



Information for press and media (06.03.18)

CUTIC is a patient group campaigning to raise awareness about chronic urinary tract infection (UTI), improve testing and treatment, and challenge the orthodoxy that chronic lower urinary tract symptoms (LUTS) are caused by inflammation rather than bacteria.

UTI accounts for 1-3% of GP appointments. A third of women will have a UTI before they are 24, with one in 10 girls and one in 30 boys having a UTI by the age of 16. Even in healthy patients, 20-30% fail initial antibiotic treatment.¹ About 70% experience another UTI within a year.² *Up to 1.4 million women in Britain suffer from chronic bladder pain and urinary dysfunction – and a similar number of men are thought to be affected.*³

More strains of bacteria that cause UTIs – particularly E. coli – are becoming resistant to front-line antibiotics. This means that more patients will find that standard antibiotics will fail to clear their infection. There is also a worrying rise in potentially fatal sepsis caused by antibiotic-resistant UTIs.

Time and again, the story we hear from UTI sufferers is that they are denied antibiotics despite having clear signs and symptoms of an infection. They are increasingly caught between an over-reliance on unreliable diagnostic tests and reluctance to prescribe in the face of current debates about antimicrobial stewardship and Government strategies to reduce inappropriate use of antibiotics. Untreated or poorly treated UTIs can become chronic – causing years of suffering.

Rates of UTI and urinary sepsis are rising sharply

CUTIC's Freedom of Information Requests to NHS Trusts across England in January 2018 found:

1. The number of adults aged 16-64 attending A&E with UTI rose 54% from 2012 to 2016; hospital admissions for UTI rose 23%; and there was a 34% increase in urosepsis diagnoses.
2. The number of adults aged 65 and over attending A&E rose 61% from 2012 to 2016; hospital admissions rose 21%; and there was a 39% increase in urosepsis diagnoses.
3. The number of children aged 18 and under attending A&E with UTI rose 57%; hospital admissions for UTI rose 21%; and there was a 37% increase in urosepsis diagnoses.

		2012	2013	2014	2015	2016	Period Increase 2012 vs. 2016	No. Trusts Responded
Children <18 Years	Children Attending A&E	16,148	16,363	18,615	17,921	19,431	20%	63
	Children Admitted to Hospital (exc. GOSH)	9,045	9,243	9,975	10,046	10,854	20%	80
	Children Admitted to Hospital (Inc. GOSH)	9,995	9,725	10,278	10,312	11,088	11%	81
	Children Diagnosed with Urinary Sepsis	2,682	2,916	3,249	3,189	3,278	22%	51
Adults 16-64 Years	Adults 16-64 Attending A&E	44,838	49,296	57,687	59,967	68,848	54%	63
	Adults 16-64 Admitted to Hospital	47,350	50,278	56,395	55,201	58,184	23%	80
	Adults 16-64 Diagnosed with Urinary Sepsis	11,977	12,874	13,670	14,721	16,005	34%	54
Adults >65 Years	Adults 65+ Attending A&E	36,110	40,488	46,702	48,882	58,174	61%	61
	Adults 65+ Admitted to Hospital	101,619	104,474	116,619	120,153	122,648	21%	78
	Adults 65+ Diagnosed with Urinary Sepsis	32,166	35,985	39,909	44,079	44,648	39%	59
Total Adults 16+	Adults 16+ Attending A&E	80,948	89,784	104,389	108,849	127,022	57%	61
	Adults 16+ Admitted to Hospital	148,969	154,752	173,014	175,354	180,832	21%	78
	Adults 16+ Diagnosed with Urinary Sepsis	44,143	48,859	53,579	58,800	60,653	37%	59

Standard tests for UTI are failing patients

Tests and diagnostic criteria used to diagnose UTIs have been shown to be flawed and unreliable in numerous studies.^{4 5}

Compared with new testing methods (expanded-spectrum EQUC testing), standard urine culture missed 67% of uropathogens overall and 50% in participants with severe urinary symptoms.⁶ Standard culturing was unable to differentiate between the urine of patients with overactive bladder syndrome and healthy controls, while enhanced testing methods found significant differences in the bacteria present in their bladders (the microbiome).⁷

Urine culture missed 20% of infections in a 2017 GP-led study of first-time consultations which concluded: *“The woman that is visiting you with typical urinary complaints has an infection. There is nothing more to explore.”*⁸

Time and again, doctors equate a lack of evidence of bacterial infection as evidence of no bacterial infection and disregard patients’ symptoms. Failure to respond to front-line antibiotics is also frequently and incorrectly held up as evidence of no bacterial infection.

