BMJ Open

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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-018557 |
| Article Type: | Research |
| Date Submitted by the Author: | 06-Jul-2017 |
| Complete List of Authors: | O'Sullivan, Jack; Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences<br>Albasri, Ali<br>Nicholson, B; University of Oxford,<br>Perera, Rafael; University of Oxford, Primary Health Care<br>Aronson, Jeffrey; University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences<br>Roberts, Nia; University of Oxford, UK, Bodleian Health Care Libraries,<br>Heneghan, Carl; Oxford University, Primary Health Care |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Diagnostics, General practice / Family practice |
| Keywords: | PRIMARY CARE, RADIOLOGY & IMAGING, EPIDEMIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT |
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# Over and undertesting in primary care: a systematic review and meta-analysis.

O'Sullivan J[1], Albasri A[1], Nicholson B[1], Perera R[1], Aronson J[1], Roberts N[2], Heneghan C[1]

[1] Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Science, University of Oxford, UK

[2] Bodleian Health Care Libraries, University of Oxford.

Jack W O'Sullivan, Clinical Researcher, jack.osullivan@phc.ox.ac.uk

Ali Albasri, Clinical Researcher, ali.albasri@gtc.ox.ac.uk

Brian D Nicholson, Clinical Researcher, brian.nicholson@phc.ox.ac.uk

Rafael Perera, Professor of Medical Statistics, rafael.perera@phc.ox.ac.uk

Jeffrey Aronson, Reader in Evidence-Based Medicine, jeffrey.aronson@phc.ox.ac.uk

Nia Roberts, Medical Librarian, nia.roberts@bodleian.ox.ac.uk

Carl Heneghan, Professor of Evidence-Based Medicine, carl.heneghan@phc.ox.ac.uk

**Correspondence to:** Dr Jack O'Sullivan

Centre for Evidence-Based Medicine

Nuffield Department of Primary Care Health Sciences

Radcliffe Observatory Quarter, Oxford, OX2 6GG

**Abstract**

*Background*

Health systems are currently subject to unprecedented financial strains. As most patient care is provided in primary care, inappropriate test use wastes finite health resources (overuse) and delays diagnoses and treatment (underuse).

*Objective*

To identify over and under use of diagnostic tests in primary care.

*Design*

Systematic review and meta-analysis.

*Data sources and eligibility criteria*

We searched MEDLINE and EMBASE from January 1999 to February 2016 for studies that measured the inappropriateness of any diagnostic test (measured against a national or international guideline) ordered for adult patients in primary care.

*Results*

We included 206,601 patients from 55 observational studies in 15 countries. We extracted 94 measures of inappropriateness (39 underuse, 55 overuse) from included studies for 45 different diagnostic tests.

The overall rate of inappropriate diagnostic test ordering varied substantially (0.2% to 100%).

18 tests were underused >50% of the time. Of these, echocardiography was the most frequently studied (n=4 measures) and was consistently underused (between 54% and 89%). There was large variation in the rate of inappropriate underuse of pulmonary function tests (38% to 78%, n = 8) and colonoscopy (8% to 69%, n=2).

Nine tests were inappropriately overused >50% of the time. Echocardiography was consistently overused (78% to 92%), whereas inappropriate overuse of both urinary cultures and upper endoscopy varied widely, from 36% to 77% (n=3) and 10% to 54% (n=10) respectively.

*Conclusions*

There is marked variation in the appropriate use diagnostic tests in primary care. Specifically, the use of echocardiography (both under and overuse) is consistently poor. There is substantial variation in the rate of inappropriate underuse of pulmonary function tests and colonoscopy and overuse of upper endoscopy and urinary cultures.

Registration number: PROSPERO Registration ID: CRD42016048832

**Manuscript word count:** 3,252

**Strengths and limitations of this study**

*Strengths*

- Generates rate of under and overtesting for specific diagnostic tests against national or international guidelines
- Only includes data from real clinical encounters rather than surveys or hypothetical clinical vignettes.
- Quantified inappropriate ordering of all types of diagnostic tests, rather than just laboratory.

*Limitations*

- Systematic reviews are restricted to published literature, thus rates of inappropriate ordering is not available for all tests available to primary care physicians.
- Included studies measure appropriateness of testing in a particular health care setting against a particular guideline, thus reflect test ordering in a specific health care setting.

## Introduction

Reaching a diagnosis in primary care is exceedingly complex. The combination of undifferentiated symptoms, a low prevalence of serious disease, a high degree of symptom overlap between serious and benign conditions, patients with multiple complaints, and psychological or social distress manifesting somatically all complicate reaching a diagnosis [1]. In around 40% of primary care consultations a diagnosis cannot be established from the history and physical examination alone [2], and tests are therefore often needed [1,3].

Primary care consultations make up most of the care provided in healthcare systems (90% of consultations in the UK [4], 55% of consultations in the USA[5]) and inappropriate diagnostic testing in primary care therefore has enormous resource implications. Given the calls for £22 billion in efficiency savings from the UK's National Health Service (NHS) [6] and the $660 billion US Medicare deficit predicted by 2023 [7], ensuring the appropriateness of primary care diagnostic testing is crucial to the sustainability of healthcare systems [8].

Inappropriate diagnostic tests in primary care can be both inappropriately underused and overused. Underuse of tests, failure to order a test when clearly indicated, can lead to diagnostic errors and delays in diagnosis and the delivery of effective treatment, leading to adverse patient outcomes and further healthcare costs [9,10]. Overuse of tests, the delivery of tests with no clear benefit or when potential harms outweigh potential benefits, subjects patients to direct harms, such as radiation exposure, as well as potential adverse outcomes (e.g. contrast nephropathy) [11], incidental findings [12], and overdiagnosis [13]. Overuse is also a waste of finite healthcare expenditure, diverting resources from beneficial tests and treatments [14–16].

Many drivers encourage inappropriate under and overuse of diagnostic tests in primary care. Greater access to tests [17], the medicolegal consequences of under-testing [18], few if any disincentives to overinvestigate [14], and clinical performance measures [19] may all contribute to overuse. Increasing primary care workload [4], time constraints [19], and difficulty keeping up-to-date with rapidly increasingly evidence [20] may contribute to both inappropriate underuse and overuse.

Guidelines set the standard of care across most health-care settings [21,22]. Furthermore, they provide a medicolegal framework [23], inform health-care policy, and improve both care outcomes and processes of care [24]. Despite some recognised limitations, including varying quality of guidelines [25–27], guidelines are often used as markers of health-care appropriateness [28–31]. Zhi et al, for instance, used guidelines as a measure of appropriateness to estimate under and overuse of laboratory testing [29]. They estimated that 45% (95%CI 34 – 56%) of secondary care laboratory testing is underused and 21% (95%CI 16 – 25%) is overused.

Despite the increasing use of healthcare resources [32], rising healthcare expenditure [6–8], increasing demands placed on primary care [4], and apparent drivers of inappropriate testing [1,4,14,17–20], it is not clear how often diagnostic tests are inappropriately overused or underused in primary care. We therefore conducted a systematic review to quantify the frequency of appropriate ordering of all types of diagnostic tests from primary care in relation to their respective guidelines.

## Methods

This study was conducted and is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [33] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) statements [34].

*Protocol and Registration*

The protocol has been published and is available online (open access) via the International prospective register for systematic reviews (PROSPERO) database (Registration ID: CRD42016048832).

*Patient involvement*

Patient and Public Involvement (PPI) interviews have been conducted, which underpin a series of studies examining test ordering from primary care. However, patients were not explicitly involved in the design, analyses or interpretation of this study.

*Search Strategy*

We searched EMBASE (OvidSP) and MEDLINE (OvidSP) databases from January 1999 to February 2016 for studies of any design measuring how often diagnostic test guidelines were followed in primary care (Supplementary file: Search Strategy). Conference abstracts published after 2015 were also searched for in these databases to capture data not yet published. We also searched the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov, and the reference lists of included studies.

*Eligibility Criteria*

We included studies of any design if they measured the rate of inappropriate ordering (overuse) or not ordering (underuse) of diagnostic tests ordered from primary care against national or international guidelines. We considered all diagnostic tests ordered in adults. We also included studies that measured diagnostic tests ordered from primary care but performed in secondary care (e.g. upper endoscopy). We included the control arms of RCTs if they offered exclusively usual care, and the pre-intervention periods of studies that used interrupted time series designs (before and after studies).

We excluded studies if they met the following criteria: >20% of participants were children (>20% under 18 years old); diagnostic tests not ordered by General Practitioners; screening or monitoring tests, or publication before 1999 (studies after 1999 were considered to ensure that results would more closely reflect current practice). We defined a screening test as a test on an asymptomatic or symptomatic person without signs or symptoms related to that test [35,36]. We defined monitoring tests as 'a test for a patient with an established diagnosis, for which the test is used to measure progression of the disease' [37]. We excluded studies if they did not give a measure of appropriateness or if appropriateness was measured against local guidelines, such as a guideline specific to a hospital or region, rather than international or national guidelines.

*Study selection and data extraction*

Three reviewers (JS and AA or BN) independently screened titles, abstracts, and full texts for eligibility. The same reviewers assessed risks of bias and extracted the following data from included studies: patient demographics, eligibility criteria, name and type of diagnostic test, duration of study (days), guideline name and recommendation, total number of tests performed, and the number of tests ordered when the specific guideline recommended not ordering (inappropriate overuse) or the number of tests not ordered when the guideline recommended ordering it (inappropriate underuse). The last two data points (overuse and underuse) represent 'measures of inappropriateness'. When studies measured inappropriateness of multiple tests we extracted data on each test and presented them as

individual measures of inappropriateness. When studies measured tests across different periods we extracted measures for each time point and considered each one as an individual measure of inappropriateness.

We assessed the quality of included studies using a modified version of the Hoy risk of bias tool [38]. This tool has been validated to assess the internal and external validity of prevalence studies [38]. Our modified version of this tool kept the same domains, but adjusted the wording of the tool to reflect prevalence of inappropriate testing rather than prevalence of disease. Our tool (and results) is available in Supplementary Table 3.

*Statistical analysis*

The primary outcome was the prevalence of inappropriate diagnostic testing. Inappropriate testing was measured in two ways:

1) Overuse: A diagnostic test was ordered when the relevant guideline recommends not ordering it, for instance, imaging for non-red flag low back pain (LBP).

2) Underuse: A diagnostic test was not ordered when the relevant guideline recommended ordering it, for instance, spirometry for suspected COPD.

We expressed measures of inappropriateness as proportions (%), where the numerator represents the total number of times a guideline recommendation was not followed and the denominator the total number of times a guideline recommendation could have been followed. For instance, the number of times imaging was inappropriately ordered for non-red flag headache as a proportion of the total number of patients who presented with non-red flag headache. Given these data are proportions, we calculated Clopper-Pearson 95% confidence intervals for each individual measure of appropriateness. We conducted sensitivity analyses with high risk of bias studies excluded.

Where the same guideline and recommendation were used by multiple studies (e.g. five studies measured inappropriate underuse of spirometry testing in patients with COPD [39–43] using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline) we pooled the measures and assessed heterogeneity. We combined measures of inappropriateness using a random-effects meta-analysis with 95% confidence intervals (Clopper-Pearson), for this reason each measure of appropriateness contributed relatively evenly to pooled estimates. We performed double arcsine transformation on prevalence data to stabilize the variance [44], and pooled the data using the inverse variance method [45]. We assessed heterogeneity using the $I^2$ statistic [46]. We did not combined measures of overuse and underuse, as they have different denominators: overuse involves the total number of tests ordered, whereas underuse involves the total number of times a test should have been ordered. We performed analyses using R version 3.3.2 (R project).

## Results

*Study selection and characteristics*

We included 55 observational studies from 12,824 references identified from independent searches by two authors (JOS and AA or BN) (see Figure 1). These studies were conducted in 15 countries and included 206,601 patients (Supplementary Table 1). Supplementary Table 2 shows the 94 measures of inappropriateness extracted from included studies for 45 different diagnostic tests measured against 69 guideline recommendations (39 measured underuse and 55 measured overuse). Guideline recommendations came from 35 different guideline organisations from 15 countries.

Fourteen studies measured inappropriateness of more than one diagnostic tests for the same condition (e.g. chest x-ray (CXR), electrocardiography (ECG), and transthoracic echocardiography (TTE) to confirm or refute a diagnosis of heart failure). Two studies [47,48] measured inappropriateness across multiple time periods.

Included studies measured inappropriateness in one of three ways:

1. Patients with specific symptoms were recruited and followed up to see if they had received an inappropriate diagnostic test (overuse) or hadn't received the appropriate diagnostic test (underuse) in line with the relevant guideline recommendation (e.g. patients with non-red flag LBP recruited and followed up to see if they received imaging [49]).

2. Patients who had undergone a diagnostic test were identified (via hospital or national databases) and an assessment of whether the test was inappropriate (as per the defined guideline recommendations) via individual patient data was made (overuse). For instance, patients who had an upper endoscopy[50]).

3. Patients with a diagnosis were identified via hospital or national databases and assessed to see whether they had received the appropriate diagnostic test (as per the defined guideline) to confirm or refute the diagnosis via individual patient data (underuse). For instance, assessing if patients with a diagnosis of COPD had spirometry to confirm or refute the diagnosis [39]).

*Risk of bias*

Two thirds of the studies (n=36) were graded as being at low risk of bias, 15 (27%) at moderate risk, and 4 (7%) at high risk (Supplementary Table 3). Moderate or high risk studies were at an increased risk of non-response bias (>20%), non-objective collection of data, and/or unclear intervals between symptom onset and diagnostic test use. Supplementary Table 3 outlines risk of bias scores in detail.

*Proportions of diagnostic tests ordered in line with specific guideline recommendations*

There was large variation in the rate of inappropriate diagnostic test ordering. The 94 diagnostic test guideline recommendations were not followed 0.2 - 100% of the time (Figure 2), wide variation was largely sustained (0.2 – 99.94%) when a further analysis was conducted excluding studies judged high risk of bias. The prevalence of underuse varied 8.2% to 100%, whereas overuse prevalence varied between 0.2% and 94.2%. Similarly, this variation was essentially maintained upon exclusion of high risk studies (under use 9.8% - 99.9%, overuse 0.2 – 99.9%).

*Underused tests*

Table 2 (supplementary) shows that 18 tests were underused more than 50% of the time. Echocardiography was the most frequently studied (n=4 measures in Poland, UK (2), Brazil). In patients with heart failure, echocardiography was underused between 54% and 89% (n=3) of the time and in atrial fibrillation 56-64% (n=2).

For some tests there was large variation in the rate of underuse (Figure 3). Underuse of pulmonary function tests (PFTs) to confirm or refute COPD, measured against the Global Initiative for Chronic Obstructive Lung Disease (GOLD), NICE (UK) and Danish National Board of Health guidelines, varied from 38% to 78% (n=8). Similarly, underuse of colonoscopy for numerous clinical scenarios (such as 'unexplained iron deficiency anaemia') also varied substantially, from 8% to 69% (n=2). None of the studies that studied echocardiography, PFTs or colonoscopy were considered high risk of bias and thus results didn't change upon further analysis excluding high risk studies.

*Overused tests*

Nine tests were overused more than 50% of the time (Supplementary Table 2). Echocardiography was consistently overused, for instance in 'routine perioperative evaluation of ventricular function with no symptoms or signs of cardiovascular disease', whereas other tests (urinary cultures and endoscopy) were overused at varying rates. The over use of echocardiography was studied in the UK [51] and the Netherlands [52]. The rates of overuse varied between the two settings: between 78% (Netherlands) and 92% (UK). Overuse of urinary cultures for uncomplicated urinary tract infections was studied in the USA [53,54] and Spain [55] the rate varied from 57% to 77% in the USA, but was as low as 36% in Spain. Overuse of upper endoscopy was studied widely (n=10); in Australia [56,57], Saudi Arabia [58,59], UK [60], Italy [61–63], USA [50], and Malaysia [64]. The overuse varied markedly, from and 7.5% to 54% (n=10) respectively (figure 4, Supplementary Table 2). None of the above studies were considered high risk of bias and thus results didn't change upon further analysis excluding high risk studies.

