**Introduction**

Urinary tract infection (UTI) is the fourth most common reason for prescribing antibiotics, accounting for approximately 8% of all antibacterial prescriptions.(1) Appropriate diagnosis and treatment of UTI in children presenting to primary care is particularly challenging because symptoms and signs are often non-specific. The costs of a urine sample, laboratory test and antibiotic are relatively low.(2) However, the economic impact may be substantial due to: the large number of acutely unwell children who present to primary care; additional diagnostic tests for structural abnormalities of the urinary tract;(3) rare but serious complications of UTI; and the wider impact of antibiotic prescribing on bacterial resistance.(4)

The few economic evaluations of UTI diagnosis in children(2, 5, 6) have compared the cost-effectiveness of urine tests once a urine sample has been obtained. There is very limited economic evidence to help primary care clinicians decide which children should have a urine sample taken and whether dipstick testing can guide therapy. Evidence is particularly needed for young children for whom current NICE clinical guidelines(3) are not based on strong evidence of cost-effectiveness. In the DUTY study we report the development of a two-step clinical rule and demonstrate its superiority to routine clinical practice in the diagnosis of UTI in acutely unwell young children presenting to primary care in whom a clean catch urine sample was obtained. In this paper we estimate the cost-effectiveness of these two steps. The first step evaluates whether clinical rules based on signs and symptoms identified in the DUTY study as predictive of UTI are more cost-effective than clinical judgement in identifying which children to test and treat for UTI. The second step evaluates the additional value of dipstick testing, once a urine sample has been obtained.

**Methods**

*The DUTY study*

Diagnosis of Urinary Tract Infection in Young children (DUTY) was a multi-center, prospective, diagnostic cohort study that recruited children seeking care at National Health Service (NHS) primary care sites in Bristol, Cardiff, London, and Southampton. Children were eligible if aged under 5 years and with complaints of any acute (less than 28 days) illness episode which was associated with at least one potential marker for UTI.(7) Ethical approval was granted by the South West Southmead Research Ethics Committee, ref #09/ H0102/64.

*Diagnostic strategies*

In the first step, we compared a ‘clinical judgement’ diagnostic strategy with three strategies based on the DUTY ‘coefficient score’ and four based on the simpler DUTY ‘points score’. Clinical judgement was defined by GP responses to questions on the DUTY case report form about working diagnosis and planned management prior to urine sampling. In the clinical judgement strategy, the proportion of lower risk children was identified as those where the GP answered 'No' to the question 'If this child was NOT in the DUTY study would you have requested a urine sample?' or indicated a working diagnosis of ‘Not UTI’. Higher risk children were those where the GP had a working diagnosis of UTI and answered 'Yes' to the question 'Before seeing the dipstick results, are you planning on treating this child with antibiotics for suspected UTI?’. Finally intermediate risk children were those where the GP had a working diagnosis of UTI and the GP answered 'Yes' to the question 'If this child was NOT in the DUTY study would you have requested a urine sample?

The DUTY coefficient score is calculated from seven parent- or clinician-reported symptoms and signs, weighted according to the strength of independent association with UTI (Supplemental table 1). The simpler DUTY points score ranges from 0 to 9 and is calculated from a subset of five symptoms and signs which were dichotomised (e.g. present/absent) and assigned an integer score (i.e. 1 or 2) representing the strength of association with UTI (Supplemental table 2). The coefficient-based score is more accurate than the points-based score, but requires computational assistance to calculate. The cut-points for the DUTY diagnostic strategies (Supplemental table 3) were selected to represent a range from more highly targeted (i.e. high specificity) to less highly targeted (i.e. high sensitivity) urine sampling strategies.

In the second step, we compared the short-term cost-effectiveness of immediate treatment based on point-of-care dipstick testing (DT) versus delayed treatment after laboratory testing (LT). Nitrites and leukocytes (trace or more) were strongly and independently predictive of UTI in the DUTY study(8). We evaluated two DT strategies: 1) immediate antibiotic if nitrite or leukocyte positive; 2) immediate antibiotic if nitrite and leukocyte positive.

