain; Pre existing hypertension, renal disease, diabetes, lupus, thrombophilia, other auto immune diseases; Multiple pregnancy; Symptoms-headache, epigastric pain, nausea, visual disturbance or combination of symptoms
	Examination	Blood pressure; Peripheral oedema; Exaggerated tendon reflexes; Clonus; Papilloedema; Retinal changes; Oliguria; Symphysio fundal height; Oxygen saturation
	Investigations	**Biochemical**: Serum uric acid, urine dipstick (Bedside Urinalyses) 24 hour urine protein, urinary calcium excretion, hypoalbuminaemia, microalbuminuria, fibronectin, protinuria, renal and liver function tests; **Ultrasound**: Growth, liquor volume, Doppler (uterine, umbilical artery, Middle cerebral artery, venous, uteroplacental) Bio Physical Profile; **Haematological**: Anti thrombin III, platelet count, haemoglobin, fibrinogen, thrombophilia screen, Maternal serum Alpha feto protein(MSAFP), Serum Human Chorionic Gonadotropin (HCG); Computerised Tomography; Magnetic Resonance Imaging
Outcome		*Maternal* Eclampsia; Pulmonary oedema; Cerebral Haemorrhage; Hepatic, renal, haematological complications; Cardiac arrest; Abruption; Thromboembolism; stroke; psychiatric problems; Complications of labour and delivery; Maternal death; Need for hospitalisation, Day care unit visits, Use of intensive care, ventilation and dialysis
		Fetal Intra uterine growth restriction; Pre maturity; Abnormal p H at birth or antenatal; Abnormal Apgar; Hypoxic Ischemic Encephalopathy; Perinatal death; Long term effect, learning disabilities, Developmental and special needs after discharge; Need for neonatal intensive care admission, mechanical ventilation and duration of hospital stay
	Study design	**Systematic review of test accuracy studies**

Table 2: Search term combinations for identification of studies predicting complications of pre eclampsia