Our results also suggest that the inappropriate overuse of CT and MRI scans for non-red flag headache (a headache without symptoms suggesting a malignant underlying pathology) has more than doubled in the last ten years in the USA (*2000*: 6.7% (95%CI: 5.4 to 8.2%, *2010*: 14% (95%CI 12. to 16%) (Supplementary Table 2) [48]. Conversely, the rate of inappropriate overuse of radiology tests for non-red flag low back pain was consistently low, with all (n=11) but one measure showing inappropriate overuse less than 25% of the time (Supplementary Table 2). The one study [65] that showed inappropriate overuse around 50% of the time was conducted in 2001, which may reflect improvements in practice over time. None of these studies were considered high risk of bias and thus results didn't change upon further analysis excluding high risk studies.

*Variation of inappropriateness against the same guideline recommendation*

Eleven different guideline recommendations were studied more than once (Figure 2). There was significant heterogeneity ($I^2$ >50%) in nine of these pooled measures. Significant heterogeneity may have occurred for several reasons: 1) vastly different populations (for instance, one studied measured the inappropriateness of upper endoscopy in Saudi Arabia [59] using the American Gastroenterological Association recommendations, whereas another study used the same recommendations in the USA [66]; 2) Contrasting healthcare systems [67,68]; 3) Relevance and applicability of one country's national guideline to another country [69]; 4) A low number of measures for meta-analysis [46] and/or 5) Significant heterogeneity, reflecting significant variation in inappropriate ordering.

*Overall rates of inappropriate testing*

To be consist with previous research [29], we calculated combined rates of over and under test of testing. Overuse of testing occurred on average one-fourth of the time (25%, 95%CI 16 to 35%;

n=55), whereas underuse was more prevalent, occurring in nearly two-thirds of the tests ordered (60% 95%CI 51 to 69%; n=39). The overall rate of inappropriate overuse for laboratory tests was 49% (95%CI: 30% to 68%; n=6), compared with only 15% for radiology tests (95%CI: 8.6% to 25%; n=38) and 34% (95%CI: 26 to 44%) for 'other tests'. These results combine estimates from multiple different health care settings and capture only the studied selection of diagnostic tests available in primary care, thus we feel conclusions from these estimates should be made with caution.

**Discussion**

There is marked variation in the rate of underuse and overuse of diagnostic tests from many primary care settings across the world. This variation suggest improvement can be made in the rate of appropriate diagnostic test ordering.

Primary care use of echocardiography is consistently poor. Echocardiography is inappropriately underused for some clinical situations, e.g. confirming a diagnosis of heart failure, and inappropriately overused in others, e.g. perioperative assessment. This was consistent across the countries where appropriateness of echocardiogram has been studied. This is of concern, given the expertise and resource requirements to perform the test and the increasing availability of direct access ordering for primary care physicians.

For four tests we found marked variation in the rate of inappropriate use. Underuse of pulmonary function tests and colonoscopy varied by 40% and 60% respectively, whereas overuse of urinary cultures and endoscopy both varied by around 40%.

Radiology tests for both non-red flag low back pain and non-red flag headache were frequently ***not*** overused, but the rate of overuse imaging for non-red flag headache showed concerning trends, more than doubling from 2000 to 2010 (Supplementary Table 2).

*Implications*

Four conclusions can be drawn from our results: 1.Ordering of echocardiograms from primary care appears to require improvement, 2. Markedly varying rates of inappropriate use for pulmonary function tests (underuse), colonoscopy (underuse), upper endoscopy (overuse), and urinary cultures (overuse) suggests that ordering can be improved, 3. Determining reasons for deviation from guidelines is an appropriate next step, and 4. An assessment of the quality of guidelines supporting diagnostic test use would be advantageous.

*Strengths in relation to other studies*

Compared with other studies of inappropriate use of healthcare resources, we used data from real clinical encounters. This allowed a more robust assessment of diagnostic test inappropriateness, where other studies used surveys and hypothetical clinical vignettes [19,75,76]. Furthermore, we quantified the appropriateness of all types of diagnostic tests, rather than focusing on a specific test or specific disease (such as only laboratory tests [29]). Zhi et al [29] quantified the mean rates of overuse and underuse of laboratory tests. Our review is the first systematic pooling of studies that measured inappropriateness of all diagnostic tests ordered from primary care.

Our use of guideline recommendations as the metric of appropriateness allowed a direct measure of diagnostic test appropriateness. Other studies that have assessed temporal and geographical variation in the use of diagnostic tests [77,78] have noted substantial differences in diagnostic practices across different regions, irrespective of disease prevalence and patient characteristics [78]. These studies, however, could not quantify what proportion of the temporal increase in the use of a diagnostic test is inappropriate and what proportion of variation between regions is inappropriate. We have quantified the proportion of inappropriate testing.

*Limitations*

The use of guidelines to quantify appropriateness of diagnostic tests could be considered a limitation of this study. Guidelines are often criticised for varying quality [25–27,79] and panel members' conflicts of interests [80]. However, clinical practice guidelines have been shown to improve both care outcomes and processes of care [24], allow assessment of care on a population level, inform health policy [81,82], set the standard of care across many health care settings [21,22], and provide a medicolegal framework [23]. One major medical insurance company advises that 'doctors must be prepared to explain and justify their decisions and actions, especially if they depart from guidelines produced by a nationally recognised body' [23]. Furthermore, guidelines have been used to measure appropriateness of the use of tests in other published peer-review studies [29]. There will always be times when it is appropriate to depart from guidelines, but dramatic, consistent variation from guidelines requires investigation and is unlikely to be caused entirely by the quality of guidelines.

Furthermore, our study includes only a selection of diagnostic tests and is thus not an all-encompassing reflection of clinical practice. The data reflects the use of a specific test, sometimes for a particular clinical situation, in a particular country's health care system. Thus, policy makers and those interested in improving the quality of primary care diagnostic test use, can use our results as a resource to identify tests in their healthcare setting that require improvement and/or investigation to decipher why such deviation from guidelines exists. Our conclusions from this paper, however, are not generalisble to all primary care settings nor all primary care diagnostic tests.

*Conclusion*

There is marked variation in under and overuse of appropriate diagnostic test use in primary care across the world. From the available data, echocardiograms are ordered particularly poorly, while the substantial variation in appropriate ordering of pulmonary function tests, colonoscopy, upper endoscopy, and urinary cultures suggest a need for improvement.

**Funding:**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

All author declare no conflicts of interests.

**Ethical approval:** Not required

**Data sharing:** Data extracted from the included studies in this review are available on request from the corresponding author.

**Registration:** PROSPERO protocol Registration ID: CRD42016048832 (https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016048832)

**Competing interest statement.**

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and jointly declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

**Contribution statement:**

Conception and design: Jack O'Sullivan, Rafael Perera and Carl Heneghan

Screening, extraction and risk of bias: Jack O'Sullivan, Ali Albasri and Brian Nicholson.

Analysis and interpretation of the data: Jack O'Sullivan, Rafael Perera, Jeffrey Aronson and Carl Heneghan.

Drafting of the article: Jack O'Sullivan (all authors critically reviewed and approved manuscript)

Statistical expertise: Rafael Perera

Clinical expertise: Jack O'Sullivan, Brian Nicholson, Jeffrey Aronson and Carl Heneghan

Jack O'Sullivan is the guarantor.



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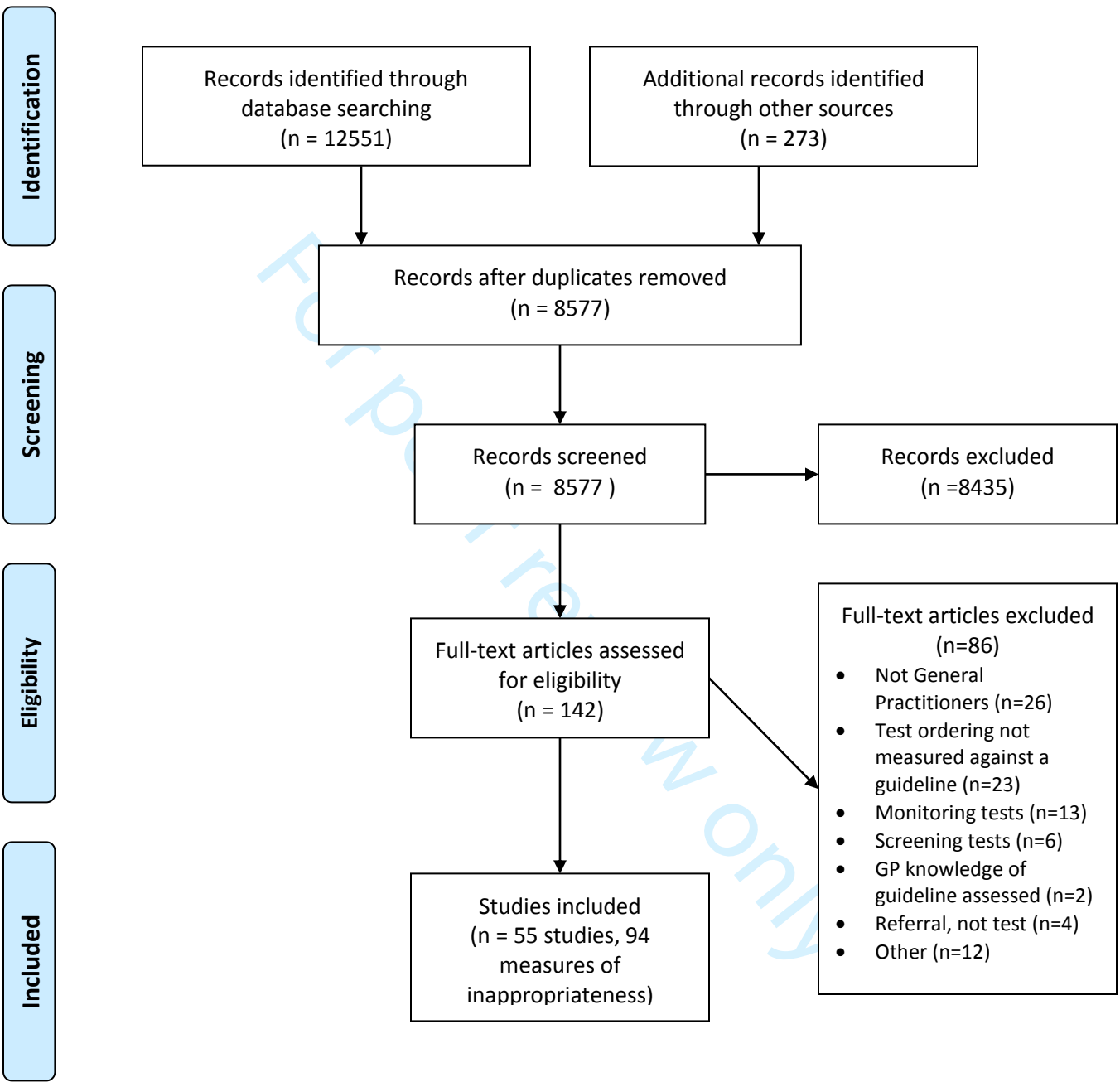
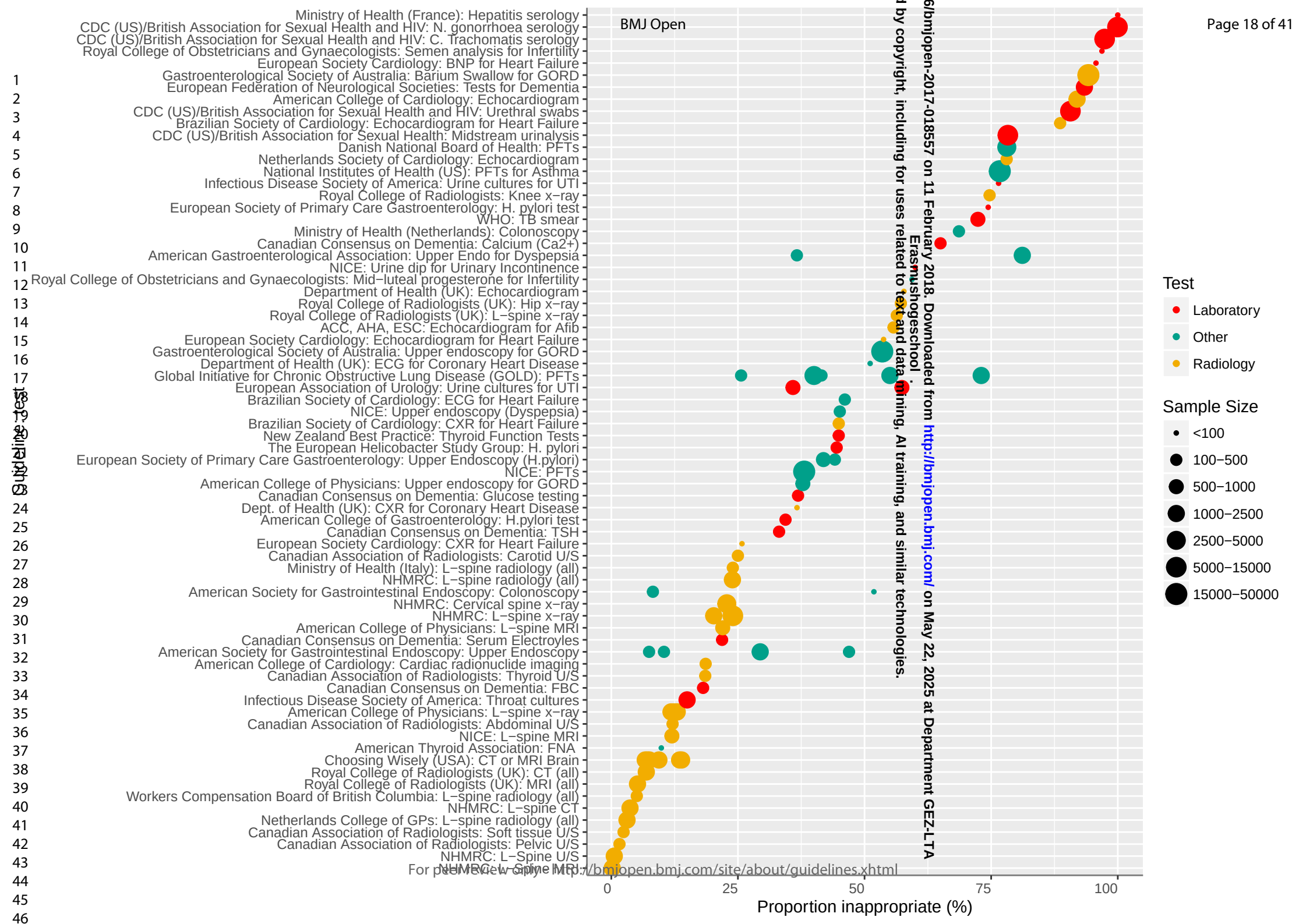
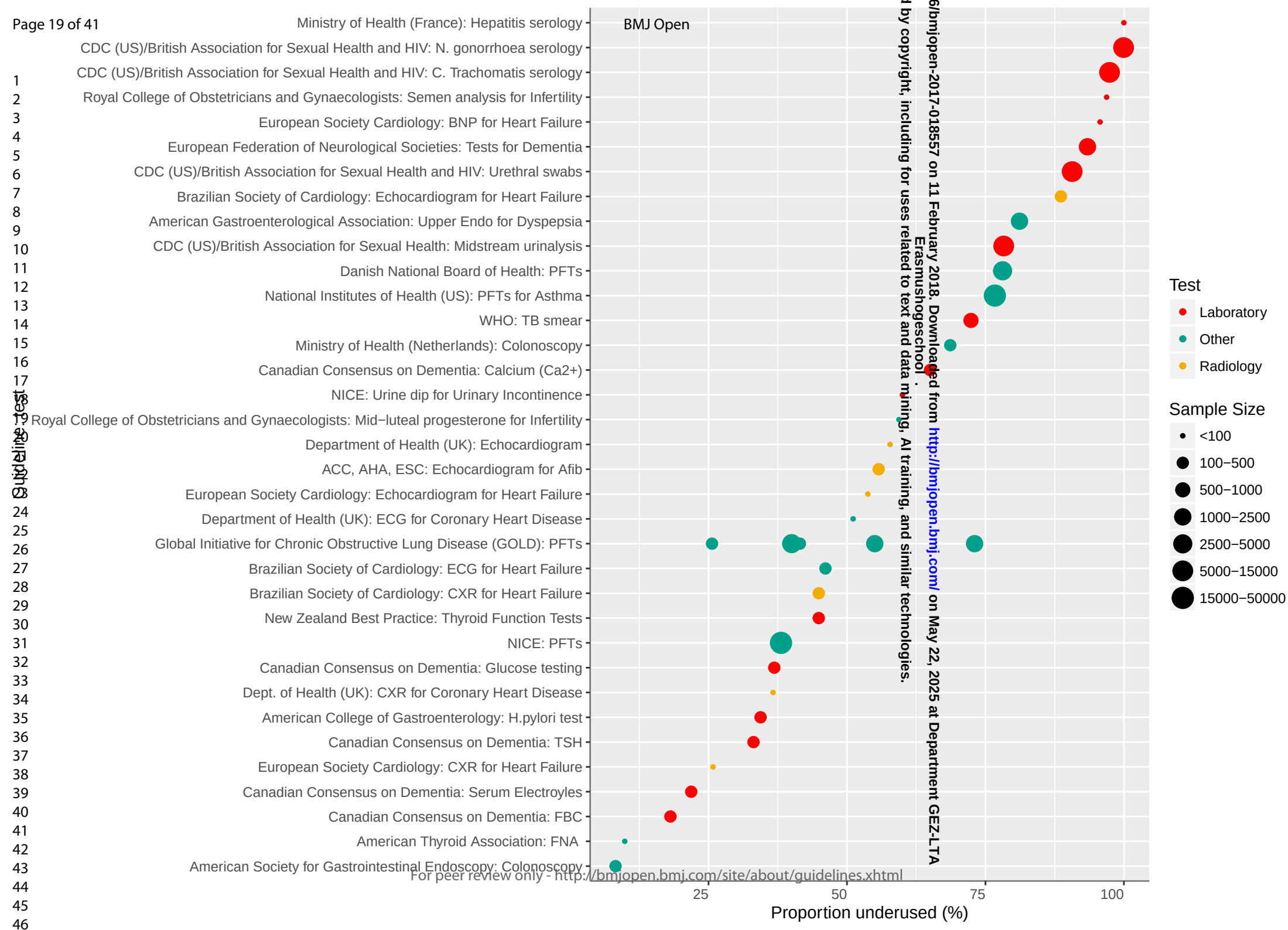
# PRISMA Flow Diagram