*Model overview*

The overall model is comprised of several sub-models. First, a short-term decision tree (Figure 1) models testing and treatment during the index consultation. The acute illness phase is handled by a nine-state Markov model (Supplemental figure 1) estimating the time taken to recover (maximum 21 days) based on the illness of the child and the treatment they received. Correct UTI diagnosis can also lead to early diagnosis of vesicoureteral reflux (VUR), an abnormality which allows urine to flow backwards from the bladder the kidneys. Children with VUR are at increased risk of recurrent UTI (and subsequent pyelonephritic attacks), although this can be reduced through prophylactic antibiotic treatment or surgery. Another Markov model (Supplemental figure 2) is used to calculate the number of recurrent UTIs and pyelonephritic attacks in the three years following the index consultation. Finally, a long-term (lifetime) decision tree (Supplemental figure 3) models the impact of renal scarring in the earlier phases on the model, which is an important risk factor for long-term, potentially life-limiting, renal complications such as end stage renal disease. In each sub-model costs were estimated from a health service perspective and outcomes expressed using quality adjusted life years (QALYs) or days (QALDs).(9)

Improved testing could lead to more targeted antibiotic treatment and quicker symptom resolution during the initial infection; better preventative treatment in the medium-term leading to fewer renal scars (due to VUR treatment); and, consequently, fewer long-term complications.

*Short-term decision tree*

The structure of the decision tree (Figure 1) is identical for all eight diagnostic strategies. Strategies differ in the proportion of children classified as ‘lower’, ‘intermediate’ or ‘higher risk’ of UTI. We identified the proportion of children who are very unwell and referred directly to hospital for testing and treatment (for both UTI and non-UTI related problems) as those where the GP answered ‘Yes’ to the question 'Before seeing the dipstick results, would you have referred this child to a paediatrician or admitted this child to hospital’. A urine sample is requested in children considered at 'higher' risk of UTI and antibiotics prescribed. If laboratory culture demonstrates bacteriuria resistant to the prescribed antibiotic, the prescription will be changed. If no UTI is found the GP may contact the parent to stop treatment. If the sample is contaminated a repeat is sought. If no urine sample is obtained in a ‘higher risk’ child, symptoms are reviewed in two days. If symptoms have not improved the child is referred to hospital.

Urine sampling is attempted in children classified as 'intermediate risk’ of UTI but antibiotic treatment is delayed until a positive laboratory result is returned. Children who cannot provide a sample are reviewed in two days and antibiotics are only prescribed if symptoms have not resolved and the working diagnosis is a (non-UTI) microbial infection. No urine sample is requested in children classified as 'lower risk’ of UTI, although antibiotics may be prescribed if the working diagnosis is a (non-UTI) microbial infection. Therefore, children in whom a UTI is undiagnosed may receive antibiotics serendipitously, although higher rates of uropathogen resistance to non-targeted antibiotics meant they often had slower symptom resolution than those with correctly identified UTIs. Children with UTI may be referred for ultrasound and, following a positive result, micturating cystourethrogram (MCUG) to test for VUR(3). We assumed that children with a positive VUR diagnosis were treated with prophylactic antibiotics according to NICE guidelines.(3)

In the second step of our analyses we assumed that dipstick testing would be used to determine the initial treatment of children considered, based on symptoms and signs, to be at ‘intermediate risk’ of UTI (Figure 1). Children with a positive dipstick result are prescribed antibiotics immediately, whereas no antibiotic is initiated until laboratory culture results are known in those with negative dipstick results.

*Acute Illness*

Recovery in the 21 days following the initial consultation is modelled using a nine-state Markov process with a single-day cycle length (Supplemental figure 1). Each health state has a cost and a utility score. The transition probabilities vary by state depending on the child’s health status (e.g. whether pyelonephritis is present) and treatment prescribed. For example, UTI promptly diagnosed and treated with an antibiotic will become asymptomatic more rapidly than undiagnosed and untreated UTI.

*Medium and long-term models*

The medium-term model (Supplemental figure 2) estimates the number of recurrent UTIs and pyelonephritic attacks, with the associated costs and dis-utility, in the three years after the index consultation. We made the simplifying assumptions that children present with symptoms or signs potentially indicative of UTI at most annually and hence our cycle length was one year. Children with untreated VUR or previous UTI were at increased risk of recurrent of UTI and PA, however these risks were constant across all years of the medium-term model and were not affected by antibiotic treatment received during the index consultation. Costs and utilities of repeat presentations are identical to the index consultation and therefore dependent on the diagnostic strategy adopted. The long-term model (Supplemental figure 3), which is based on previous work(2), calculates the lifetime cost, quality of life and mortality consequences of the most severe UTI complications (progressive renal scarring and end-stage renal disease). The probability of these complications increases with the number of pyelonephritic attacks in the short- and medium- phases of the model.