Population	Test			Outcome	
	History	Examination	Investigation		Final Refinement
1. pre adj eclampsia	12. history	43. blood adj pressure	63. serum near uric adj acid	99. complicat$	137. 11 and 98 and 136
2. preeclampsia	13. parity	44. oedema or edema	64. urin near analys $	100. (renal or kidney$) near (disease$ or complicat$)	(Captures *Population* and *Test* and *Outcome*)
3. hypertens $	14. multiparity or nulliparity	45. tendon$ near reflex$	65. urin$	101. (hepatic or liver$) near (disease$ or complicat$)	138. animal = yes
4. pregnan $	15. matern$ near age	46. hyperreflexia	66. maternal near (feto adj protein$ or fetoprotein$ or alphafetoprotein$)	102. death or mortality	139. human = yes
5. pre-eclampsia #.DE.	16. (previous or prior) near eclampsia	47. clonus	67. urin$ near calcium	103. morbidity	140. 138 not 139
6. hypertension #.DE.	17. (previous or prior) near preeclampsia	48. papilledema or papilloedema	68. hypoalbuminemia or hypoalbuminaemia	104. eclampsia	141. 137 not 140
7. pregnancy #.DE.	18. (previous or prior) near pre adj eclampsia	49. retina$ near change$	69. microalbuminuria	105. (pulmonary or lung) near (complicat$ or disease$)	142. PT = comment or PT = letter
8. 3 or 6 (hypertension)	19. multiple near pregnan$*	50. oliguria	70. fibronectin$	106. thromboembolism	
9. 4 OR 7 (pregnancy)	20. twin$ or triplet$ or quadruplet$	51. symphys$ near fundal	71. proteinuria	107. pulmonary near (oedema or edema)	
10. 8 and 9	21. symptom$	52. symphys$ near height	72. renal adj function near test$	108. ventilat$	
(pregnancy and hypertension)	22. headache	53. cardiotocogra$	73. liver adj function near test$	109. stroke	
	23. epigastric near pain	54. oxygen near saturat$	74. liquor near volume	110. uter$5 near haemorrhage	
	24. naus$ or vomit$	55. blood-pressure-determination#.DE.	75. biophysical near profile	111. abruption	
	25. race	56. edema#.DE.	76. ultraso$	112. (heart or cardiac) near arrest$	
	26. diabet$	57. reflex-abnormal#.DE.	77. antithrombin$	113. (psychiatric or mental) near (illness$ or complication$1 or disorder)	
	27. stress	58. retinal-diseases#.DE.	78. platelet adj count	114. hospitali$	
	28. lupus	59.oliguria#.DE.	79. anti adj thrombin$	115. hypox$ near isch$	
	29. thrombophilia	60. cardiotocography#.DE.	80. fibrinogen	116. (development$ or learning) near (disorder$ or difficult$)	
	30. medical-history-taking#.DE.	61.oximetry#.DE.	81. antiphospholipid $	117. pregnancy-complications#.DE.	
	31. maternal-age#.DE.		82. haemoglobin	118. kidney-diseases#.DE.	
	32. pregnancy-multiple#.DE.		83. uric-acid-QN.DE	119. renal-dialysis#	
	33. headache#.DE.		84. alpha-fetoproteins #.DE	120. liver-diseases#.DE.	
	34. signs-and-symptoms-digestive#.DE.		85. calcium-ur. DE	121. death#	
	35. vision-disorders#.DE.		86. hypoalbuminemi a#.DE.	122. eclampsia#	
	36. weight gain#.DE.		87. fibronectins .DE.	123. pulmonary-embolism.DE.	
	37. population-groups#.DE.		88. proteinuria #.DE.	124. respiration-artificial#	
	38. diabetes-mellitus#.DE.		89. kidney-function-test s#.DE.	125. cerebrovascular-disorders#.DE.	
	39. stress-psychological#.DE.		90. liver-function-tests #.DE.	126. brain-edema.DE.	
	40. autoimmune-diseases#.DE.		91. ultrasonography #.DE.	127. intracranial-hypertension#.DE.	
	41. thrombophilia#.DE.		92. haematologic-test s#.DE.	128. uterine-haemorrhage.DE.	
			93. antithrombin-III. DE.	129. abruption-placentae#.DE.	
			94. fibrinogen #.DE.	130. heart-diseases#	
			95. antibodies-antiphospholipid #.DE.	131. mood-disorders#.DE.	
			96. diagnostic-imaging #.DE.	132. hospitalization#	
				133. infant-newborn-diseases#	
				134. respiratory-distress-syndrome-newborn.DE.	
				135. mental-disorders-diagnosed-in-childhood#.DE.	
11. 1 OR 2 OR 5 OR 10 (Captures *Population*)	**42. OR/12–41** (Captures history)	**62. or/43–61** (Captures examination)	**97. or/63–96** (Captures investigation)	**136. or/99–135** (Captures *Outcome*)	**143. 141 not 142** *Final citation set (animal only studies, comments and letters excluded)*

98. 42 or 62 or 97 (Captures *Test*)

Key to commands and codes used in Dialog interface:
Adj = words adjacent;; near = words within five words of each other in any order;.DE. = descriptor (MeSH heading);# = Exploded MeSH heading
$ = Truncated to allow for variant word endings; QN = Quick analysis pre-exploded subheading (including analysis, blood, urine, cerebrospinal fluid, isolation and purification PT = Publication Type