*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

**For more information, visit www.prisma-statement.org.**





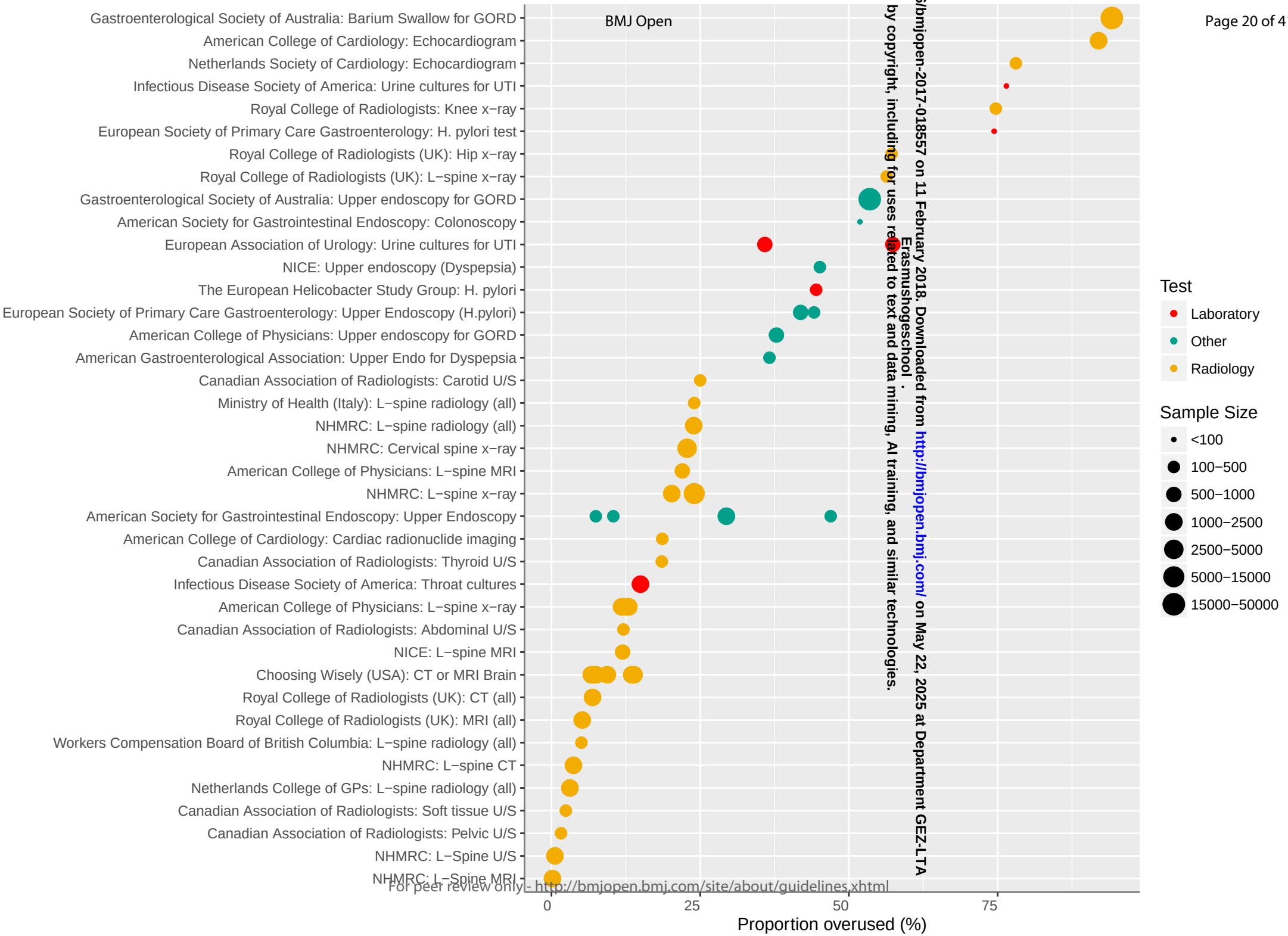


Table 1: Study Characteristics

| Study | Country | Study length (days) | N (men%) | Population | Test |
|---|---|---|---|---|---|
| **Under-use** | | | | | |
| Ahmad 2012 | Indonesia | 181 | 554 (41%) | Patients registered at health clinics where TB was suspected | Sputum smear microscopy |
| Belletti 2013 | USA | N/S | 1517 (46%) | Patients with COPD | Pulmonary function tests (PFT) |
| Bertella 2013 | Italy | 1765 | 437 (286) | Patients with COPD | PFTs |
| Caplan 2000 | USA | 365 | 81 | Patients who under went FNA of thyroid | FNA of thyroid |
| Chavez 2009 | USA | 2920 | 200 (48%) | Patients with COPD | PFT |
| Droogendijk 2011 | Netherlands | 730 | 287 (45%) | Women >50yrs and men >18 years with Iron Deficiency Anaemia | Upper endoscopy and colonoscopy |
| Gerrits 2008 | Netherlands | 2556 | 65 (0%) | Women aged 18 – 65 yrs with newly diagnosed urinary incontinence | Urine dipstick |
| Gibbons 2010 | New Zealand | 364 | 265 | Patients with subclinical hypothyroidism | Free T4 |
| Gnani 2004 | UK | 365 | 90 (53%) | Patients with heart failure | CXR, ECG and Echocardiogram |
| Girard 2010 | France | 28 | 19 (37%) | Patients with acute hepatitis | Hepatitis serology (HBs antigens, anti-HBc anitbodies) |
| Hughes-Anderson 2002a | Australia | 1613 | 4400 (55%) | Patients who had colonoscopy | Colonoscopy |
| Lange 2007 | Denmark | 91 | 2549 (44%) | Patients with COPD | PFTs |
| Lipczynska 2012 | Poland | 61 | 93 | Aged ≥ 55 with Heart Failure (HF) or HF risk factors | Echocardiogram, BNP, CXR |
| Loo 2009 | UK | 364 | 131 (50%) | Patients with Atrial Fibrillation | Echocardiogram |
| Majumdar 2003 | USA | 2371 | 1130 (47%) | Patients with dyspepsia and patients with peptic ulcer disease (PUD) | Upper endoscopy and H.pylori |
| Moscavitch 2009 | Brazil | 61 | 167 (43%) | Patients with Heart Failure | ECG, CXR, Echocardiogram |
| Musicco 2004 | Italy | N/S | 1549 (38%) | Patients being assessed for Dementia | Collection of laboratory tests to rule out conditions with similar presenting symptoms to dementia |
| Nicholson 2010 | UK | 1827 | 6943 (100%) | Men with epididymo-orchtitis | C. trachomatis, N. gonorrhoeae, urethral swabs and midstream urinalysis. |

| | | | | | |
|---|---|---|---|---|---|
| Nicopoullos 2003 | UK | 242 | 32 | Patients with subfertility | Mid-luteal progesterone and semen analysis |
| Pimlott 2006 | Canada | 1611 | 160 (34%) | Patients with Dementia | FBC, TSH, serum electrolytes, serum calcium, glucose |
| Smith 2008 | UK | 731 | 29870 (52%) | Patients with COPD | PFT |
| Sokol 2015 | USA | 3652 | 75902 (23%) | Patients with Asthma | PFT |
| Ulrik 2010 | Denmark | 121 | 1716 (44%) | Patients with COPD | PFT |
| Ulrik 2013 | Denmark | 731 | 4058 | Patients with COPD | PFT |
| **Over-use** | | | | | |
| Aljebreen 2013 | Saudi Arabia | 365 | 147 (51%) | Patients who had upper endoscopy | Upper endoscopy |
| Azzam 2015 | Saudi Arabia | 121 | 161 (30%) | Dyspeptic patients who had upper endoscopy | Upper endoscopy |
| Bhatt 2001 | UK | 504 | 437 (65%) | Patients referred for pelvis x-rays | Pelvis x-ray |
| Bishop 2003 | Canada | 28 | 139 | Patients with non-red flag LBP | Advanced imaging (CT, MRI or bone scan) |
| Cai 2015 | USA | 121 | 550 (46%) | Patients who under went upper endoscopy | Upper endoscopy |
| Chan 2004 | Malaysia | 153 | 250 (45%) | Patients who under went upper endoscopy | Upper endoscopy |
| Chan 2006 | Malaysia | 184 | 27 (63%) | Patients who underwent 'diagnostic colonoscopies' | Colonoscopy |
| Cardin 2005 | Italy | 151 | 1678 | Patients with uninvestigated dyspepsia | Upper endoscopy |
| Cardin 2007 | Italy | 182 | 1/04/2001 | Dyspeptic patients who had upper endoscopy | Upper endoscopy |
| Eccles 2001 | UK | 182 | 275 | Patients who had knee or lumbar x-ray | Lumbar or knee x-ray |
| Elwyn 2007 | UK | 184 | 215 | Patients who under went upper endoscopy | Upper endoscopy |
| Grover 2007 | USA | 364 | 68 (0%) | Patients with uncomplicated UTI | Urine culture and sensitivity analysis |
| Gurzun 2014 | UK | 7 | 1070 (54%) | Echocardiogram | Echocardiogram |
| Hassan 2007 | Italy | 30 | 3769 (46%) | Patients who under went upper endoscopy | Upper endoscopy |
| Hughes-Anderson 2002b | Australia | 1613 | 4400 (55%) | Patients who had upper endoscopy, | Upper endoscopy |
| Ip 2014 | USA | 1096 | 100 (43%) | Patients with non-red flag LBP | MRI lumbar spine |

| | | | | | |
|---|---|---|---|---|---|
| Johnson 2011 | USA | 510 | 779 (0%) | Patients with uncomplicated UTI | Urine culture |
| Kovacs 2013 | Spain | 183 | 602 (48%) | Patients with non-red flag LBP | MRI lumbar spine |
| Lalude 2014 | USA | 121 | 102 | Patients who had SPECT Myocardial perfusion imaging (MPI) studies | Single Photon Emission CT (SPECT) MPI |
| Landry 2011 | USA | 272 | 124 | Patients who had U/S of thyroid, pelvis, abdo, carotid or soft tissue | Thyroid, pelvis, abdomen, carotid or soft tissue ultrasound |
| Linder 2006 | USA | 608 | 1076 (19%) | Patients with pharyngitis | Strep testing (rapid antigen detection test, throat culture) |
| Llor 2011 | Spain | 122 | 658 (0%) | Women with UTI | Urine cultures |
| Mafi 2013 | USA | 4377 | 8066 | Patients with non-red flag LBP | X-ray, CT or MRI |
| Mafi 2015 | USA | 4018 | 9362 (25%) | Patients with uncomplicated headache (non-red flag | CT and MRI |
| Michaleff 2012 | Australia | 3621 | 3070 (70%) | Patients reporting first time neck pain or LBP (non-specific, non red flag) | Any radiological test |
| Noya 2008 | Israel | N/S | 209 (35%) | Patients who had H.pylori testing | H. pylori test |
| Piccoliori 2013 | Italy | 63 | 475 (43%) | Acute or chronic non-red flag LBP | Any radiological test |
| Piterman 2008 | Australia | 550 | 19219 | Patients with GORD | Endoscopy. Barium Swallow |
| Remedios 2014 | UK | N/S | 2026 | Patients who had CTs and/or MRIs | CT and/or MRI |
| Schers 2000 | Netherlands | 214 | 1096 (50%) | Patients with non-red flag LBP | X-ray |
| Van Gurp 2013 | Netherlands | 366 | 155 (38%) | Patients who had Echocardiogram | Echocardiogram |
| Williams 2010 | Australia | 1005 | 1706 (43%) | Patients with non-red flag LBP | All imaging |