*Risk stratification*

Of the 3036 children in the DUTY providing a clean catch urine sample, we excluded those with a missing or contaminated research laboratory result (n=346; 11.4%), dipstick result (n=8; 0.3%), or information on GP clinical judgement (n=6; 0.2%). Microbiologically confirmed UTI was defined as ≥10^5 Colony Forming Units (CFU)/mL of a single or predominant uropathogen in the research laboratory culture. Contamination was defined as a NHS laboratory report of heavy mixed growth greater than 10^5 CFU/mL of more than two organisms.(10)

In all strategies 5% (133/2676) of children, including 5 with UTI, were reported by the GP to be ‘very unwell’ and assumed to be referred to hospital for treatment. Based on clinical judgement, the majority of the remainder (2276/2488; 91%) who did not have UTI were classified as ‘lower risk’, but only 56% (31/55) of children with UTI were classified as ‘intermediate’ or ‘higher risk’ (Table 1). When using the DUTY score, the DUTY5% and DUTY≥6 strategies had highest specificity while the DUTY20% and DUTY≥3 strategies had highest sensitivity.

*Short-term model probabilities*

In the DUTY study, 60 (2.2%) of 2,676 children with an uncontaminated clean catch urine sample had a research laboratory confirmed UTI (Table 2). 9 (16.3%) of 55 children with confirmed UTI and temperature recorded had fever (>38°C) and were assumed to have PA. The prevalence of VUR among children with UTI is estimated from a previous meta-analysis.(11)

UTI resistance to non-UTI and UTI antibiotics were based on observed resistance (amoxicillin and trimethoprim respectively) in the DUTY research laboratory reports. We estimated the proportion of children where an antibiotic was prescribed for another disease (not UTI) by calculating the proportion of children without UTI in DUTY whose parents reported antibiotic use within two days of the initial consultation. We assumed that 19% of children would return to primary care before symptom resolution(12) while the probability of further investigation of VUR was based on the proportion of DUTY children with UTI who had an ultrasound scan within three months. The diagnostic accuracy of dipstick tests and NHS laboratory results were defined against the research laboratory in the DUTY study. Estimates of the diagnostic accuracy of ultrasound scans are taken from a previous meta-analysis(2).

*Symptom resolution*

Daily symptom resolution data were collected from parents in DUTY for 14 days after the consultation and used to estimate symptom resolution in children with treated UTI and in children without UTI (Supplemental figure 4). We extrapolated these results to 21 days using Weibull survival models as symptoms had not resolved by 14 days for some children. We estimated the symptom resolution rate in children with untreated UTI based on a small RCT comparing nitrofurantoin to placebo in women with bacteriologically proven UTI (Table 2)(13). We assumed that symptom resolution was reduced by 30% where uropathogens were resistant to the prescribed antibiotic.

For children with delayed antibiotic treatment (e.g. waiting for a laboratory test result), we assumed that daily symptom resolution probabilities were the same as untreated UTI for the first two days. We assumed that the antibiotic treatment effect persisted for seven days, meaning treated and untreated symptom resolution probabilities were identical between day 8 and 21, and that all symptoms resolved by 21 days.

*Medium and long-term model*

Estimates of the probability of primary care re-consultation with or without UTI, effectiveness of prophylactic treatment in children with VUR, long-term incidence of PRS and ESRD and survival are described in Table 2 and detailed elsewhere.(10)

*Costs and Utilities*

Based on observations in the DUTY study, the average time taken for a urine sample with and without a dipstick test was 12.0 minutes (Cost: £8.10) and 9.1 minutes (Cost: £7.03) respectively (Supplemental table 4). We assumed that GPs spent 45 seconds (£2.42) interpreting laboratory results and 5 minutes (£16.08) contacting parents to revise prescriptions. We estimated antibiotic costs based on amoxicillin (125mg/5mL) for children treated for a non-UTI diagnosis and trimethoprim (50mg/5mL) for children with a UTI diagnosis. Other costs of initial care were based on a questionnaire completed by parents in the DUTY study 14 days post-consultation. We mapped drugs to BNF codes(14) using the 2011 prescription cost analysis dataset(15). In the longer-term we assumed that children with PRS have no increased costs of care until the onset of ESRD. Individuals with ESRD are treated by dialysis with an on-going annual cost until death(16) or renal transplant with a treatment cost at the time of procedure. All costs were inflated to 2014/15 prices using the hospital and community health services pay and prices inflation factor.(17)