articles. Hand-searching of selected specialist journals and conference proceedings will be done to identify reports of studies for the review. Reference lists of articles obtained by iterative search will be checked as an adjunct to other methods[11]. Language restrictions will not be applied. A comprehensive database of relevant articles will be constructed. The search will be updated every year to enable inclusion of current evidence in the reviews and including other databases like SCOPUS where needed. A search term combination was constructed after exhaustive planning and piloting of possible search concepts capturing the relevant population, tests and outcomes. Our search terms and flow chart of search strategy are shown in Table 2 and in Fig 1. An initial search in Medline yielded 11711 citations. The search strategy was adapted for searching in Embase to obtain a total of 19500 citations. From this citation set, studies will be selected for inclusion in the review in a two-stage process.
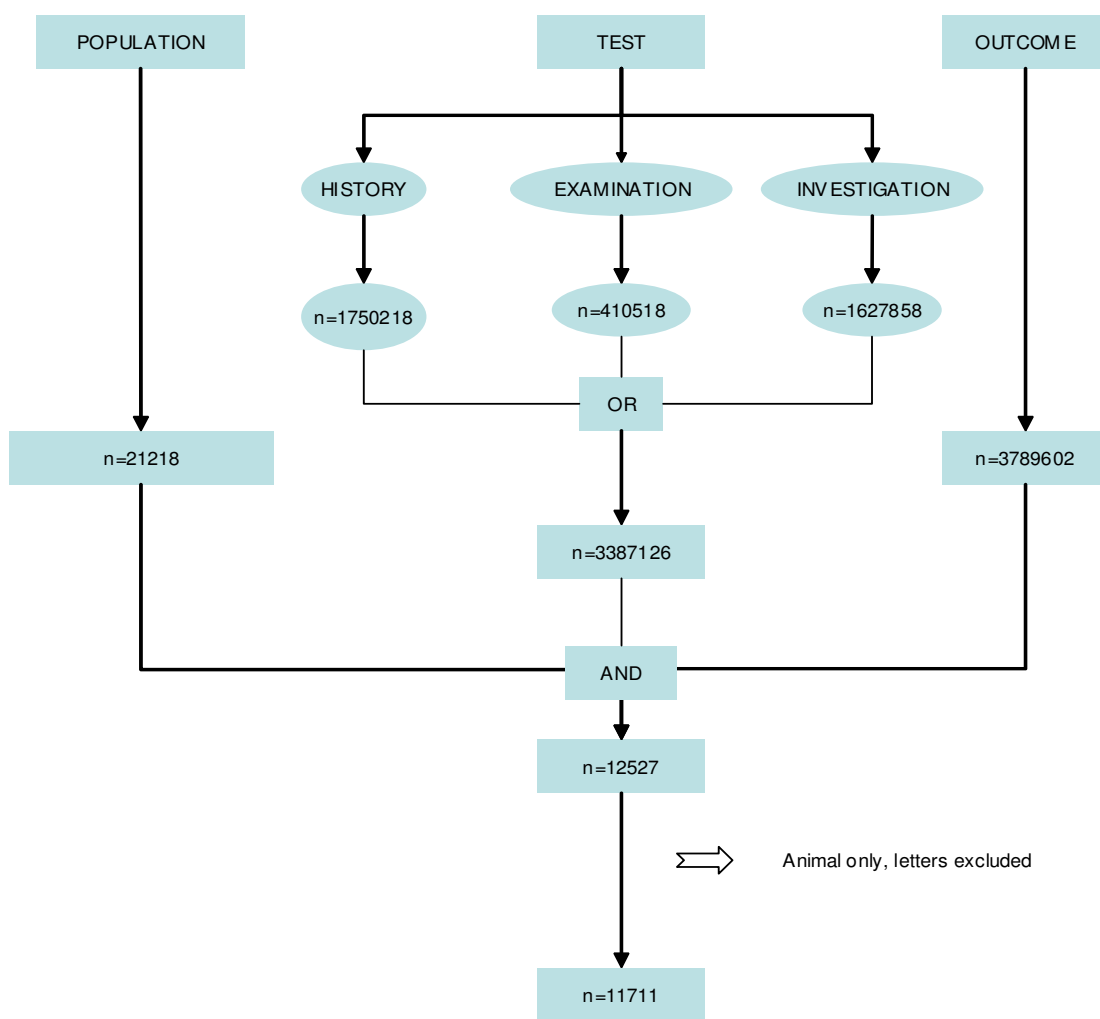
Figure 1: Flow diagram of study selection process

Figure 1
Flow diagram of study selection process in Medline.

In the first stage the electronic searches will be scrutinised by two independent reviewers and full manuscripts of all citations that are likely to meet the predefined selection criteria will be obtained. All available reports, irrespective of language will be included to reduce bias[12]. Subsequent final inclusion or exclusion decisions will be made on examination of these manuscripts. In cases of duplicate publication, the most recent and complete versions will be selected. Two reviewers will then independently select the studies, which meet predefined and explicit criteria regarding population, tests, outcomes and study design (Table 1). These criteria will be piloted using a sample of papers and agreement between reviewers will be measured. When disagreements occur, the two reviewers will meet and if necessary the issue will be resolved by consensus involving a third reviewer.