Where does this leave patients?

Patients are left with debilitating, life-changing symptoms including needing to pee dozens of times a day, urinary urgency, agonizing pain, being unable to sleep properly, work, look after children and have normal sexual relationships. Their lives grind to a halt.

The standard pathway for referral is to a urologist. Patients are then subjected to a raft of invasive procedures such as cystoscopies, bladder biopsies, urodynamics testing and bladder and urethral stretches. The latter are currently considered a quality of care problem in the US for the paucity of evidence.⁹

Interstitial cystitis and painful bladder syndrome

Many chronic UTI sufferers are eventually told that they have interstitial cystitis (IC) or painful bladder syndrome (PBS). But these are not proper diagnoses – merely descriptions of symptoms. NHS Choices website says that IC is “poorly understood”, “the exact cause is not clear” and “there is no cure”. The picture painted is of an incurable, progressive and life-limiting disease.

Sufferers are prescribed painkillers, including opiates, bladder relaxants and bladder instillations. Studies show they achieve ‘limited symptom relief’ while carrying a considerable list of potentially serious side effects.¹⁰

When, at the end of this, the patient is still no better they are routinely dismissed as anxious and offered counselling and psychiatric referrals. Sufferers are forced to live in agony and lack of quality of life without ever finding effective treatment.

NICE Guidelines

Current guidelines are contradictory and flawed. For example, the Scottish Intercollegiate Guidelines Network on which NICE and PHE guidance for diagnosing UTI is based call for a

positive test result but also state that “tests for bacteria or pyuria do not establish the diagnosis of UTI” and “the diagnosis of UTI is primarily based on symptoms and signs”.

NICE itself says there is a ‘need for evidence-based guidance for recurrent UTIs’ but states that ‘no source guidance is currently available’.¹¹

The LUTS Clinic at the Whittington Hospital in north London

Many of CUTIC's members have been or are patients at the Lower Urinary Tract Symptoms (LUTS) Clinic which is pioneering treatment of and research into chronic UTI. The clinic uses patient case histories, a specific symptom score, physical signs and analyses of fresh urine under a microscope to count white blood cells and cells of the bladder wall in the urine.

It will then treat with long-term first line oral antibiotics and a urinary antiseptic until symptoms, signs and urine analysis become normal.

It is not yet certain why protracted treatment and higher antibiotic doses are necessary. Microbes can hide inside the cells of the bladder and form protective biofilms which may protect them from antibiotic attack. Longevity of disease may play a part since the patients have suffered for an average of six years by the time that they first attend.

Long-term antibiotic treatments are going to be associated with increased risks. This is explained to the patients, who understand the situation. The clinic shares everyone's worries about antibiotic resistance and overuse and research is ongoing into shortening treatment duration and developing topical antibiotics rather than using them systemically.

PATIENT TESTIMONIALS

The following are excerpts from “bladder stories” as told to CUTIC by chronic UTI sufferers.

KL:

“I spent a year going to my GP, for them to send off urine samples, only to be told countless times that there was nothing wrong with me. I was finally referred for a cystoscopy but all they found was inflammation. I bled terribly for months after that and my symptoms became much worse. I was bed-bound for nearly six months. In 2014 I was admitted to hospital 24 times with extreme bladder and kidney pain.

I was told by Urology that I had interstitial cystitis and that all they could do was manage my symptoms. I lost my identity, my job and all of my confidence. I was countlessly told I was imagining this, and that would I benefit from CBT counselling.”

FE:

“Several urine tests at the GP surgery and samples that were sent to the laboratory came back as clear apart from three that registered as 'mixed growth' and were interpreted as 'contamination'.

After the initial urology appointment I was given a full examination and tests to check the functions of the bladder. The results proved to be normal and I was told that what I was experiencing was 'just a post-menopausal problem – it's nothing'.