In the absence of utility studies in infants with UTI(18), we used estimates from a study on rotavirus(19) (Supplemental table 4) as the TAPQOL questionnaire, administered to children in the DUTY study, demonstrated that health-related quality of life for children with UTI and gastroenteritis were similar (Supplemental table 5). We used utility values for pyelonephritis in adults reported in the literature.(20) We assumed that individuals with PRS experience no quality of life decrement until ESRD onset. Utility estimates for patients on dialysis and following renal transplant were estimated from previous research.(21)

*Analysis*

Data management was conducted in Stata and the model was implemented in Winbugs 1.4.3(22) using diffuse prior distributions for all parameters. The full model code is available in Supplementary file 1. We calculated the expected costs, benefits and incremental net monetary benefit (iNMB)(23) of each strategy compared to clinical judgement assuming the health service is willing to pay £20,000 per QALY(24). Outcomes and costs beyond the first year were discounted at 3.5%.(24) We assigned probability distributions to each model parameter and used Markov chain Monte Carlo sampling to propagate parameter uncertainty through to the outcomes.

We undertook the following deterministic sensitivity analyses to evaluate the robustness of our conclusions to model assumptions: 1) increase in UTI prevalence to 10%; 2) perfectly accurate NHS laboratory cultures; 3) doubled antibiotic treatment effect; 4) doubled disutility from UTI infection 5) Simpler model excluding VUR and pyelonephritis 6) doubled probability of PRS; 7) doubled cost of ESRD

**Results**

*Diagnostic accuracy and treatment*

DUTY study GPs reported a working diagnosis of UTI in 9.1% of children when using clinical judgement including just over half of children who had a confirmed UTI (sensitivity = 56.4%; Table 3). Using the DUTY5% strategy urine sampling could be approximately halved (4.8%) without any loss of sensitivity (58.2%). Alternatively, the DUTY10% strategy samples a similar proportion (9.6%) of children as clinical judgement, but has substantially higher sensitivity (70.9%). The most sensitive DUTY clinical rules (DUTY20%, DUTY≥3) achieved sensitivities in excess of 80%, but resulted in large increases in urine sampling (19.9% and 26.4% respectively). The sensitivity of each strategy is reduced by the laboratory culture as NHS laboratories had imperfect diagnostic accuracy. Compared to clinical judgement, the DUTY10% rule results in a higher proportion of children with UTI treated with an antibiotic to which the bacterium was sensitive (56.4% versus 49.2%). However, a substantial proportion (>34%) of children with UTI receive either no or an inappropriate antibiotic under all strategies.

*Short-term costs and outcomes*

Mean sampling, laboratory culture and antibiotic costs were lowest in the high-specificity diagnostic strategies (e.g. DUTY≥6 £1.08; DUTY5% £1.22; clinical judgement £1.99; Table 3). Short-term outcomes were very similar between diagnostic strategies. Short-term average QALDs were 20.73 for all strategies, while the number of asymptotic days ranged from 16.34 to 16.35, although small differences existed at the third and fourth decimal place. These similarities are driven by the low prevalence of UTI, the small differences in diagnostic accuracy of strategies and the limited effect of antibiotics on acute symptom duration.

The high specificity DUTY clinical rules (DUTY5%, DUTY≥6, DUTY≥5) were more cost-effective than clinical judgement in the short-term (iNMB = £0.78, £0.84 and £0.42 respectively; Table 3). These efficiencies are predominantly due to financial savings arising from fewer, better targeted, urine samples compared to clinical judgement. The DUTY10% rule had similar short-term cost-effectiveness to clinical judgement (iNMB = £0.00). For the highest sensitivity DUTY clinical rules (DUTY20%, DUTY≥4, DUTY≥3) the benefit of identifying and treating slightly more UTIs was outweighed by the higher costs of sampling and testing substantial numbers of children (iNMB = £-1.69, £-1.93, £-2.61 respectively).