Table 2: Measures of inappropriateness

| Study | Test | Guideline authority and recommendation | Measure of inappropriateness (95%CI) |
|---|---|---|---|
| **Under-use** | | | |
| Girard 2010 | Hepatitis B serology | Ministry of Health (France): Hepatitis serology for suspected acute hepatitis | 100% (82.4 to 100%) |
| Nicholson 2010 | Neisseria Gonorrhoea serology | CDC (US)/British Association for Sexual Health and HIV: Test for N. gonorrhoea for suspected Epididymitis | 99.9% (99.85 to 99.98%) |
| Nicholson 2010 | Chlamydia Trachomatis | CDC (US)/British Association for Sexual Health and HIV: Test for C. Trachomatis for suspected Epididymitis | 97.4% (97.0 to 97.8%) |
| Nicopoullos 2003 | Semen Analysis | Royal College of Obstetricians and Gynaecologists: Semen analysis for Infertility | 96.9% (95%CI: 83.8 to 99.9%) |
| Lipczynska 2012 | Brain Natriuretic Peptide (BNP) | European Society Cardiology: BNP for Heart Failure | 95.7% (95%CI: 89.4 to 98.8%) |
| Musicco 2004 | Collection of laboratory tests | European Federation of Neurological Societies: Collection of laboratory tests to rule out conditions with similar presenting symptoms to dementia | 93.42% (95%CI: 92.1 to 94.6%) |
| Nicholson 2010 | Urethral swabs | CDC (US)/British Association for Sexual Health and HIV: Urethral swabs for suspected epididymitis (Urethral swabs) | 90.7% (95%CI:89.9 to 91.3%) |
| Moscavitch 2009 | Echocardiogram | Brazilian Society of Cardiology: Echocardiography for Heart Failure | 88.6% (95%CI: 82.8 to 93.0%) |
| Majumdar 2003 | Upper Endoscopy | American Gastroenterological Association: Appropriate use of Upper Endoscopy for Dyspepsia | 81.2% (78.8 to 83.4%) |
| Nicholson 2010 | Mid stream | CDC (US)/British Association for Sexual Health and HIV: Midstream urinalysis for suspected Epididymitis | 78.2 (95%CI: 77.3 to 79.3%) |
| Ulrik 2013 | Pulmonary function tests (PFTs) | Danish National Board of Health: PFTs to diagnosis COPD | 78.1 (76.8% to 79.4%) |
| Sokol 2015 | Pulmonary function tests (PFTs) | National Asthma Education and Prevention Program (US): PFTs for asthma | 76.5% (64.6 to 85.9%) |
| Belletti 2013 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 73.0% (10.7 to 75.3%) |
| Ahmad 2012 | Tuberculosis smear | World Health Organisation: Smear for suspected TB | 72.4% (68.5 to 76.1%) |

| | | | |
|---|---|---|---|
| Droogendijk 2011 | Colonoscopy | Ministry of Health (Netherlands): Colonoscopy for unexplained Iron Deficiency Anaemia | 68.6% (62.9 to 74.0%) |
| Pimlott 2006 | Serum Calcium | Canadian Consensus Conference on Dementia: Serum Calcium for Dementia | 65.0 (57.1 to 72.4%) |
| Gerrits 2008 | Urine dip stick | NICE: Urine dip stick for urinary incontinence | 60.0% (47.1 to 72.0%) |
| Nicopoullos 2003 | Mid-luteal progesterone | Royal College of Obstetricians and Gynaecologists: Mid-luteal progesterone for Infertility | 59.4% (40.6 to 76.3%) |
| Gnani 2004 | Echocardiogram | Department of Health (UK): Echocardiogram for Heart Failure | 57.8% (46.1 to 68.1%) |
| Loo 2009 | Echocardiogram | ACC, AHA, ESC: Echocardiogram to identify causes or complications of atrial fibrillation | 55.7% (46.8 to 64.39%) |
| Ulrik 2010 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 55.0% (52.6 to 57.4%) |
| Lipczynska 2012 | Echocardiogram | European Society Cardiology: Echocardiogram for Heart Failure | 53.8% (43.1 to 64.2%) |
| Gnani 2004 | ECG | Department of Health (UK): ECG for Heart Failure | 51.1% (40.4% to 61.8%) |
| Moscavitch 2009 | ECG | Brazilian Society of Cardiology: ECG for Heart Failure | 46.1 (38.4 to 54.0) |
| Moscavitch 2009 | Chest X-ray | Brazilian Society of Cardiology: CXR for Heart Failure | 44.9% (37.2 to 52.8%) |
| Gibbons 2010 | Thyroid function tests | New Zealand Best Practice: Appropriate use of Thyroid Function tests | 44.9% (38.8 to 51.1%) |
| Chavez 2009 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 41.5% (34.6 to 48.7%) |
| Lange 2007 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 40.0% (38.1 to 42.0) |
| Smith 2008 | Pulmonary Function Tests (PFTs) | NICE: PFTs for COPD | 38.1% (37.5 to 38.6%) |
| Pimlott 2006 | Glucose testing | Canadian Consensus Conference on Dementia: Glucose testing for Dementia | 36.9% (29.4% to 44.9%) |
| Gnani 2004 | Chest X-ray | Department of Health (UK): CXR for Heart Failure | 36.7% (26.8 to 47.5%) |
| Majumdar 2003 | H.pylori | American Gastroenterological Association/American College of Gastroenterology: appropriateness of H.pylori test | 34.4% (28.9 to 40.3%) |
| Pimlott 2006 | Thyroid Stimulating Hormone (TSH) | Canadian Consensus Conference on Dementia: TSH for dementia | 33.1% (25.9 to 41.0%) |

| | | | |
|---|---|---|---|
| Lipczynska 2012 | Chest x-ray (CXR) | European Society Cardiology: CXR for Heart Failure | 25.8% (17.3 to 35.9%) |
| Bertella 2013 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 25.6% (21.6 to 30.0%) |
| Pimlott 2006 | Serum electrolytes | Canadian Consensus Conference on Dementia: Serum electrolytes for dementia | 21.9% (15.7 to 29.1%) |
| Pimlott 2006 | Full Blood Count (FBC) | Canadian Consensus Conference on Dementia: FBC for dementia | 18.1% (12.5 to 25.0%) |
| Caplan 2000 | Fine needle aspiration (FNA) of thyroid | American Thyroid Association/American Association of Clinical Endocrinologists: FNA for thyroid nodules | 9.9% (4.4 to 18.5%) |
| Hughes-Anderson 2002a | Colonoscopy | American Society for Gastrointestinal Endoscopy: Appropriateness of Colonoscopy | 8.2% (5.3 to 12.1%) |
| | | | |
| **Over-use** | | | |
| Piterman 2008 | Barium Swallow | Gastroenterological Society of Australia: Barium Swallow for GORD | 94.20% (95%CI: 93.9 to 94.5%) |
| Gurzun 2014 | Echocardiogram | American College of Cardiology: Appropriate use of Echocardiography | 92.0% (95%CI: 90.2% to 93.5%) |
| van Gurp 2013 | Echocardiogram | Netherlands Society of Cardiology: Appropriate use of Echocardiography | 76.7% (76.4 to 77.0%) |
| Grover 2007 | Urine cultures | Infectious Disease Society of America: Urine cultures not required for uncomplicated UTI diagnosis | 76.5% (64.6 to 85.9%) |
| Eccles 2001 | Knee x-ray | Royal College of Radiologists: No x-ray for knee pain without restriction of movement | 74.7% (69.6 to 79.3%) |
| Cardin 2005 | H. Pylori breath test | European Society of Primary Care Gastroenterology: Appropriate use of H. pylori | 74.4% (58.8 to 86.5%) |
| Johnston 2011 | Urine cultures | European Association of Urology: Urinary cultures not required for uncomplicated urinary tract infections | 57.4% (53.8 to 60.9%) |
| Bhatt 2001 | Hip x-ray | Royal College of Radiologists (UK): No hip x-ray for hip pain without restriction of movement | 57.2% (52.5 to 61.8%) |
| Eccles 2001 | Lumbar spine x-ray | Royal College of Radiologists (UK): no x-ray for non-red flag LBP | 56.4% (50.3 to 62.3%) |
| Piterman 2008 | Upper endoscopy | Gastroenterological Society of Australia: Upper endoscopy for GORD | 53.5% (52.8 to 54.2%) |
| Chan 2006 | Colonoscopy | American Society for Gastrointestinal Endoscopy: Appropriateness of Colonoscopy | 51.9% (32.0 to 71.3%) |

| | | | |
|---|---|---|---|
| Aljebreen 2013 | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 46.9% (38.7 to 55.3%) |
| Elwyn 2007 | Upper endoscopy | NICE: Appropriate tests for dyspepsia | 45.1% (38.3 to 52.0%) |
| Noya 2008 | H.Pylori | The European Helicobacter Study Group: Appropriate use of H. pylori | 44.5 (37.6 to 51.5%) |
| Cardin 2005 | Upper endoscopy | European Society of Primary Care Gastroenterology: Upper Endoscopy for H.pylori | 44.1% (35.9 to 52.6%) |
| Cardin 2007 | Upper endoscopy | European Society of Primary Care Gastroenterology: Upper Endoscopy for H.pylori | 41.9% (38.3 to 45.5%) |
| Cai 2015 | Upper endoscopy | American College of Physicians: Upper endoscopy for GORD | 37.7% (33.8 to 42.0%) |
| Azzam 2015 | Upper endoscopy | American Gastroenterological Association: Upper Endoscopy for Dyspepsia | 36.7 (29.2 to 44.6%) |
| Llor 2011 | Urine cultures | European Association of Urology: Urinary cultures not required for uncomplicated urinary tract infections | 35.9% (32.2 to 40.0%) |
| Hassan 2007 | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 29.4% (28.0 to 30.9%) |
| Landry 2011 | Carotid ultrasound | Canadian Association of Radiologists 2005 guidelines: Carotid U/S | 25.0% (17.7 to 33.6%) |
| Piccoliori 2013 | Lumbar spine radiology (all) | Ministry of Health (Italy): No imaging for non-red flag LBP | 24.0% (20.2 to 28.1%) |
| Michaleff 2012 | Lumbar spine x-ray | National Health and Medical Research Council (Australia) (NHMRC): No x-ray for non-red flag LBP | 24.0% (22.9 to 25.1%) |
| Williams 2010 | Lumbar spine radiology (all) | National Health and Medical Research Council (Australia) (NHMRC): No imaging for non-red flag LBP | 23.9% (21.9 to 26.0%) |
| Michaleff 2012 | Cervical spine x-ray | Australian National Health and Medical Research Council: No x-ray for neck pain | 22.8% (21.3 to 24.3%) |
| Ip 2014 | Lumbar spine MRI | American College of Physicians/American Pain Society: no MRI for non-red flag LBP | 22.0% (14.3 to 31.4%) |
| Williams 2010 | Lumbar spine x-ray | National Health and Medical Research Council (Australia) (NHMRC): No x-ray for non-red flag LBP | 20.2% (18.3 to 22.2%) |
| Landry 2011 | Thyroid ultrasound | Canadian Association of Radiologists 2005 guidelines: Thyroid U/S | 19.0% (12.1 to 27.0%) |
| Lalude 2014 | Single Photon Emission Computed Tomography | American College of Cardiology: SPECT for chest pain | 18.6% (11.6 to 27.6%) |

| | | | |
|---|---|---|---|
| Linder 2006 | Streptococcal throat cultures | American College of Physicians/Infectious Disease Society of America: Pharyngitis | 15.0 (12.9 to 17.2%) |
| 'Mafi 2013 | Lumbar spine x-ray | American College of Physicians/American Pain Society: no x-ray for non-red flag LBP: *2009-2010* | 13.0% (11.1 to 15.1%) |
| | | *2007-2008* | 12.9% (11.1 to 14.9%) |
| | | *2005-2006* | 12.8% (11.0 to 14.8%) |
| | | *2003-2004* | 12.3% (10.7 to 14.0%) |
| | | *2001-2002* | 12.0% (10.3 to 13.8%) |
| | | *1999 - 2000* | 11.8% (10.2 to 13.6%) |
| Landry 2011 | Abdominal ultrasound | Canadian Association of Radiologists 2005 guidelines: Abdominal U/S | 12.1% (6.9 to 19.2%) |
| Mafi 2015 | CT or MRI Brain | The American Headache Society/American Academy of Neurology for Choosing Wisely: No CT or MRI for non-red flag headache *2009 - 2010* | 13.9% (12.2 to 15.7%) |
| | | *2007 – 2008* | 13.5% (11.8 to 15.3%) |
| | | *2005 – 2006* | 9.4% (8.0 to 11.0%) |
| | | *2003 – 2004* | 7.5% (6.3 to 8.9%) |
| | | *2001 – 2002* | 7.1% (5.9 to 8.4%) |
| | | *1999 - 2000* | 6.7% (5.4 to 8.2%) |
| Kovacs 2013 | Lumbar spine radiology tests (all) | NICE, ACP: No imaging for LBP | 12.0% (9.5 to 14.8%) |
| Chan 2004 | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 10.4% (6.9 to 14.9%) |
| Hughes-Anderson 2002b | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 7.5% (4.7 to 11.1%) |
| Remedios 2014 | CT (any) | Royal College of Radiologists (UK): CT | 6.9% (5.8 to 8.1%) |
| | MRI (any) | Royal College of Radiologists (UK): MRI | 5.2% (4.1 to 6.5%) |
| Bishop 2003 | Lumbar spine radiology tests (all) | Workers Compensation Board of British Columbia: No imaging for non-red flag LBP | 5.0% (2.1 to 10.1%) |
| Williams 2010 | Lumbar spine CT | National Health and Medical Research Council (Australia) (NHMRC): No CT for non-red flag LBP | 3.7% (2.9 to 4.7%) |

| | | | |
|---|---|---|---|
| Schers 2000 | Lumbar spine radiology tests (all) | The Netherlands College of General Practitioners: No imaging for non-red flag LBP | 3.1% (2.2 to 4.3%) |
| Landry 2011 | Soft tissue ultrasound | Canadian Association of Radiologists 2005 guidelines: Soft tissue U/S | 2.4% (0.5 to 6.9% |
| Landry 2011 | Pelvic ultrasound | Canadian Association of Radiologists 2005 guidelines: Pelvic U/S | 1.6% (0.2 to 5.7%) |
| Williams 2010 | Lumbar spine Ultrasound | National Health and Medical Research Council (Australia) (NHMRC): No U/S for non-red flag LBP | 0.59% (0.28 to 1.1%) |
| Williams 2010 | Lumbar spine MRI | National Health and Medical Research Council (Australia) (NHMRC): No MRI for non-red flag LBP | 0.18% (0.04 to 0.5%) |