I explained that I was still in intense pain but the consultant was dismissive. I told him again that it felt like a bladder infection and he said that I should seek a referral to him in three months' time if I still thought that was the case. I left the hospital in complete despair.

I must stress that it is the pain of this condition that is not to be underestimated. At times it has felt as if a razor blade is being slowly dragged across the bladder wall and through the urethra – it is pure torture. Obviously this has a terrible impact on day-to-day living and on quality of life in general.”

PH:

“I can't remember how many times I went to the doctor. They started putting on my notes that I was an anxious woman. Eventually they sent me to a psychiatrist. He basically said: 'You're quite anxious. You've regressed back to being a baby'. That was terrifying to hear. Being told it's in your head when you're in so much pain is incredibly scary.

AP:

“At the age of six my daughter had pain, urgency and frequency. She was unable to sleep at night and attend school. She had faecal incontinence. At worst she was only able to hold 10ml of urine. She told me that she wanted to die.

Short courses of antibiotics cleared the infection, only for it to return 48 hours later. Urine cultures came back as contaminated sample, mixed growth. These were deemed negative by the GP.

At the local hospital the consultant suggested A had painful bladder syndrome and prescribed cimetidine (inhibits stomach acid production and mainly used in the treatment of heartburn and peptic ulcers) even though she would have a temperature, pain urgency and frequency – clear signs of infection.”

KD:

“S had her first urinary tract infection at the age of two. By the age of four she was having regular, acute infections with fever, vomiting, severe stomach pain, pain on passing urine and extreme tiredness.

One consultant told me: “she is just one of those children that gets infections”. A paediatrician declared that urine test results showed there was no infection and constipation was the cause of the stomach pain. She asked me to stop asking S if she has pain on passing urine.

Four years of this is a long time in a little girl’s life. My very bright, happy little girl is now anxious, in constant pain and is missing her friends and schooling.”

GH:

“As a child, I received a misdiagnosis of Overactive Bladder Syndrome following several urine cultures showing mixed growth. My doctor suggested that I should be denied access to a toilet for long periods while at school in order to ‘train’ my bladder. The incredible pain, embarrassment, deterioration and fear that I suffered meant that I became too terrified to attend.

Due to increasingly worsening symptoms, I underwent two urodynamics studies, three KUB ultrasounds and two rigid cystoscopies under anaesthetic. During the second one I also underwent a ureteroscopy, retrograde study, urethral dilation, dilation of both ureters and bladder distension.

These investigations came at a massive cost to my health and I was hospitalised on multiple occasions with severe uncontrollable pain, vomiting, septicaemia, kidney infections, urinary retention and passing frank blood clots that were so thick that I was unable to pass urine.

Despite seeing five urologists, multiple doctors, nurses and incontinence specialists, I was offered no answers or solutions to my problems.”

JG:

“From 2008 to 2014 I became more and more unwell and suffered constant and severe urethral and bladder pain which spread into my pelvic floor as well as constant irritation, burning, frequency, urgency and incontinence.

I had CT and MRI scans, further tests and consultations with gynaecologists, urologists, uro-neurologists, pain consultants and pelvic floor specialists. I saw around 10 consultants. I tried many treatments: specialist pelvic physical therapy, OAB medications, nerve treatments, pain medications, PTNS, acupuncture and hormonal therapies.

In seven years I did not find one doctor who had any diagnosis or treatment plan. I was told that I should learn to live with this pain and that there was no hope of improvements.

At various times I told consultants and GPs I felt I had an infection – they just dismissed me saying I was having a ‘flare’ of pain. I had raised levels of white blood cells at various times but was told it meant nothing by many different doctors and clinics. I asked often for a sample to be sent off for culturing but was repeatedly refused.

I had no diagnosis and no hope. I had relentless pain every day and night with no ending in sight.”

VM:

“The pain was difficult to live with. I told my urogynaecologist about my bladder pain but he just did urodynamics tests said there was nothing wrong. I asked for further investigation but he told me there was no reason to do this.

All the time my GP kept testing my urine and occasionally giving me short antibiotic courses due to me having white blood cells in my urine but no bacteria could be grown from my urine.