*Medium / long-term costs and outcomes*

In the medium and long-term, diagnostic strategies with the highest sensitivity led to VUR treatment in a larger proportion of cases and had slightly lower rates of UTI recurrence (Table 4). However, differences between strategies in life expectancy and QALYs were negligible. The high specificity diagnostic strategies (i.e. DUTY5%, DUTY≥6, DUTY≥5) were more cost-effective than clinical judgement in the long-term (iNMBs £2.31, £2.50, and £1.22 respectively). Even small differences in net benefits per child are important given the large number of children with acute illness presenting to primary care (Table 4, final row).

*Laboratory vs. dipstick-based treatment*

In the DUTY5% strategy, 2.3% of children (18.8% of whom have UTI) are considered intermediate risk (Table 1) and, in the absence of a dipstick test, clinicians would have delayed treatment pending the laboratory test result. Dipstick testing and treatment for children with positive leukocytes and nitrites results in 25.0% of those with intermediate risk of UTI receiving immediate antibiotics to which the bacterium was sensitive (Table 5). However dipstick testing increased the proportion of children without UTI incorrectly treated compared to LT (3.3% versus 2.3%). Average sampling, testing and treatment costs are higher in this DT strategy (£17.13) than in the LT strategy (£15.66), mainly due to the additional time and cost of the dipstick test. Both DT strategies had poorer cost-effectiveness compared to those based on laboratory testing of children at intermediate risk of UTI (iNMB = £-1.41 for leukocytes and nitrites; iNMB = £-1.91 for leukocytes or nitrites).

*Sensitivity analysis*

Both the probabilistic (Tables 3 and 4) and deterministic sensitivity analyses (Supplemental tables 6 and 7) indicate that the finding that the DUTY5% strategy is more cost-effective than clinical judgement is robust to substantial changes in key model parameters. Our short-term results were similar when using a simplified model which did not seek to estimate the impact of VUR or pyelonephritis suggesting these elements did not play an important role in driving our conclusions.

**Discussion**

**Summary of findings**

We evaluated the cost-effectiveness of a two-step clinical rule using symptoms, signs and dipstick test results to select children for urine sampling and antibiotic treatment. Compared to GPs’ clinical judgement, the DUTY5% clinical rule could substantially reduce urine sampling, achieving lower costs and equivalent patient outcomes. DUTY points-based rules are more cost-effective than clinical judgement at high specificity thresholds (DUTY≥5, DUTY≥6) and could be used where it is infeasible to estimate the DUTY coefficient-based score. Our findings suggest that urine sampling should be more carefully targeted, rather than increased, but do not support the use of dipstick testing in children at intermediate risk of UTI. The benefits of immediate dipstick-guided treatment were counterbalanced by imperfect test specificity resulting in more antibiotic prescriptions in children without UTI.

**Strengths and limitations**

Our model was based on individual patient data from a large, rigorously conducted, prospective diagnostic cohort study. Therefore, most of the parameters underlying the short-term model come from a consistent, high-quality data source. In the DUTY study, urine samples were analysed by both health service and research laboratories providing more accurate estimates of the prevalence of UTI and contamination. Furthermore, we were able to model the impact of false negative laboratory results and antibiotic resistance on the efficiency of UTI diagnosis. Our results are based on evidence from children in whom clean catch samples were collected and are not necessarily generalizable to younger children where nappy pads are generally used for sampling. The ‘clinical judgement’ diagnostic strategy aimed to represent current practice, based on clinicians’ responses to questions about working diagnoses and testing and treatment plans. However, DUTY study participation may have sensitised clinicians to the possibility of UTI, leading to an over-estimate of urine sampling rates. While this would not alter our conclusion that selected symptoms and signs can help primary care clinicians to target urine sampling, it does strengthen the interpretation that high specificity diagnostic strategies (e.g. DUTY 5%, DUTY≥5) are most likely to be cost-effective in diagnosing and treating UTI.

Some of the evidence underlying the model was imprecise and potentially biased. For example, there is no RCT-based evidence on the effect of antibiotics in young children with UTI. The evidence underlying the long-term model is based on observational associations between recurrent UTI and renal disease which continues to evolve: the RIVUR trial comparing daily trimethoprim–sulfamethoxazole prophylaxis to placebo in children with VUR recently reported a 50% reduction in recurrent UTI, but no trend for reduced incidence of renal scarring(25). Similarly, the choice of sampling distribution for some parameters, in particular costs and utilities, was based on convention rather than primary data introducing subjectivity into the probabilistic sensitivity analysis.