| | Was the study"s target population a close representation of the national population in relation to relevant variables? | Does the inclusion criteria match the target population of guideline? | Were all eligible participants included in the study? | Was the likelihood of non-response bias <2High%? | Was an acceptable disease, test or symptom definition used? | Was data extracted/collected in an objective | Was the interval from symptoms to test clinically appropriate for the diagnosis of interest? | Did they report extractable measures? | Other bias? |
|---|---|---|---|---|---|---|---|---|---|
| Ahmad2012 | Low | Unclear | Low | Unclear | Low | Unclear | Unclear | Low | Low |
| Aljebreen 2013 | Low | Low | Low | Low | Unclear | Unclear | Low | Low | High |
| Azzam 2015 | Low | Low | Unclear | High | Low | Unclear | Low | Low | Low |
| Belletti2013 | Low | Unclear | Unclear | Unclear | Low | Low | Low | Low | Low |
| Bertella 2013 | Low | Low | Low | Low | Unclear | Low | Unclear | Low | Low |
| Bhatt 2001 | Low | Low | Low | High | High | Unclear | Unclear | Low | High |
| Bishop 2003 | High | Low | Low | Low | Low | Low | Low | Low | Low |
| Cai 2015 | Low | Low | Unclear | Low | Unclear | Unclear | Unclear | Low | Low |
| Caplan 2000 | Low | Low | Low | Low | Unclear | Unclear | Unclear | Low | Low |
| Cardin 2005 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Cardin 2007 | Low | Low | Low | Unclear | Low | Low | Low | Low | Low |
| Chan 2004 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Chan 2006 | Low | Low | Low | High | Unclear | Low | Unclear | Low | Low |
| Chavez 2009 | Low | Low | Low | Low | Low | Low | High | Low | High |
| Droogendijk 2011 | Unclear | Low | High | Unclear | Low | Unclear | Low | Low | Low |
| Eccles 2001 | Low | Low | Low | Low | Unclear | Unclear | Unclear | Low | Low |
| Elwyn 2007 | Low | Low | Unclear | Unclear | Unclear | Low | Low | High | High |
| Gerrits2008 | Low | Unclear | High | Low | Low | Low | Unclear | Low | Low |
| Gibbons 2010c | Low | Low | Low | Low | Low | High | Low | Low | Low |
| Girard 2010 | High | Low | Unclear | High | Unclear | High | Unclear | Low | High |
| Gnani 2004 | Low | Low | Unclear | Low | Unclear | Low | Unclear | Low | Low |
| Grover 2007 | Low | Low | Unclear | Low | Low | High | Unclear | Low | Low |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Gurzun 2014 | Low | Low | High | Low | High | Low | Unclear | Low | High |
| Hassan 2007 | Low | Low | Low | High | Unclear | Low | Unclear | Low | Low |
| Hughes-Anderson 2002 | High | Low | Unclear | Low | Unclear | Unclear | unclear | Low | Low |
| Ip2014 | Low | Low | High | Unclear | Low | Unclear | Unclear | Low | High |
| Johnson 2011 | Low | Unclear | Unclear | Low | High | Low | Low | Low | Low |
| Kovacs 2013 | Low | Unclear | High | Low | Low | Low | Unclear | Low | High |
| Lalude 2014 | Low | Low | Low | Low | High | Low | Unclear | Low | High |
| Landry 2011 | Low | Unclear | Low | Low | Unclear | Unclear | Unclear | Low | Low |
| Lange 2007 | Low | Low | Unclear | Low | Unclear | Unclear | Unclear | Low | Low |
| Linder 2006 | Low | High | Unclear | Low | Low | Low | Low | Unclear | Low |
| Lipczynska 2012 | High | High | Unclear | Low | Low | Unclear | Low | Low | High |
| Llor 2011 | Low | Low | Low | High | Low | Low | Low | Low | Low |
| Loo 2009 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Mafi2013 | Low | Low | Unclear | Unclear | Low | Low | Unclear | Low | Low |
| Mafi2015 | Low | Low | Unclear | Unclear | Low | Low | Unclear | Low | Low |
| Majumdar 2003 | Low | Low | Unclear | Low | Low | Low | Unclear | Low | Low |
| Michaleff 2012 | Low | Low | Low | Unclear | High | Low | Unclear | Low | Low |
| Moscavitch 2009 | Low | Low | Unclear | Low | Low | Unclear | Low | Low | Low |
| Musicco 2004 | High | Low | Low | Unclear | Unclear | Unclear | Unclear | High | High |
| Nicholson 2010 | Low | Low | Low | Low | Unclear | Low | Low | Low | Low |
| Nicopoullos 2003 | High | High | Low | High | Low | Unclear | Unclear | Low | High |
| Noya 2008 | Low | Low | Low | Low | Unclear | Unclear | Unclear | Low | High |
| Piccoliori 2013 | Low | Low | Low | Low | Low | Unclear | Low | Low | High |
| Pimlott 2006 | Low | Low | Unclear | High | Unclear | Unclear | Unclear | Low | Low |
| Piterman 2008 | Low | Unclear | Low | Unclear | Unclear | Low | Unclear | High | High |
| Remedios 2014 | Low | Unclear | Low | High | Unclear | Low | Unclear | Low | High |
| Schers 2000 | Low | Low | Low | Unclear | Unclear | Low | Unclear | Low | Low |
| Smith 2008 | Low | Low | Low | Low | Unclear | Low | Unclear | Low | Low |
| Sokol 2015 | Low | Low | Low | Low | Low | Low | High | Low | High |
| Ulrik 2010 | Low | Low | Low | High | Low | Low | unclear | Low | High |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ulrik 2013 | Low | Low | Low | High | Low | Low | unclear | Low | Low |
| van Gurp 2013 | Low | Low | Low | Low | Unclear | Low | Unclear | Low | Low |
| Williams2010 | Low | Low | Unclear | Low | Low | Unclear | Unclear | Low | Low |

**MEDLINE Search Strategy**

1. Ambulatory Care/
2. exp Ambulatory Care Facilities/
3. general practice/ or family practice/
4. general practitioners/ or physicians, family/ or physicians, primary care/
5. Primary Health Care/
6. Office visits/
7. Academic Medical Centers/
8. (ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
9. ((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.
10. (primary care or primary health care or primary healthcare or family medicine or community medicine or community health).ti,ab.
11. (gp or gps).ti,ab.
12. (after hour? or afterhour? or "out of hour?" or ooh).ti,ab.
13. (clinic? or visit?).ti,ab.
14. ((health* or medical) adj2 (center? or centre?)).ti,ab.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp Emergency Service, Hospital/
17. Emergency Medical Services/
18. (emergency adj3 (care or setting? or facilit* or ward? or department? or service? or room?)).ti,ab.
19. (emergency medicine or ed or er or a&e).ti,ab.
20. 16 or 17 or 18 or 19
21. 15 or 20
22. guidelines as topic/ or practice guidelines as topic/
23. (guideline? or guidance?).ti,ab.
24. 22 or 23
25. (adhere* or non-adhere* or nonadhere* or concord* or non-concord* or nonconcord* or discord* or comply or complian* or non-complian* or noncomplian* or align* or nonalign* or nonalign* or congruen* or incongruen* or consisten* or inconsisten* or contradict*).ti,ab.
26. ((does or "does not" or doesn?t or did or "did not" or didn?t or "not" or fail*) adj3 (follow* or met or meet or meeting or match or matching or "in line with")).ti,ab.
27. ((follow* or met or meet or meeting or match or matching or "in line with" or keep or kept or keeping or utili?ation or utile?e? or change?) adj5 (criteria or recommend* or guideline? or guidance)).ti,ab.
28. Physician's Practice Patterns/
29. clinical competence/ or nursing competence/
30. 25 or 26 or 27 or 28 or 29
31. 24 and 30
32. Guideline Adherence/
33. 31 or 32
34. exp *"diagnostic techniques and procedures"/
35. exp "diagnostic techniques and procedures"/ut
36. (diagnos* or detect* or test* or screen* or manag*).ti.

37. (imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra*).ti,ab.
38. ((medical or clinical or diagnos* or screening or routine or laboratory) adj5 (test* or investigation?)).ti,ab.
39. ((h?ematolog* or blood or urin* or saliva*) adj5 test*).ti,ab.
40. ((stress* or physical or function*) adj5 test*).ti,ab.
41. 34 or 35 or 36 or 37 or 38 or 39 or 40
42. 21 and 33 and 41
43. ((necessary or unnecessary or appropriate* or inappropriate* or waste* or utili?ation or indicated or excess* or less or more or increas* or decreas*) adj10 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
44. ((order* or request*) adj5 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
45. Unnecessary Procedures/
46. 43 or 44 or 45
47. 21 and 24 and 46
48. 21 and 41 and 45
49. 42 or 47 or 48
50. limit 49 to yr="1999 -Current"
51. limit 50 to english language
52. exp animals/ not humans.sh.
53. 51 not 52

**EMBASE Search Strategy**

1. Ambulatory Care/
2. general practice/
3. general practitioners/
4. Primary Health Care/
5. (ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
6. ((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.
7. (primary care or primary health care or primary healthcare or family medicine or community medicine or community health).ti,ab.
8. (gp or gps).ti,ab.
9. (after hour? or afterhour? or "out of hour?" or ooh).ti,ab.
10. (clinic? or visit?).ti,ab.
11. ((health* or medical) adj2 (center? or centre?)).ti,ab.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Emergency Ward/
14. (emergency adj3 (care or setting? or facilit* or ward? or department? or service? or room?)).ti,ab.
15. (emergency medicine or ed or er or a&e).ti,ab.
16. 13 or 14 or 15
17. 12 or 16
18. *practice guideline/

19. (guideline? or guidance?).ti,ab.
20. 18 or 19
21. (adhere* or non-adhere* or nonadhere* or concord* or non-concord* or nonconcord* or discord* or comply or complian* or non-complian* or noncomplian* or align* or nonalign* or nonalign* or congruen* or incongruen* or consisten* or inconsisten* or contradict*).ti,ab.
22. ((does or "does not" or doesn?t or did or "did not" or didn?t or "not" or fail*) adj3 (follow* or met or meet or meeting or match or matching or "in line with")).ti,ab.
23. ((follow* or met or meet or meeting or match or matching or "in line with" or keep or kept or keeping or utili?ation or utile?e? or change?) adj5 (criteria or recommend* or guideline? or guidance)).ti,ab.
24. clinical competence/ or nursing competence/
25. 21 or 22 or 23 or 24
26. 20 and 25
27. diagnostic procedure/ or exp blood examination/ or exp cardiovascular system examination/ or exp digestive system examination/ or exp endocrine system examination/ or exp neurologic examination/ or exp respiratory tract examination/ or exp urogenital system examination/
28. (diagnos* or detect* or test* or screen* or manag*).ti.
29. (imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra*).ti,ab.
30. ((medical or clinical or diagnos* or screening or routine or laboratory) adj5 (test* or investigation?)).ti,ab.
31. ((h?ematolog* or blood or urin* or saliva*) adj5 test*).ti,ab.
32. ((stress* or physical or function*) adj5 test*).ti,ab.
33. 27 or 28 or 29 or 30 or 31 or 32
34. 17 and 26 and 33
35. ((necessary or unnecessary or appropriate* or inappropriate* or waste* or utili?ation or indicated or excess* or less or more or increas* or decreas*) adj10 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
36. ((order* or request*) adj5 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
37. Unnecessary Procedures/
38. 35 or 36 or 37
39. 17 and 20 and 38
40. 17 and 33 and 37
41. 34 or 39 or 40
42. limit 41 to yr="1999 -Current"
43. limit 42 to english language
44. (exp animals/ or nonhuman/) not human/
45. 43 not 44
46. conference*.pt.
47. 45 and 46
48. 45 not 46
49. exp child/ not (exp Child/ and exp Adult/)

50. 48 not 49
51. 48 not 49
52. limit 47 to yr="2015 -Current"

## MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

| Reporting Criteria | Reported (Yes/No) | Reported on Page |
|---|---|---|
| **Reporting of Background** | | |
| Problem definition | YES | 4 |
| Hypothesis statement | YES | 4 |
| Description of Study Outcome(s) | YES | 4 |
| Type of exposure or intervention used | N/A | N/A |
| Type of study design used | YES | 5, 6 |
| Study population | YES | 5 |
| **Reporting of Search Strategy** | | |
| Qualifications of searchers (eg, librarians and investigators) | YES | 5 |
| Search strategy, including time period included in the synthesis and keywords | YES | 5, supplementary file |
| Effort to include all available studies, including contact with authors | YES | 5 |
| Databases and registries searched | YES | 5 |
| Search software used, name and version, including special features used (eg, explosion) | YES | 5 |
| Use of hand searching (eg, reference lists of obtained articles) | YES | 5 |
| List of citations located and those excluded, including justification | NO | |
| Method for addressing articles published in languages other than English | NO | |
| Method of handling abstracts and unpublished studies | YES | 5 |
| Description of any contact with authors | N/A | |
| **Reporting of Methods** | | |
| Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | YES | 5,6 |
| Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | YES | 6 |
| Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability) | YES | 6 |
| Assessment of confounding (eg, comparability of cases and controls in studies where appropriate | N/A | N/A |
| Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | YES | 5,6 |
| Assessment of heterogeneity | YES | 6 |

| | | |
|---|---|---|
| Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | YES | 6 |
| Provision of appropriate tables and graphics | YES | Tables 1,2, Figures 2,3,4 |
| **Reporting of Results** | | |
| Table giving descriptive information for each study included | YES | Table 1 and Table 2 |
| Results of sensitivity testing (eg, subgroup analysis) | N/A | N/A |
| Indication of statistical uncertainty of findings | YES | 6,8,9 |
| **Reporting of Discussion** | | |
| Quantitative assessment of bias (eg, publication bias) | YES | 8,9 |
| Justification for exclusion (eg, exclusion of non–English-language citations) | YES | 5 |
| Assessment of quality of included studies | YES | 7, Table 3 |
| **Reporting of Conclusions** | | |
| Consideration of alternative explanations for observed results | YES | 9, 10 |
| Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | YES | 10 |
| Guidelines for future research | YES | 9, 10 |
| Disclosure of funding source | YES | 11 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supplementary file 'Search strategy' |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5 & supplementary figure |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 & 6 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5 & 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5, 6, 7 & supplementary figure |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 5,6 |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis. | 6 |



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 6 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 7 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 7 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 7 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 7, 8 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 7, 8 , 9 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 7 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 7, 8 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 9 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 10 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 10 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 11 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

# Over and undertesting in primary care: a systematic review and meta-analysis.

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-018557.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 25-Oct-2017 |
| Complete List of Authors: | O'Sullivan, Jack; Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences<br>Albasri, Ali<br>Nicholson, Brian; University of Oxford,<br>Perera, Rafael; University of Oxford, Primary Health Care<br>Aronson, Jeffrey; University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences<br>Roberts, Nia; University of Oxford, UK, Bodleian Health Care Libraries,<br>Heneghan, Carl; Oxford University, Primary Health Care |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Diagnostics, General practice / Family practice |
| Keywords: | PRIMARY CARE, RADIOLOGY & IMAGING, EPIDEMIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT |
| | |

# Over and undertesting in primary care: a systematic review and meta-analysis.

O'Sullivan J[1], Albasri A[1], Nicholson B[1], Perera R[1], Aronson J[1], Roberts N[2], Heneghan C[1]

[1] Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Science, University of Oxford, UK

[2] Bodleian Health Care Libraries, University of Oxford.

Jack W O'Sullivan, Clinical Researcher, jack.osullivan@phc.ox.ac.uk

Ali Albasri, Clinical Researcher, ali.albasri@gtc.ox.ac.uk

Brian D Nicholson, Clinical Researcher, brian.nicholson@phc.ox.ac.uk

Rafael Perera, Professor of Medical Statistics, rafael.perera@phc.ox.ac.uk

Jeffrey Aronson, Reader in Evidence-Based Medicine, jeffrey.aronson@phc.ox.ac.uk

Nia Roberts, Medical Librarian, nia.roberts@bodleian.ox.ac.uk

Carl Heneghan, Professor of Evidence-Based Medicine, carl.heneghan@phc.ox.ac.uk

**Correspondence to:** Dr Jack O'Sullivan

Centre for Evidence-Based Medicine

Nuffield Department of Primary Care Health Sciences

Radcliffe Observatory Quarter, Oxford, OX2 6GG

**Abstract**

*Background*

Health systems are currently subject to unprecedented financial strains. Inappropriate test use wastes finite health resources (overuse) and delays diagnoses and treatment (underuse). As most patient care is provided in primary care, it represents an ideal setting to mitigate waste.

*Objective*

To identify over and under use of diagnostic tests in primary care.

*Design*

Systematic review and meta-analysis.

*Data sources and eligibility criteria*

We searched MEDLINE and EMBASE from January 1999 to October 2017 for studies that measured the inappropriateness of any diagnostic test (measured against a national or international guideline) ordered for adult patients in primary care.

*Results*

We included 357,171 patients from 63 studies in 15 countries. We extracted 103 measures of inappropriateness (41 underuse, 62 overuse) from included studies for 47 different diagnostic tests.

The overall rate of inappropriate diagnostic test ordering varied substantially (0.2% to 100%).

17 tests were underused >50% of the time. Of these, echocardiography (n=4 measures) was consistently underused (between 54% and 89%, n=4). There was large variation in the rate of inappropriate underuse of pulmonary function tests (38% to 78%, n = 8).

Ten tests were inappropriately overused >50% of the time. Echocardiography was consistently overused (77% to 92%), whereas inappropriate overuse of urinary cultures, upper endoscopy and colonoscopy varied widely, from 36% to 77% (n=3), 10% to 54% (n=10) and 8% to 52% (n=2) respectively.

*Conclusions*

There is marked variation in the appropriate use of diagnostic tests in primary care. Specifically, the use of echocardiography (both under and overuse) is consistently poor. There is substantial variation in the rate of inappropriate underuse of pulmonary function tests and the overuse of upper endoscopy, urinary cultures and colonoscopy.

Registration number: PROSPERO Registration ID: CRD42016048832

**Manuscript word count:** 3,531

**Strengths and limitations of this study**

*Strengths*

- Generates rate of under and overtesting for specific diagnostic tests against national or international guidelines
- Only includes data from real clinical encounters rather than surveys or hypothetical clinical vignettes.
- Quantified inappropriate ordering of all types of diagnostic tests, rather than just laboratory.