I then saw another urogynaecologist. They also did urodynamics – invasive testing which made me feel worse. I was given a flexible cystoscopy. The nurse tried to put the tube into my urethra but it was so swollen that the flexible cystoscopy tube first went into my vagina. The infection in my bladder wall could be seen on the screen. The nurse explained to me that I had follicular cystitis which had been caused by an infection not having been treated correctly. I bled for five days quite badly from the tube being inserted.

I was given antibiotics for a few weeks but the infection got far worse. Even getting to the hospital for my appointments was very difficult. I felt suicidal with the pain that went on 24 hours a day and was impossible to sleep through. My GP just didn’t know what to do because the lab tests kept coming back negative.”

The inadequacy of standard dipstick tests and urine cultures – notes by Professor James Malone-Lee

The gold standard test for diagnosing urinary tract infection during the last sixty years has been to culture a midstream urine specimen and identify a pure growth of a known urinary pathogen.

Different institutions vary in the threshold count of the number of microbes of a known urinary pathogen that they use. The range is 10^2 to 10^6 . People argue about the appropriate threshold (the original Kass threshold being 10^5) but that is to miss the point.

It is not correct to claim that the problems with this gold standard are overcome by dropping the threshold count for the diagnosis of UTI.

The original work conducted on UTI by Kass in 1957 to 1960 compared patients, experiencing the severe infections of pyelonephritis, with normal controls. This causes a spectrum bias so that Kass' criterion should not be applied to patients with simple cystitis or lower urinary tract symptoms. The test was never validated for such purposes

The quantitative urinary culture thresholds rest on a number of assumptions that were not properly checked:

(1) The normal bladder is sterile – It is not. Several researchers have refuted that in recent years ^{1,2}.

(2) There is a quantitative relationship between the culture results and the probability of infection - This has not been proved – Culture numbers are more likely to depend on the ease of growth rather than anything else UTI ^{1,3-12}.

(3) The infection should be caused by a single species – Modern published data imply that this is far from the case and that infection with mixed organisms is all too possible ^{6,13,14}.

(4) Cultures of mixed organisms imply contamination - This has never been proven – It is only an assumption and modern data refute this, providing solid evidence of a bladder origin for mixed growths ^{6,13,14}.

(5) If epithelial cells are seen in the midstream urine specimen then it indicates contamination ¹⁵ – This is an assumption – It has not been proven – Modern data demonstrate that the majority of urinary epithelial cells come from the urinary tract. The numbers of these cells are elevated in patients with urinary infection and a proportion are parasitised by microbes. The proportion of parasitised cells is higher amongst patients in comparison to controls. These false assumptions result in samples, exhibiting a pathological signal, being rejected for analysis ¹⁶⁻²¹.

(6) That if the culture is negative then there is no infection – This is an assumption – It has not been proven – There is much evidence that urinary infection can be caused by non-

culturable microbes, microbes that grow in small numbers, and microbes with fastidious culture requirements ^{3,14,22-28}.

The wrong gold standard

Since 1983 the literature has published data that cast considerable doubt on the veracity of the urine culture. Nevertheless it persists as the gold standard reference for diagnosing urinary infection.

There is much evidence to suggest that the culture method is insensitive ^{3,14,22-28}. However, it is commonplace for a patient with appropriate symptoms to be told that they do not have infection because the culture is negative. That is to confuse absence of evidence of disease with evidence of absence of disease – These are wholly different.

Screening tests

The popular screening test for UTI, used throughout the health services, involving dipstick analysis of the urine, has been calibrated to quantitative urine culture assuming it to be an accurate gold standard. By doing this, it adds the errors of the culture to the inherent errors of the dipstick method. It should be no surprise therefore that there is a substantial literature that criticises the sensitivity and performance of this test. Nevertheless numerous symptomatic people are dismissed as normal on the grounds of a negative dipstick test. There is no scientific justification for this ^{3,8,9,10,12,29-31}.