Study quality assessment

A review of papers meeting the eligibility criteria will be conducted by the same reviewers who judged eligibility,

but this time rating the methodological quality of the primary research. Methodological quality is a reflection of the degree to which the study design, conduct and analysis has minimised bias in addressing the research question. This ensures a high level of internal validity (i.e. the degree to which the results of an observation are correct for the patients being studied). The potential sources of bias and variability arising from spectrum composition and other variations in test protocol or the use of reference standard in individual studies will be considered when interpreting the results[13]. In addition to using study quality as possible explanation for differences in results, the extent to which primary research met methodological standards is important per se for assessing the strength of any conclusions that are reached[8]. We will evaluate elements of study design which are likely to have a direct relationship to bias and variability in a test accuracy study [13-19]. The criteria for study validation are shown in Fig 2.
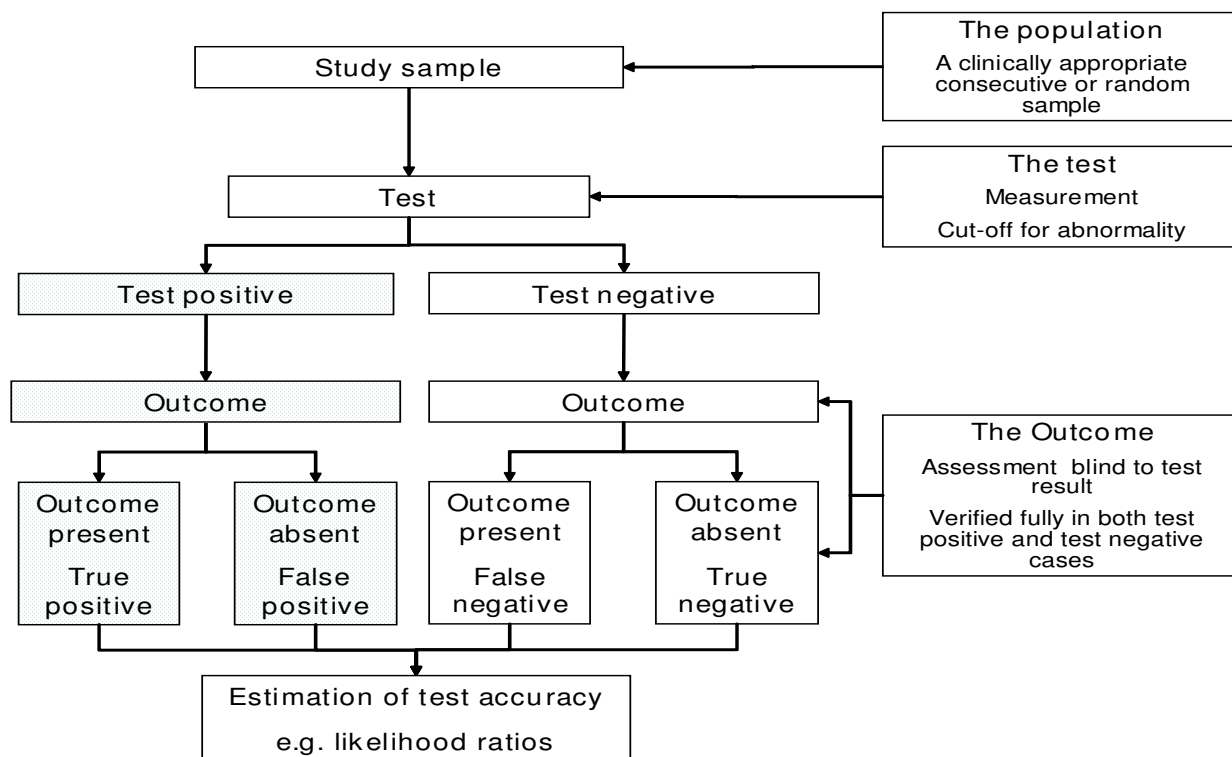
Figure 2
Criteria for quality assessment to be used in the review of tests predicting complications of pre eclampsia.
a) Generic quality items · Recruitment of subjects (consecutive or random sample) · Blinding of observers assessing the outcome to the findings of the test · Verification of diagnosis by outcome in all tested cases · 90% or more of enrolled population followed up
b) Specific quality items related to features of this project   Population Description of spectrum composition   Test Adequate description of test and its measurements determining cut-off level for abnormality a priori Outcome Complications of pre eclampsia