*Limitations*

- Systematic reviews are restricted to published literature, thus rates of inappropriate ordering are not available for all tests available to primary care physicians.
- Included studies measure appropriateness of testing in a particular health care setting against a particular guideline, thus reflect test ordering in a specific health care setting.

## Introduction

Reaching a diagnosis in primary care is exceedingly complex. The combination of undifferentiated symptoms, a low prevalence of serious disease, a high degree of symptom overlap between serious and benign conditions, patients with multiple complaints, and psychological or social distress manifesting somatically all complicate reaching a diagnosis [1]. In around 40% of primary care consultations a diagnosis cannot be established from the history and physical examination alone [2], and tests are therefore often needed [1,3].

Primary care consultations make up most of the care provided in healthcare systems (90% of consultations in the UK [4], 55% of consultations in the USA[5]) and inappropriate diagnostic testing in primary care therefore has enormous resource implications. Given the calls for £22 billion in efficiency savings from the UK's National Health Service (NHS) [6] and the $660 billion US Medicare deficit predicted by 2023 [7], ensuring the appropriateness of primary care diagnostic testing is crucial to the sustainability of healthcare systems [8].

Inappropriate diagnostic tests in primary care can be both inappropriately underused and overused. Underuse of tests, failure to order a test when clearly indicated, can lead to diagnostic errors and delays in diagnosis and the delivery of effective treatment, leading to adverse patient outcomes and further healthcare costs [9,10]. Overuse of tests, the delivery of tests with no clear benefit or when potential harms outweigh potential benefits, subjects patients to direct harms, such as radiation exposure, as well as potential adverse outcomes (e.g. contrast nephropathy) [11], incidental findings [12], and overdiagnosis [13]. Overuse is also a waste of finite healthcare expenditure, diverting resources from beneficial tests and treatments [14–16].

Many drivers encourage inappropriate under and overuse of diagnostic tests in primary care. Greater access to tests [17], the medicolegal consequences of under-testing [18], few if any disincentives to overinvestigate [14], and clinical performance measures [19] may all contribute to overuse. Increasing primary care workload [4], time constraints [19], and difficulty keeping up-to-date with rapidly increasingly evidence [20] may contribute to both inappropriate underuse and overuse.

Guidelines set the standard of care across most health-care settings [21,22]. Furthermore, they provide a medicolegal framework [23], inform health-care policy, and improve both care outcomes and processes of care [24]. Despite some recognised limitations, including varying quality of guidelines [25–27], guidelines are often used as markers of health-care appropriateness [28–31]. Zhi et al, for instance, used guidelines as a measure of appropriateness to estimate under and overuse of laboratory testing [29]. They estimated that 45% (95%CI 34 – 56%) of secondary care laboratory testing is underused and 21% (95%CI 16 – 25%) is overused.

Despite the increasing use of healthcare resources [32], rising healthcare expenditure [6–8], increasing demands placed on primary care [4], and apparent drivers of inappropriate testing [1,4,14,17–20], it is not clear how often diagnostic tests are inappropriately overused or underused in primary care. We therefore conducted a systematic review to quantify the frequency of appropriate ordering of all types of diagnostic tests from primary care in relation to their respective guidelines and identify tests that are frequently over and underused.

## Methods

This study was conducted and is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [33] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) statements [34].

*Protocol and Registration*

The protocol has been published and is available online (open access) via the International prospective register for systematic reviews (PROSPERO) database (Registration ID: CRD42016048832).

*Search Strategy*

We searched EMBASE (OvidSP) and MEDLINE (OvidSP) databases from January 1999 to October 2017 for studies of any design measuring how often diagnostic test guidelines were followed in primary care (Supplementary File 1: Search Strategy). Our search strategy can be summarised as: 'Ambulatory Care AND adherence AND guideline AND diagnostic tests AND inappropriate'. Conference abstracts published after 2015 were also searched for in these databases to capture data not yet published. We also searched the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov, and the reference lists of included studies.

*Eligibility Criteria*

We included studies of any design if they measured the rate of inappropriate ordering (overuse) or not ordering (underuse) of diagnostic tests ordered from primary care against national or international guidelines. We considered all diagnostic tests ordered in adults. We also included studies that measured diagnostic tests ordered from primary care but performed in secondary care (e.g. upper endoscopy). We included the control arms of RCTs if they offered exclusively usual care, and the pre-intervention periods of studies that used interrupted time series designs (before and after studies).

We excluded studies if they met the following criteria: >20% of participants were children (>20% under 18 years old); diagnostic tests not ordered by General Practitioners; screening or monitoring tests, or publication before 1999 (studies after 1999 were considered to ensure that results would more closely reflect current practice). We defined a screening test as a test on an asymptomatic or symptomatic person without signs or symptoms related to that test [35,36]. We defined monitoring tests as 'a test for a patient with an established diagnosis, for which the test is used to measure progression of the disease' [37]. We excluded studies if they did not give a measure of appropriateness or if appropriateness was measured against local guidelines, such as a guideline specific to a hospital or region, rather than international or national guidelines.

*Study selection and data extraction*

Three reviewers (JS and AA or BN) independently screened titles, abstracts, and full texts for eligibility. The same reviewers assessed risks of bias and extracted the following data from included studies: patient demographics, eligibility criteria, name and type of diagnostic test, duration of study (days), guideline name and recommendation, total number of tests performed, and the number of tests ordered when the specific guideline recommended not ordering (inappropriate overuse) or the number of tests not ordered when the guideline recommended ordering it (inappropriate underuse). The last two data points (overuse and underuse) represent 'measures of inappropriateness'. When studies measured inappropriateness of multiple tests we extracted data on each test and presented them as individual measures of inappropriateness. When studies measured tests across different periods we

extracted measures for each time point and considered each one as an individual measure of inappropriateness.

We assessed the quality of included studies using a modified version of the Hoy risk of bias tool [38]. This tool has been validated to assess the internal and external validity of prevalence studies [38]. Our modified version of this tool kept the same domains, but adjusted the wording of the tool to reflect prevalence of inappropriate testing rather than prevalence of disease. Our tool (and results) is available in Supplementary File 2: Risk of Bias.

*Statistical analysis*

The primary outcome was the prevalence of inappropriate diagnostic testing. Inappropriate testing was measured in two ways:

1) Overuse: A diagnostic test was ordered when the relevant guideline recommends not ordering it, for instance, imaging for non-red flag low back pain (LBP).

2) Underuse: A diagnostic test was not ordered when the relevant guideline recommended ordering it, for instance, spirometry to confirm or refute the diagnosis of COPD.

We expressed measures of inappropriateness as proportions (%), where the numerator represents the total number of times a guideline recommendation was not followed and the denominator the total number of times a guideline recommendation could have been followed. For instance, the number of times imaging was inappropriately ordered for non-red flag headache as a proportion of the total number of patients who presented with non-red flag headache. Given these data are proportions, we calculated Clopper-Pearson 95% confidence intervals for each individual measure of appropriateness. We conducted sensitivity analyses with high risk of bias studies excluded.

Where the same guideline and recommendation were used by multiple studies (e.g. five studies measured inappropriate underuse of spirometry testing in patients with COPD [39–43] using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline) we pooled the measures and assessed heterogeneity. We combined measures of inappropriateness using a random-effects meta-analysis with 95% confidence intervals (Clopper-Pearson), for this reason each measure of appropriateness contributed relatively evenly to pooled estimates. We performed double arcsine transformation on prevalence data to stabilize the variance [44], and pooled the data using the inverse variance method [45]. We assessed heterogeneity using the $I^2$ statistic [46]. We did not combine measures of overuse and underuse, as they have different denominators: overuse involves the total number of tests ordered, whereas underuse involves the total number of times a test should have been ordered. We performed analyses using R version 3.3.2 (R project).

## Results

*Study selection and characteristics*

We included 63 studies from 14,716 references identified from independent searches by two authors (JOS and AA or BN) (see Figure 1). Of the 63 included studies, 55 were observational studies, 6 were before and after studies and 2 were RCTs. These studies were conducted in 15 countries and included 357,171 patients (Supplementary File 3: Table 1). Table 2 (Supplementary File 4: Table 2) shows the 103 measures of inappropriateness extracted from included studies for 47 different diagnostic tests measured against 77 guideline recommendations (41 measured underuse and 62 measured overuse). Guideline recommendations came from 42 different guideline organisations from 15 countries.

Fourteen studies measured inappropriateness of more than one diagnostic tests for the same condition (e.g. chest x-ray (CXR), electrocardiography (ECG), and transthoracic echocardiography (TTE) to confirm or refute a diagnosis of heart failure). Two studies [47,48] measured inappropriateness across multiple time periods. No studies measured both under and overuse of the same test.

Included studies measured inappropriateness in one of three ways:

1. Patients with specific symptoms were assessed (prospectively or retrospectively) to see if they had received an inappropriate diagnostic test (overuse) or hadn't received the appropriate diagnostic test (underuse) in line with the relevant guideline recommendation (e.g. records for patients with non-red flag LBP to see if they received imaging [49]). 18 studies used this method.

2. Patients who had undergone a diagnostic test were identified (via hospital or national databases) and an assessment of whether the test was inappropriate (as per the defined guideline recommendations) via individual patient data was made (overuse). For instance, patients who had an upper endoscopy[50]). 22 studies used this method.

3. Patients with a diagnosis were identified via hospital or national databases and assessed to see whether they had received the appropriate diagnostic test (as per the defined guideline) to confirm or refute the diagnosis via individual patient data (underuse). For instance, assessing if patients with a diagnosis of COPD had spirometry to confirm or refute the diagnosis [39]). 23 studies used this method.

*Risk of bias*

Two thirds of the studies (n=44) were graded as being at low risk of bias, 15 (24%) at moderate risk, and 4 (6%) at high risk (Supplementary File 2 Risk of Bias). Moderate or high risk studies were at an increased risk of non-response bias (>20%), non-objective collection of data, and/or unclear intervals between symptom onset and diagnostic test use. Supplementary File 2 Risk of Bias outlines risk of bias scores in detail.

*Proportions of diagnostic tests ordered in line with specific guideline recommendations*

There was large variation in the rate of inappropriate diagnostic test ordering. The 103 diagnostic test guideline recommendations were not followed 0.2 - 100% of the time (Supplementary File 4 Table 2), wide variation was largely sustained (0.2 – 99.94%) when a further analysis was conducted excluding studies judged to be of high risk of bias. The prevalence of underuse varied 8.2% to 100%, whereas overuse varied between 0.2% and 94.2%. Similarly, this variation was essentially maintained upon exclusion of high risk studies (under use 9.8% - 99.9%, overuse 0.2 – 94.2%).

*Underused tests*

Table 2 (Supplementary File 4) shows that 17 tests were underused more than 50% of the time. Echocardiography was the most frequently studied (n=4 measures in Poland, UK (2), Brazil). In

patients with heart failure, echocardiography was underused between 54% and 89% (n=3) of the time and in atrial fibrillation 56% (n=1).

For some tests there was large variation in the rate of underuse (Figure 2). Underuse of pulmonary function tests (PFTs) to confirm or refute COPD, measured against the Global Initiative for Chronic Obstructive Lung Disease (GOLD), NICE (UK) and Danish National Board of Health guidelines, varied from 26% to 78% (n=8). None of the studies that studied echocardiography, or PFTs were considered high risk of bias and thus results didn't change upon further analysis excluding high risk studies.

*Overused tests*

Ten tests were overused more than 50% of the time (Figure 3). Echocardiography was consistently overused, for instance in 'routine perioperative evaluation of ventricular function with no symptoms or signs of cardiovascular disease', whereas other tests (urinary cultures, upper endoscopy and colonoscopy) were overused at varying rates. The over use of echocardiography was studied in the UK [51] and the Netherlands [52]. The rates of overuse varied between the two settings: between 77% (Netherlands) and 92% (UK). Overuse of urinary cultures for uncomplicated urinary tract infections was studied in the USA [53,54], Spain [55] and Sweden [56] the rate varied from 57% to 77% in the USA, was around 50% in Sweden and was as low as 36% in Spain. Overuse of upper endoscopy was studied widely (n=11); in Australia [57,58], Saudi Arabia [59,60], UK [61], Italy [62–64], USA [50,65], and Malaysia [66]. The overuse varied markedly, from 7.5% to 54% (n=11) respectively (Figure 3, Supplementary File 4 Table 2). Similarly, the inappropriate over-use of colonoscopy varied substantially; from 8% in Australia [58] to 52% in Malaysia [67]. None of the above studies were considered high risk of bias and thus results didn't change upon further analysis excluding high risk studies.

Our results also suggest that the inappropriate overuse of CT and MRI scans for non-red flag headache (a headache without symptoms suggesting a malignant underlying pathology) has more than doubled in the last ten years in the USA (*2000*: 6.7% (95%CI: 5.4 to 8.2%, *2010*: 14% (95%CI 12. to 16%) (Supplementary File 4 Table 2) [48]. Conversely, the rate of inappropriate overuse of radiology tests for non-red flag low back pain was consistently low, with all (n=18 measures) but two measure showing inappropriate overuse less than 25% of the time (Supplementary File 4 Table 2). One of these studies [68] estimated overuse to be about 50%, but was conducted in 2001 and thus may reflect improvements over time. The other study is current, but used a small sample size [69]. None of these studies were considered high risk of bias and thus results didn't change upon further analysis excluding high risk studies.

*Variation of inappropriateness against the same guideline recommendation*

Eleven different guideline recommendations were studied more than once. There was significant heterogeneity ($I^2$ >50%) in nine of these pooled measures. Significant heterogeneity may have occurred for several reasons: 1) vastly different populations (for instance, one study measured the inappropriateness of upper endoscopy in Saudi Arabia [60] using the American Gastroenterological Association recommendations, whereas another study used the same recommendations in the USA [70]; 2) Contrasting healthcare systems [71,72]; 3) Relevance and applicability of one country's national guideline to another country [73]; 4) A low number of measures for meta-analysis [46] and/or 5) Significant heterogeneity, reflecting significant variation in inappropriate ordering.

## Discussion

There is marked variation in the rate of underuse and overuse of diagnostic tests from many primary care settings across the world. This variation suggests improvement can be made in the rate of appropriate diagnostic test ordering.

Primary care use of echocardiography is consistently poor. Echocardiography is inappropriately underused for some clinical situations, e.g. confirming a diagnosis of heart failure, and inappropriately overused in others, e.g. perioperative assessment. This was consistent across the countries where appropriateness of echocardiogram has been studied. This is of concern, given the expertise and resource requirements to perform the test and the increasing availability of direct access ordering for primary care physicians.

For four tests we found marked variation in the rate of inappropriate use. Underuse of pulmonary function tests varied by >50% , whereas overuse of urinary cultures, upper endoscopy and colonoscopy all varied by around 40%.

Radiology tests for both non-red flag low back pain and non-red flag headache were frequently ***not*** overused, but the rate of overuse of imaging for non-red flag headache showed concerning trends, more than doubling from 2000 to 2010 (Supplementary File 4 Table 2).

*Implications and future research*

Two principle conclusions can be drawn from our results: 1.Ordering of echocardiograms from primary care appears to require improvement, 2. Markedly varying rates of inappropriate use for pulmonary function tests (underuse), colonoscopy (overuse), upper endoscopy (overuse), and urinary cultures (overuse) suggests that ordering can be improved.

Future research should focus on: Determining the reasons for deviation from guidelines, assessing the quality of guidelines supporting diagnostic test use and systematic reviews quantifying inappropriate screening and monitoring tests. Further, investigators wishing to undertake primary studies measuring inappropriate use should focus on developing objective data extraction methods for assessing patient notes and define clearly the interval they (investigators) will consider a test ordered for a particular symptom or disease.