These tests cannot exclude acute or chronic UTI ^{1,3-12}, and do not take into account differences in bacterial strain virulence, host genetic variability, intracellular bacterial reservoirs, or even the dilution of the urine specimen due to high liquid intake before the test. Therefore, it is conceivable that legitimate infections will be missed when relying on a rigid numerical threshold to distinguish between 'infected' and 'not infected'.

References

1. Hilt EE, McKinley K, Pearce MM, et al. Urine is not sterile: use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. *J Clin Microbiol*. 2014;52(3):871-876.
2. Ollberding NJ, Volgyi E, Macaluso M, et al. Urinary Microbiota Associated with Preterm Birth: Results from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) Study. *Plos One*. 2016;11(9):e0162302.
3. Stamm WE, Counts GW, Running KR, Fihn S, Turck M, Holmes KK. Diagnosis of coliform infection in acutely dysuric women. *N Engl J Med*. 1982;307(8):463-468.
4. Kunin CM, White LV, Hua TH. A reassessment of the importance of "low-count" bacteriuria in young women with acute urinary symptoms. *Annals of internal medicine*. 1993;119(6):454-460.
5. Walsh CA, Siddins A, Parkin K, Mukerjee C, Moore KH. Prevalence of "low-count" bacteriuria in female urinary incontinence versus continent female controls: a cross-sectional study. *International urogynecology journal*. 2011;22(10):1267-1272.
6. Wolfe AJ, Toh E, Shibata N, et al. Evidence of uncultivated bacteria in the adult female bladder. *J Clin Microbiol*. 2012;50(4):1376-1383.
7. Khasriya R, Sathiananthamoorthy S, Ismail S, et al. Spectrum of bacterial colonization associated with urothelial cells from patients with chronic lower urinary tract symptoms. *J Clin Microbiol*. 2013;51(7):2054-2062.

8. Khasriya R, Khan S, Lunawat R, et al. The Inadequacy of Urinary Dipstick and Microscopy as Surrogate Markers of Urinary Tract Infection in Urological Outpatients With Lower Urinary Tract Symptoms Without Acute Frequency and Dysuria. *JUrol*. 2010;183(5):1843-1847.
9. Kupelian AS, Horsley H, Khasriya R, et al. Discrediting microscopic pyuria and leucocyte esterase as diagnostic surrogates for infection in patients with lower urinary tract symptoms: results from a clinical and laboratory evaluation. *Bju Int*. 2013 Jul;112(2):231-8.
10. Hurlbut TA, 3rd, Littenberg B. The diagnostic accuracy of rapid dipstick tests to predict urinary tract infection. *American journal of clinical pathology*. 1991;96(5):582-588.
11. Gorelick MH, Shaw KN. Screening tests for urinary tract infection in children: A meta-analysis. *Pediatrics*. 1999;104(5):e54.
12. Deville WL, Yzermans JC, van Duijn NP, Bezemer PD, van der Windt DA, Bouter LM. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMCUrol*. 2004;4:4.
13. Price TK, Dune T, Hilt EE, et al. The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. *J Clin Microbiol*. 2016;54(5):1216-1222.
14. Bartlett RC, Treiber N. Clinical significance of mixed bacterial cultures of urine. *American journal of clinical pathology*. 1984;82(3):319-322.
15. Collier S, Matjiu F, Jones G, Harber M, Hopkins S. A prospective study comparing contamination rates between a novel mid-stream urine collection device (Peezy) and a standard method in renal patients. *J Clin Pathol*. 2014;67(2):139-142.
16. Rosen DA, Hooton TM, Stamm WE, Humphrey PA, Hultgren SJ. Detection of intracellular bacterial communities in human urinary tract infection. *PLoS Med*. 2007;4(12):e329.
17. Dalal E, Medalia O, Harari O, Aronson M. Moderate stress protects female mice against bacterial infection of the bladder by eliciting uroepithelial shedding. *Infect Immun*. 1994;62(12):5505-5510.
18. Smith YC, Rasmussen SB, Grande KK, Conran RM, O'Brien AD. Hemolysin of uropathogenic *Escherichia coli* evokes extensive shedding of the uroepithelium and hemorrhage in bladder tissue within the first 24 hours after intraurethral inoculation of mice. *Infect Immun*. 2008;76(7):2978-2990.
19. Thumbikat P, Berry RE, Zhou G, et al. Bacteria-induced uroplakin signaling mediates bladder response to infection. *PLoS pathogens*. 2009;5(5):e1000415.
20. Hannan TJ, Mysorekar IU, Hung CS, Isaacson-Schmid ML, Hultgren SJ. Early severe inflammatory responses to uropathogenic *E. coli* predispose to chronic and recurrent urinary tract infection. *PLoS Pathog*. 2010;6(8):e1001042.
21. Horsley H, Malone-Lee J, Holland D, et al. *Enterococcus faecalis* subverts and invades the host urothelium in patients with chronic urinary tract infection. *Plos One*. 2013;8(12):e83637.
22. Kass EH. Bacteriuria and the diagnosis of infection in the urinary tract. *ArchInternMed*. 1957;100:709-714.
23. NICE. Urinary tract infection (lower) - women. NICE guidelines. 2014. <http://cks.nice.org.uk/urinary-tract-infection-lower-women#!topicsummary>.
24. Epp A, Laroche A, Lovatsis D, et al. Recurrent urinary tract infection. *J Obstet Gynaecol Can*. 2010;32(11):1082-1101.
25. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52(5):e103-120.