Our model did not include other potential long-term consequences of UTI such as pregnancy-related complications or hypertension where the causal role of UTI is debated and difficult to ascertain(26, 27). It is possible that other long-term consequences of UTI exist. Identifying and including these would favour more sensitive strategies. However, our conclusions were insensitive to different assumptions about the long-term sequelae of UTI. The model results are dominated by the short-term costs of testing and treating rather than long-term sequelae because most children presenting to primary care do not have UTI, most children with UTI will not develop ESRD, and each strategy only has a small impact on the proportion of children treated appropriately.

The large number of risk thresholds and the multiple ways of using dipstick testing and laboratory culture to guide treatment, produce an almost unlimited number of potential management strategies. We evaluated some which closely reflect current practice, but other unevaluated strategies could prove more cost-effective. We did not quantify the societal costs of antibiotic resistance. Current methods may underestimate the cost of antibiotic resistance and accurate estimation may not be possible.(4) Given increasing levels of resistance and the paucity of new antibiotics, the inclusion of these costs would further strengthen the case for high specificity diagnostic strategies that limit prescriptions to those most likely to have a UTI.

**Results in context with other studies**

As far as we are aware, this is the first study to evaluate the cost-effectiveness of a clinical rule to identify children with UTI in primary care. Previous work has assessed the most cost-effective test or series of tests for diagnosing UTI rather than evaluating which children should be considered at risk of UTI. An economic model evaluating testing strategies for children with suspected UTI concluded that either presumptive treatment or treatment based on positive dipstick nitrites and leukocyte and MCUG were optimal(2). Our findings suggest that waiting for a positive laboratory culture is more cost-effective in children at ‘intermediate risk’ of UTI. The differences in findings are likely to be partly due to the inclusion of serendipitous treatment and detailed daily symptom resolution rates in our model.

**Clinical and research implications**

Each year large numbers of young children present to primary care with acute illness. Therefore, even small modifications to diagnostic strategies for common conditions such as UTI will have a large impact on aggregate costs and workload. Our findings demonstrate the need for clinicians to base the decision to collect a urine sample on symptoms and signs known to be predictive of UTI in primary care rather than on personal judgement, or evidence derived from secondary care. Our results also illustrate the trade-off between the small but certain short-term costs of UTI diagnosis and treatment against the important but less certain benefits of detecting and treating UTI, and potentially preventing renal disease.

Our findings suggest that clinicians should select low-cost, high specificity, diagnostic strategies. A GP requesting urine samples in children using the DUTY5% strategy, would sample 4.8% of all acutely unwell children, and request a sample in 58% of children who have UTI at a testing and antibiotic cost of £1.22 per child. Where symptoms and signs are routinely recorded in electronic records, this process could be automated. However, in settings where resources do not permit this, a GP using DUTY≥5 strategy would sample 6.7% of all acutely unwell children, including 53% of children who have UTI, at a testing and antibiotic cost of £1.57 per child. Both strategies are more cost-effective than clinical judgement alone.

Our research does not support the routine use of dipstick testing to guide treatment. However this conclusion is based on weak evidence about the effect of antibiotics. Trial evidence comparing the cost-effectiveness of management strategies in women with suspected UTI concluded that all strategies achieved similar symptom control and that dipstick test guided management was likely, albeit with considerable uncertainty, to be cost-effective(28, 29). A similar trial of management strategies in infants is needed. Studies of parent-reported quality of life and disutility of UTI symptoms in young children would enable more precise estimates of short-term benefits of antibiotics. Long-term epidemiological study designs are needed to better quantify and understand the association between childhood UTI and renal disease.

**Conclusions**

The DUTY coefficient and points scores were more cost-effective than GPs’ clinical judgement in selecting children for urine sampling and treatment for UTI. Small differences between strategies in cost-effectiveness are important given the large number of urine samples collected in children. High specificity thresholds, such as DUTY≥5, are simple to implement and likely to be most cost-effective than clinical judgement. Our findings do not support the routine use of dipstick testing, but trial evidence is needed to compare the cost-effectiveness of various management strategies.

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