*Strengths in relation to other studies*

Compared with other studies of inappropriate use of healthcare resources, we used data from real clinical encounters. This allowed a more robust assessment of diagnostic test inappropriateness, where other studies used surveys and hypothetical clinical vignettes [19,74,75]. Furthermore, we quantified the appropriateness of all types of diagnostic tests, rather than focusing on a specific test or specific disease (such as only laboratory tests [29]). Our paper is the first systematic review of studies that measured inappropriateness of all diagnostic tests ordered from primary care. Zhi et al [29] quantified the mean rates of overuse and underuse of laboratory tests in secondary care and focused on quantifying an overall rate of over and under use. They estimated that over and underuse of laboratory tests was around 21% and 45% respectively [29]. We choose not to quantify an overall rate of over and under use because we feel the results would not be representative; we would be combining data from multiple different health care settings and data captured only the studied selection of diagnostic tests available in primary care.

Our use of guideline recommendations as the metric of appropriateness allowed a direct measure of diagnostic test appropriateness. Other studies that have assessed temporal and geographical variation in the use of diagnostic tests [76,77] have noted substantial differences in diagnostic practices across different regions, irrespective of disease prevalence and patient characteristics [77]. These studies, however, could not quantify what proportion of the temporal increase in the use of a diagnostic test is

inappropriate and what proportion of variation between regions is inappropriate. We have quantified the proportion of inappropriate testing.

Although beyond the scope of our review, ultimately, interventions should be implemented to improve test use. A 2015 systematic review [78] concluded that 'Interventions such as educational strategies, feedback and changing test order forms may improve the efficient use of laboratory tests in primary care'. Thus, doctors, academics and policy makers can use our results to identify diagnostic tests in their particular health care settings which may benefit from intervention.

*Limitations*

The use of guidelines to quantify appropriateness of diagnostic tests could be considered a limitation of this study. Guidelines are often criticised for varying quality [25–27,79] and panel members' conflicts of interests [80]. However, clinical practice guidelines have been shown to improve both care outcomes and processes of care [24], allow assessment of care on a population level, inform health policy [81,82], set the standard of care across many health care settings [21,22], and provide a medicolegal framework [23]. One major medical insurance company advises that 'doctors must be prepared to explain and justify their decisions and actions, especially if they depart from guidelines produced by a nationally recognised body' [23]. Furthermore, guidelines have been used to measure appropriateness of the use of tests in other published peer-review studies [29]. There will always be times when it is appropriate to depart from guidelines, but dramatic, consistent variation from guidelines requires investigation and is unlikely to be caused entirely by the quality of guidelines.

Furthermore, our study includes only a selection of diagnostic tests and is thus not an all-encompassing reflection of clinical practice. The data reflects the use of a specific test, sometimes for a particular clinical situation, in a particular country's health care system. Thus, policy makers and those interested in improving the quality of primary care diagnostic test use, can use our results as a resource to identify tests in their healthcare setting that require improvement and/or investigation to decipher why such deviation from guidelines exists. Our conclusions from this paper, however, are not generalisable to all primary care settings nor all primary care diagnostic tests.

Lastly, caution must be taken when comparing results that measured inappropriateness using different denominators. The results from studies that measured inappropriateness using patients who had undergone a diagnostic test as a denominator should be interpreted differently to studies that used patients with a diagnosis or symptoms as a denominator (and vice versa).

*Conclusion*

There is marked variation in under and overuse of appropriate diagnostic test use in primary care across the world. From the available data, echocardiograms are ordered particularly poorly, while the substantial variation in appropriate ordering of pulmonary function tests, colonoscopy, upper endoscopy, and urinary cultures suggest a need for improvement.

**Funding:**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

All author declare no conflicts of interests.

**Ethical approval:** Not required

**Data sharing:** Data extracted from the included studies in this review are available on request from the corresponding author.

**Registration:** PROSPERO protocol Registration ID: CRD42016048832 (https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016048832)

**Competing interest statement.**

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and jointly declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

**Contribution statement:**

Conception and design: Jack O'Sullivan, Rafael Perera and Carl Heneghan

Search Strategy: Nia Roberts and Jack O'Sullivan

Screening, extraction and risk of bias: Jack O'Sullivan, Ali Albasri and Brian Nicholson.

Analysis and interpretation of the data: Jack O'Sullivan, Rafael Perera, Jeffrey Aronson and Carl Heneghan.

Drafting of the article: Jack O'Sullivan (all authors critically reviewed and approved manuscript)

Statistical expertise: Rafael Perera

Clinical expertise: Jack O'Sullivan, Brian Nicholson, Jeffrey Aronson and Carl Heneghan

Jack O'Sullivan is the guarantor.



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Figure legends

Figure 1: PRISMA Flow Diagram

Figure 2: Rates of underuse. FNA=Fine needle aspiration, FBC=Full Blood Count, TSH=Thyroid Stimulating Hormone, PFTs=Pulmonary function tests, CXR=Chest x-ray, ECG= Electrocardiogram, AFib= Atrial Fibrillation, TB=Tuberculosis, ACC=American College of Cardiology, AHA=American Heart Association, ESC: European Society of Cardiology.

Figure 3: Rates of overuse. NHMRC= National Health and Medical Research Council, U/S=Ultrasound

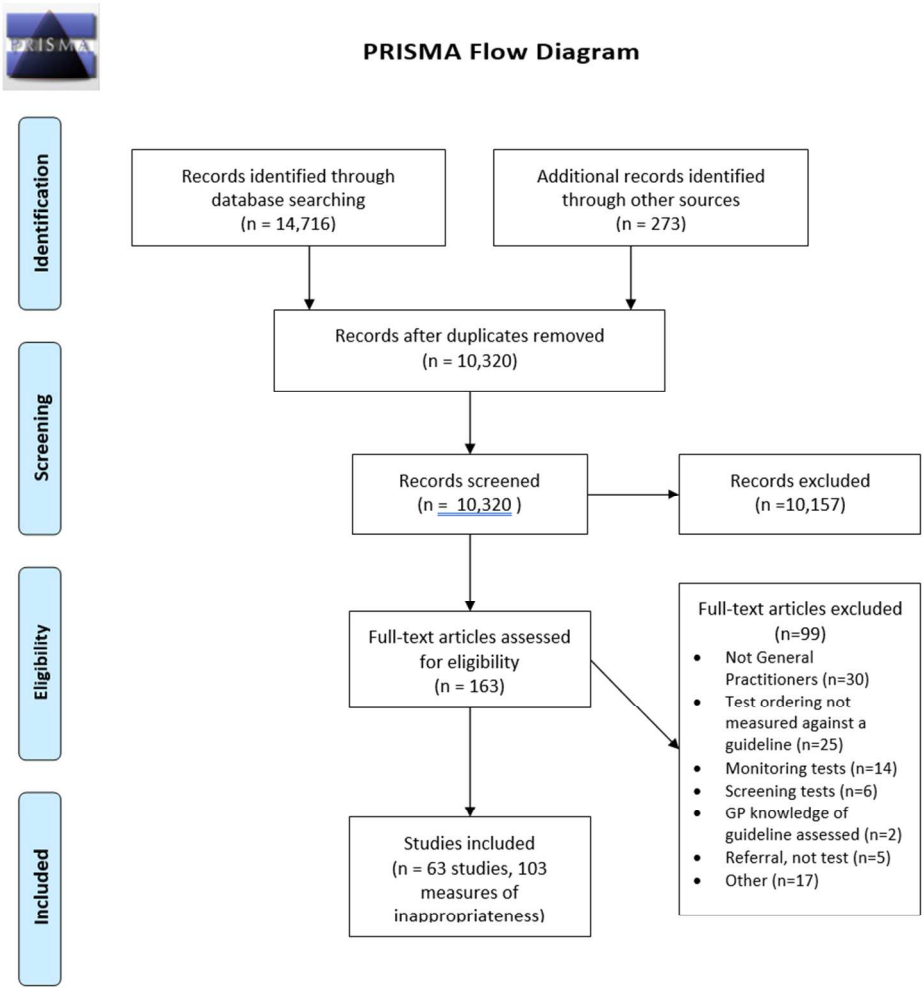


Figure 1: PRISMA flow diagram

82x85mm (300 x 300 DPI)

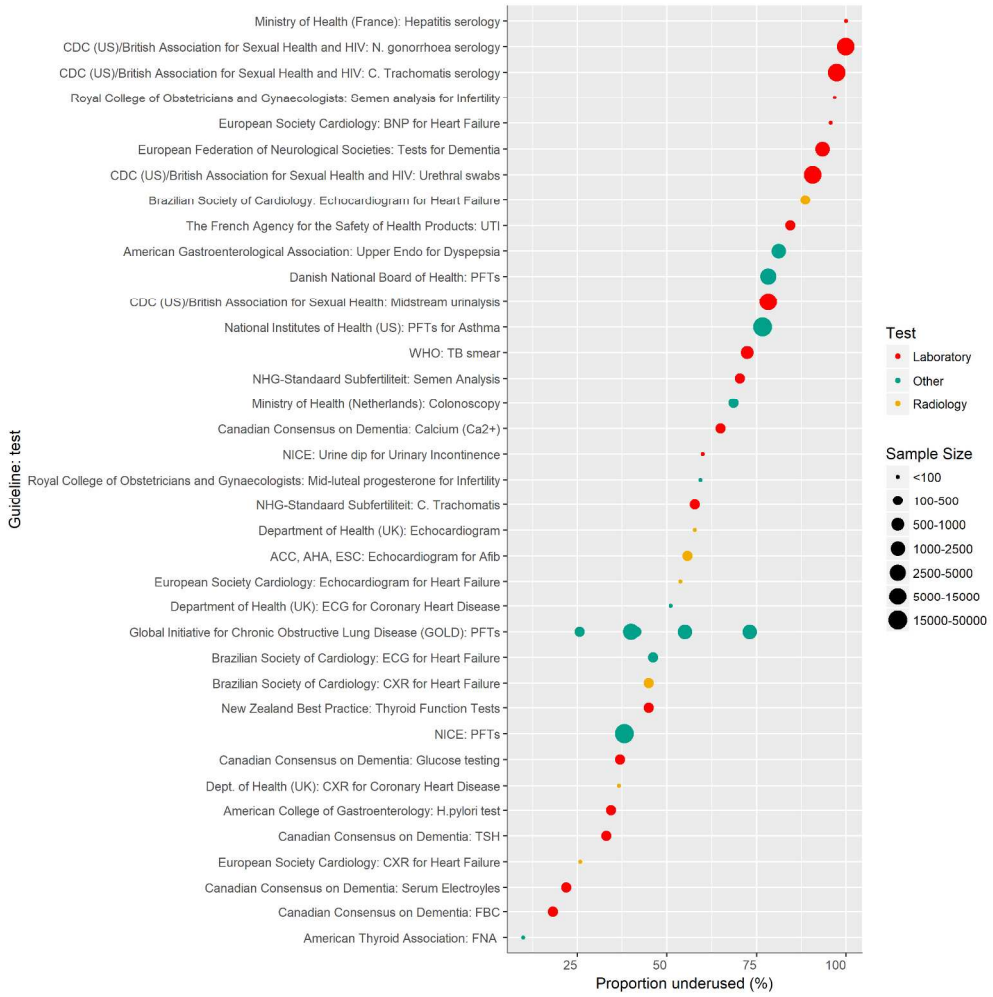


Figure 2: Rates of underuse. FNA=Fine needle aspiration, FBC=Full Blood Count, TSH=Thyroid Stimulating Hormone, PFTs=Pulmonary function tests, CXR=Chest x-ray, ECG= Electrocardiogram, AFib= Atrial Fibrillation, TB=Tuberculosis, ACC=American College of Cardiology, AHA=American Heart Association, ESC: European Society of Cardiology.

254x254mm (300 x 300 DPI)


Figure 3: Rates of overuse. NHMRC= National Health and Medical Research Council, U/S=Ultrasound

254x254mm (300 x 300 DPI)

**MEDLINE Search Strategy**

1. Ambulatory Care/
2. exp Ambulatory Care Facilities/
3. general practice/ or family practice/
4. general practitioners/ or physicians, family/ or physicians, primary care/
5. Primary Health Care/
6. Office visits/
7. Academic Medical Centers/
8. (ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
9. ((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.
10. (primary care or primary health care or primary healthcare or family medicine or community medicine or community health).ti,ab.
11. (gp or gps).ti,ab.
12. (after hour? or afterhour? or "out of hour?" or ooh).ti,ab.
13. (clinic? or visit?).ti,ab.
14. ((health* or medical) adj2 (center? or centre?)).ti,ab.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp Emergency Service, Hospital/
17. Emergency Medical Services/
18. (emergency adj3 (care or setting? or facilit* or ward? or department? or service? or room?)).ti,ab.
19. (emergency medicine or ed or er or a&e).ti,ab.
20. 16 or 17 or 18 or 19
21. 15 or 20
22. guidelines as topic/ or practice guidelines as topic/
23. (guideline? or guidance?).ti,ab.
24. 22 or 23
25. (adhere* or non-adhere* or nonadhere* or concord* or non-concord* or nonconcord* or discord* or comply or complian* or non-complian* or noncomplian* or align* or nonalign* or nonalign* or congruen* or incongruen* or consisten* or inconsisten* or contradict*).ti,ab.
26. ((does or "does not" or doesn?t or did or "did not" or didn?t or "not" or fail*) adj3 (follow* or met or meet or meeting or match or matching or "in line with")).ti,ab.
27. ((follow* or met or meet or meeting or match or matching or "in line with" or keep or kept or keeping or utili?ation or utile?e? or change?) adj5 (criteria or recommend* or guideline? or guidance)).ti,ab.
28. Physician's Practice Patterns/
29. clinical competence/ or nursing competence/
30. 25 or 26 or 27 or 28 or 29
31. 24 and 30
32. Guideline Adherence/
33. 31 or 32
34. exp *"diagnostic techniques and procedures"/
35. exp "diagnostic techniques and procedures"/ut
36. (diagnos* or detect* or test* or screen* or manag*).ti.