26. Hooton TM. Practice guidelines for urinary tract infection in the era of managed care. *IntJAntimicrobAgents*. 1999;11(3-4):241-245.
27. Naber KG, Bergman B, Bishop MC, et al. EAU guidelines for the management of urinary and male genital tract infections. Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU). *European urology*. 2001;40(5):576-588.
28. Latham RH, Wong ES, Larson A, Coyle M, Stamm WE. Laboratory diagnosis of urinary tract infection in ambulatory women. *JAMA*. 1985;254(23):3333-3336.
29. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *The New England journal of medicine*. 1978;299(17):926-930.
30. Bent S, Saint S. The optimal use of diagnostic testing in women with acute uncomplicated cystitis. *Disease-a-month : DM*. 2003;49(2):83-98.
31. St John A, Boyd JC, Lowes AJ, Price CP. The use of urinary dipstick tests to exclude urinary tract infection: a systematic review of the literature. *American journal of clinical pathology*. 2006;126(3):428-436.

1 Milo et al. Duration of Antibacterial Treatment for Uncomplicated Urinary Tract Infection in Women. *The Cochrane Database of Systematic Reviews*. 2005(2):CD004682

2 Foxman B. The Epidemiology of Urinary Tract Infection. *Nature Reviews Urology*. 2010 7(12):653-660

3 Rand Interstitial Cystitis Epidemiology Study 2010

4 Swamy, Gorny and Malone-Lee. Fallacies and Misconceptions in Diagnosing Urinary Tract Infection. July 2014 *futuremedicine.com*. <https://doi.org/10.2217/fmeb2013.13.276>

5 Kupelian et al. Discrediting Microscopic Pyuria and Leucocyte Esterase as Diagnostic Surrogates for Infection in Patients with Lower Urinary Tract Symptoms: Results from a clinical and laboratory evaluation. *BJU International* 2013

⁶ Price et al. The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. *Journal of Clinical Microbiology*. May 2016 (54) 5

⁷ Gill et al. A blinded observational cohort study of the microbiological ecology associated with pyuria and overactive bladder symptoms. *International Urogynecology Journal*. January 2018. <https://doi.org/10.1007/s00192-018-3558-x>

8 Heytens et al. Women With Symptoms of a Urinary Tract Infection but a Negative Urine Culture: PCR-based quantification of *Escherichia coli* suggests infection in most cases. *Clinical Microbiology and Infection*. 2017

9 Santucci, Richard A. et al. "Office Dilation of the Female Urethra: A Quality of Care Problem in the Field of Urology." *The Journal of urology* 180.5 (2008): 2068–2075. PMC. Web. 15 Sept. 2017.

10 'Pelvic pain in Urogynecology. Part II: treatment options in patients with lower urinary tract symptoms' and 'An Overview of Pain Management: The Clinical efficacy and Value of Treatment' by S. Nalamachu. *American Journal of Managed Care* 2013; 19 (14 suppl): S261-S266

11 SIGN 88 guidelines 1.4 Key