Data extraction

The extraction of study findings will be conducted in duplicate using a pre-designed and piloted data extraction form to avoid any errors. Two authors will independently extract information from each article in order to construct 2 × 2 tables of the diagnostic test result and outcomes. Any disagreement will be resolved by consensus. Given the extent of insufficient reporting in the medical literature, we propose to obtain missing information from investigators whenever possible. It is otherwise impossible to distinguish between what was done but not reported and what was not done. To avoid introducing bias, unpublished information will be obtained in writing, and will be coded in the same fashion as published information with equal regard for inter-coder agreement. In addition to using multiple coders to insure the reproducibility of the overview, sensitivity analyses around important or questionable judgements regarding the inclusion or exclusion of studies, the validity assessments and data extraction will be performed.

Data synthesis

We will explore causes of variation in results from study to study (heterogeneity), synthesise results from individual studies (meta-analysis) if appropriate[8,15] and assess for the risk of publication bias. Heterogeneity of results between studies will be graphically assessed looking at the distribution of rates, sensitivities and specificities in the ROC (Receiver Operating Characteristics) curve and likelihood ratios using Forest plots. To explore causes of heterogeneity we will conduct a sensitivity analysis by subgroups to see whether variations in population characteristics, tests, outcomes and study quality affect the estimate accuracy. Conclusions regarding the typical estimate accuracy will be interpreted cautiously if there is significant heterogeneity. Individual factors explaining heterogeneity will also be analysed using meta-regression to determine their unique contribution allowing for other factors. We will conduct meta-analyses to generate summary estimates of likelihood ratios (LRs), diagnostic odds ratios (ratio of LRs) and area under receiver operating characteristic (ROC) curves as appropriate[15,20,21]

The risk of publication bias is expected to be high in reviews of test accuracy[22]. Analysis for assessing the risk of publication bias will be carried out by producing funnel plots of accuracy estimates against corresponding variances. In the absence of publication bias it is to be expected that the point estimates will fill a funnel shape in the plot. Large gaps in the funnel indicate a group of possible 'missing' publications. These omissions are due to small studies showing limited accuracy and are unlikely to be missing at random. This phenomenon will also be statistically evaluated using Egger's test [23].

Discussion

In the same way as systematic reviews of effectiveness of treatments in Obstetrics have been pursued over the last decade, research on test accuracy also needs systematic reviewing[14,24]. One of the questions remaining after establishing effectiveness evidence for magnesium sulphate, steroids and anti hypertensives is to identify those who will benefit most from these interventions[25,26]. Relying on the inclusion and exclusion criteria of the trials alone is not sufficient for determining who should and shouldn't get these treatments. Women at high risk of complications of pre-eclampsia are likely to benefit most whilst in low risk women, therapy may cause more harm than good. Therefore, what is required is the prediction of risk of complications (such as eclampsia) of pre-eclampsia.

Information on women's risk stratification can be obtained from test accuracy reviews, which provide post test probabilities for a clinical outcome targeted by treatment. Integration of these with evidence for therapeutic effectiveness will enable generating estimates of Number Needed to Treat (NNT). The lower the risk, the higher the NNT and the lower are our and women's expectation of benefit from treatment. Conversely, the higher the baseline risk, the lower the NNT, the higher are our expectation of benefit and the more inclined we would be to recommend, and women to accept therapy[24,27]. This will serve to rationalise clinical decision-making.

This project will collate and synthesise the available evidence regarding the value of the tests for predicting complications of pre-eclampsia. The systematic overviews will assess the quality of the available evidence and provide estimates of rate (or risk) of complications of pre-eclampsia given various patient characteristics and other findings. It will identify a set of tests that have maximal predictive value to aid in therapeutic decision-making. An estimate of the magnitude of the benefits will be gauged by integration of the knowledge about risk with evidence of therapeutic effectiveness for various interventions. This will help to formulate practice recommendations and specific recommendations for future research.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KSK conceived the idea of the review and developed the protocol with KMKI, SO'B, FO'M, AC and ST. SS searched the electronic databases to identify the studies. KMKI, FO'M and SO'B obtained funding for ST from University Hospital North Staffordshire Research and Development Department, Stoke-on-Trent, UK. (Ref No. R 5177680). All authors read and approved the final manuscript.

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