37. (imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra*).ti,ab.
38. ((medical or clinical or diagnos* or screening or routine or laboratory) adj5 (test* or investigation?)).ti,ab.
39. ((h?ematolog* or blood or urin* or saliva*) adj5 test*).ti,ab.
40. ((stress* or physical or function*) adj5 test*).ti,ab.
41. 34 or 35 or 36 or 37 or 38 or 39 or 40
42. 21 and 33 and 41
43. ((necessary or unnecessary or appropriate* or inappropriate* or waste* or utili?ation or indicated or excess* or less or more or increas* or decreas*) adj10 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
44. ((order* or request*) adj5 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
45. Unnecessary Procedures/
46. 43 or 44 or 45
47. 21 and 24 and 46
48. 21 and 41 and 45
49. 42 or 47 or 48
50. limit 49 to yr="1999 -Current"
51. limit 50 to english language
52. exp animals/ not humans.sh.
53. 51 not 52

**EMBASE Search Strategy**

1. Ambulatory Care/
2. general practice/
3. general practitioners/
4. Primary Health Care/
5. (ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
6. ((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.
7. (primary care or primary health care or primary healthcare or family medicine or community medicine or community health).ti,ab.
8. (gp or gps).ti,ab.
9. (after hour? or afterhour? or "out of hour?" or ooh).ti,ab.
10. (clinic? or visit?).ti,ab.
11. ((health* or medical) adj2 (center? or centre?)).ti,ab.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Emergency Ward/
14. (emergency adj3 (care or setting? or facilit* or ward? or department? or service? or room?)).ti,ab.
15. (emergency medicine or ed or er or a&e).ti,ab.
16. 13 or 14 or 15
17. 12 or 16
18. *practice guideline/

19. (guideline? or guidance?).ti,ab.
20. 18 or 19
21. (adhere* or non-adhere* or nonadhere* or concord* or non-concord* or nonconcord* or discord* or comply or complian* or non-complian* or noncomplian* or align* or nonalign* or nonalign* or congruen* or incongruen* or consisten* or inconsisten* or contradict*).ti,ab.
22. ((does or "does not" or doesn?t or did or "did not" or didn?t or "not" or fail*) adj3 (follow* or met or meet or meeting or match or matching or "in line with")).ti,ab.
23. ((follow* or met or meet or meeting or match or matching or "in line with" or keep or kept or keeping or utili?ation or utile?e? or change?) adj5 (criteria or recommend* or guideline? or guidance)).ti,ab.
24. clinical competence/ or nursing competence/
25. 21 or 22 or 23 or 24
26. 20 and 25
27. diagnostic procedure/ or exp blood examination/ or exp cardiovascular system examination/ or exp digestive system examination/ or exp endocrine system examination/ or exp neurologic examination/ or exp respiratory tract examination/ or exp urogenital system examination/
28. (diagnos* or detect* or test* or screen* or manag*).ti.
29. (imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra*).ti,ab.
30. ((medical or clinical or diagnos* or screening or routine or laboratory) adj5 (test* or investigation?)).ti,ab.
31. ((h?ematolog* or blood or urin* or saliva*) adj5 test*).ti,ab.
32. ((stress* or physical or function*) adj5 test*).ti,ab.
33. 27 or 28 or 29 or 30 or 31 or 32
34. 17 and 26 and 33
35. ((necessary or unnecessary or appropriate* or inappropriate* or waste* or utili?ation or indicated or excess* or less or more or increas* or decreas*) adj10 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
36. ((order* or request*) adj5 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
37. Unnecessary Procedures/
38. 35 or 36 or 37
39. 17 and 20 and 38
40. 17 and 33 and 37
41. 34 or 39 or 40
42. limit 41 to yr="1999 -Current"
43. limit 42 to english language
44. (exp animals/ or nonhuman/) not human/
45. 43 not 44
46. conference*.pt.
47. 45 and 46
48. 45 not 46
49. exp child/ not (exp Child/ and exp Adult/)

50. 48 not 49
51. 48 not 49
52. limit 47 to yr="2015 -Current"

| | Was the study"s target population a close representation of the national population in relation to relevant variables? | Does the inclusion criteria match the target population of guideline? | Were all eligible participants included in the study? | Was the likelihood of non-response bias <20? | Was an acceptable disease, test or symptom definition used? | Was data extracted/collected in an objective way? | Was the interval from symptoms to test clinically appropriate for the diagnosis of interest? | Did they report extractable measures? | Other bias? |
|---|---|---|---|---|---|---|---|---|---|
| Ahmad2012 | Low | Unclear | Low | Unclear | Low | Unclear | Unclear | Low | Low |
| Aljebreen 2013 | Low | Low | Low | Low | Unclear | Unclear | Low | Low | High |
| Azzam 2015 | Low | Low | Unclear | High | Low | Unclear | Low | Low | Low |
| Belletti2013 | Low | Unclear | Unclear | Unclear | Low | Low | Low | Low | Low |
| Bertella 2013 | Low | Low | Low | Low | Unclear | Low | Unclear | Low | Low |
| Bhatt 2001 | Low | Low | Low | High | High | Unclear | Unclear | Low | High |
| Birk-Urovitz 2017 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Bishop 2003 | High | Low | Low | Low | Low | Low | Low | Low | Low |
| Cai 2015 | Low | Low | Unclear | Low | Unclear | Unclear | Unclear | Low | Low |
| Caplan 2000 | Low | Low | Low | Low | Unclear | Unclear | Unclear | Low | Low |
| Cardin 2005 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Cardin 2007 | Low | Low | Low | Unclear | Low | Low | Low | Low | Low |
| Chan 2004 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Chan 2006 | Low | Low | Low | High | Unclear | Low | Unclear | Low | Low |
| Chavez 2009 | Low | Low | Low | Low | Low | Low | High | Low | High |
| Droogendijk 2011 | Unclear | Low | High | Unclear | Low | Unclear | Low | Low | Low |
| Eccles 2001 | Low | Low | Low | Low | Unclear | Unclear | Unclear | Low | Low |
| Elwyn 2007 | Low | Low | Unclear | Unclear | Unclear | Low | Low | High | High |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Fiorenza 2017 | Low | Low | Low | Unclear | Low | Low | Unclear | Low | Low |
| Gerrits2008 | Low | Unclear | High | Low | Low | Low | Unclear | Low | Low |
| Gibbons 2010c | Low | Low | Low | Low | Low | High | Low | Low | Low |
| Girard 2010 | High | Low | Unclear | High | Unclear | High | Unclear | Low | High |
| Gnani 2004 | Low | Low | Unclear | Low | Unclear | Low | Unclear | Low | Low |
| Grover 2007 | Low | Low | Unclear | Low | Low | High | Unclear | Low | Low |
| Gurzun 2014 | Low | Low | High | Low | High | Low | Unclear | Low | High |
| Hassan 2007 | Low | Low | Low | High | Unclear | Low | Unclear | Low | Low |
| Heidi Lindbäck 2017 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Hughes-Anderson 2002 | High | Low | Unclear | Low | Unclear | Unclear | unclear | Low | Low |
| Ip2014 | Low | Low | High | Unclear | Low | Unclear | Unclear | Low | High |
| Johnson 2011 | Low | Unclear | Unclear | Low | High | Low | Low | Low | Low |
| Kinouani 2017 | Low | Low | low | Low | Unclear | Yes | Unclear | Low | Low |
| Kovacs 2013 | Low | Unclear | High | Low | Low | Low | Unclear | Low | High |
| Lalude 2014 | Low | Low | Low | Low | High | Low | Unclear | Low | High |
| Landry 2011 | Low | Unclear | Low | Low | Unclear | Unclear | Unclear | Low | Low |
| Lange 2007 | Low | Low | Unclear | Low | Unclear | Unclear | Unclear | Low | Low |
| Lin 2016 | Low | Low | Unclear | Unclear | Low | Low | Unclear | Low | Low |
| Linder 2006 | Low | High | Unclear | Low | Low | Low | Low | Unclear | Low |
| Lipczynska 2012 | High | High | Unclear | Low | Low | Unclear | Low | Low | High |
| Llor 2011 | Low | Low | Low | High | Low | Low | Low | Low | Low |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Loo 2009 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Mafi2013 | Low | Low | Unclear | Unclear | Low | Low | Unclear | Low | Low |
| Mafi2015 | Low | Low | Unclear | Unclear | Low | Low | Unclear | Low | Low |
| Majumdar 2003 | Low | Low | Unclear | Low | Low | Low | Unclear | Low | Low |
| Michaleff 2012 | Low | Low | Low | Unclear | High | Low | Unclear | Low | Low |
| Moscavitch 2009 | Low | Low | Unclear | Low | Low | Unclear | Low | Low | Low |
| Musicco 2004 | High | Low | Low | Unclear | Unclear | Unclear | Unclear | High | High |
| Nicholson 2010 | Low | Low | Low | Low | Unclear | Low | Low | Low | Low |
| Nicopoullos 2003 | High | High | Low | High | Low | Unclear | Unclear | Low | High |
| Noya 2008 | Low | Low | Low | Low | Unclear | Unclear | Unclear | Low | High |
| Piccoliori 2013 | Low | Low | Low | Low | Low | Unclear | Low | Low | High |
| Pimlott 2006 | Low | Low | Unclear | High | Unclear | Unclear | Unclear | Low | Low |
| Piterman 2008 | Low | Unclear | Low | Unclear | Unclear | Low | Unclear | High | High |
| Remedios 2014 | Low | Unclear | Low | High | Unclear | Low | Unclear | Low | High |
| Schers 2000 | Low | Low | Low | Unclear | Unclear | Low | Unclear | Low | Low |
| Smith 2008 | Low | Low | Low | Low | Unclear | Low | Unclear | Low | Low |
| Sokol 2015 | Low | Low | Low | Low | Low | Low | High | Low | High |
| Tahvonen 2017 | Low | Low | High | Low | Low | Low | Unclear | Low | Low |
| Ulrik 2010 | Low | Low | Low | High | Low | Low | unclear | Low | High |
| Ulrik 2013 | Low | Low | Low | High | Low | Low | unclear | Low | Low |
| van der Pluijm-Schouten 2017 | Low | Low | Low | Unclear | Low | Unclear | Unclear | Low | Low |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| van Gurp 2013 | Low | Low | Low | Low | Unclear | Low | Unclear | Low | Low |
| Williams 2010 | Low | Low | Unclear | Low | Low | Unclear | Unclear | Low | Low |

Table 1: Study Characteristics

| Study | Country | Study length (days) | N (men%) | Population | Test |
|---|---|---|---|---|---|
| **Under-use** | | | | | |
| Ahmad 2012 | Indonesia | 181 | 554 (41%) | Patients registered at health clinics where TB was suspected | Sputum smear microscopy |
| Belletti 2013 | USA | N/S | 1517 (46%) | Patients with COPD | Pulmonary function tests (PFT) |
| Bertella 2013 | Italy | 1765 | 437 (286) | Patients with COPD | PFTs |
| Caplan 2000 | USA | 365 | 81 | Patients with a thyroid nodule | FNA of thyroid |
| Chavez 2009 | USA | 2920 | 200 (48%) | Patients with COPD | PFT |
| Droogendijk 2011 | Netherlands | 730 | 287 (45%) | Women >50yrs and men >18 years with Iron Deficiency Anaemia | Upper endoscopy and colonoscopy |
| Gerrits 2008 | Netherlands | 2556 | 65 (0%) | Women aged 18 – 65 yrs with newly diagnosed urinary incontinence | Urine dipstick |
| Gibbons 2010 | New Zealand | 364 | 265 | Patients with subclinical hypothyroidism | Free T4 |
| Gnani 2004 | UK | 365 | 90 (53%) | Patients with heart failure | CXR, ECG and Echocardiogram |
| Girard 2010 | France | 28 | 19 (37%) | Patients with acute hepatitis | Hepatitis serology (HBs antigens, anti-HBc anitbodies) |
| Kinuoani 2017 | France | 150 | 61 (18%) | Patients with urinary tract infections | Urine Dipstick |
| Lange 2007 | Denmark | 91 | 2549 (44%) | Patients with COPD | PFTs |
| Lipczynska 2012 | Poland | 61 | 93 | Aged ≥ 55 with Heart Failure (HF) or HF risk factors | Echocardiogram, BNP, CXR |
| Loo 2009 | UK | 364 | 131 (50%) | Patients with Atrial Fibrillation | Echocardiogram |
| Majumdar 2003a | USA | 2371 | 531 (47%) | Patients >50 years, on Proton Pump Inhibitors with persistent dyspepsia | Upper endoscopy |
| Majumdar 2003b | USA | 2371 | 132 (47%) | Patients with peptic ulcer disease (PUD) | H.pylori |
| Moscavitch 2009 | Brazil | 61 | 167 (43%) | Patients with Heart Failure | ECG, CXR, Echocardiogram |
| Musicco 2004 | Italy | NR | 1549 (38%) | Patients being assessed for Dementia | Collection of laboratory tests to rule out conditions with similar presenting symptoms to dementia |

| | | | | | |
|---|---|---|---|---|---|
| Nicholson 2010 | UK | 1827 | 6943 (100%) | Men with epididymo-orchtitis | C. trachomatis, N. gonorrhoeae, urethral swabs and midstream urinalysis. |
| Nicopoullos 2003 | UK | 242 | 32 | Patients with subfertility | Mid-luteal progesterone and semen analysis |
| Pimlott 2006 | Canada | 1611 | 160 (34%) | Patients with Dementia | FBC, TSH, serum electrolytes, serum calcium, glucose |
| Smith 2008 | UK | 731 | 29870 (52%) | Patients with COPD | PFT |
| Sokol 2015 | USA | 3652 | 75902 (23%) | Patients with Asthma | PFT |
| Ulrik 2010 | Denmark | 121 | 1716 (44%) | Patients with COPD | PFT |
| Ulrik 2013 | Denmark | 731 | 4058 | Patients with COPD | PFT |
| van der Pluijm-Schouten 2017 | Netherlands | 840 | 100%* | Patients (couples) referred to IVF clinics | Chlamydia Antibody Titre and Semen Analysis |
| **Over-use** | | | | | |
| Aljebreen 2013 | Saudi Arabia | 365 | 147 (51%) | Patients who had upper endoscopy | Upper endoscopy |
| Azzam 2015 | Saudi Arabia | 121 | 161 (30%) | Dyspeptic patients who had upper endoscopy | Upper endoscopy |
| Bhatt 2001 | UK | 504 | 437 (65%) | Patients referred for pelvis x-rays | Pelvis x-ray |
| Birk-Urovitz 2017 | Canada | 1538 | 77 (38%) | Patients that had a Thyroid Stimulating Hormone (TSH) test | TSH |
| Bishop 2003 | Canada | 28 | 139 | Patients with non-red flag LBP | Advanced imaging (CT, MRI or bone scan) |
| Cai 2015 | USA | 121 | 550 (46%) | Patients who under went upper endoscopy | Upper endoscopy |
| Chan 2004 | Malaysia | 153 | 250 (45%) | Patients who under went upper endoscopy | Upper endoscopy |
| Chan 2006 | Malaysia | 184 | 27 (63%) | Patients who underwent 'diagnostic colonoscopies' | Colonoscopy |
| Cardin 2005 | Italy | 151 | 1678 | Patients who had upper endoscopy | Upper endoscopy |
| Cardin 2007 | Italy | 182 | NR | Dyspeptic patients who had upper endoscopy | Upper endoscopy |
| Eccles 2001 | UK | 182 | 275 | Patients who had knee or lumbar x-ray | Lumbar or knee x-ray |
| Elwyn 2007 | UK | 184 | 215 | Patients who under went upper endoscopy | Upper endoscopy |
| Fiorenza 2017 | USA | 456 | 45 (34%) | Patients who under went upper endoscopy | Upper Endoscopy |

| | | | | | |
|---|---|---|---|---|---|
| Grover 2007 | USA | 364 | 68 (0%) | Patients with uncomplicated UTI | Urine culture and sensitivity analysis |
| Gurzun 2014 | UK | 7 | 1070 (54%) | Patients who underwent an echocardiogram | Echocardiogram |
| Hassan 2007 | Italy | 30 | 3769 (46%) | Patients who underwent upper endoscopy | Upper endoscopy |
| Hughes-Anderson 2002a | Australia | 1613 | 154 (55%) | Patients who had colonoscopy | Colonoscopy |
| Hughes-Anderson 2002b | Australia | 1613 | 162 (55%) | Patients who had upper endoscopy, | Upper endoscopy |
| Ip 2014 | USA | 1096 | 100 (43%) | Patients with non-red flag LBP | MRI lumbar spine |
| Johnson 2011 | USA | 510 | 779 (0%) | Patients with uncomplicated UTI | Urine culture |
| Kovacs 2013 | Spain | 183 | 602 (48%) | Patients with non-red flag LBP | MRI lumbar spine |
| Lalude 2014 | USA | 121 | 102 | Patients who had SPECT Myocardial perfusion imaging (MPI) studies | Single Photon Emission CT (SPECT) MPI |
| Landry 2011 | USA | 272 | 124 | Patients who had U/S of thyroid, pelvis, abdo, carotid or soft tissue | Thyroid, pelvis, abdomen, carotid or soft tissue ultrasound |
| Lin 2016 | Australia | NR | NR | Patients with non-red flag LBP | Lumbar Spine X-ray |
| Lindbäck 2017 | Sweden | 59 | 0 | Patients that had urinary cultures | Urinary Culture |
| Linder 2006 | USA | 608 | 1076 (19%) | Patients with pharyngitis | Strep testing (rapid antigen detection test, throat culture) |
| Llor 2011 | Spain | 122 | 658 (0%) | Women with UTI | Urine cultures |
| Mafi 2013 | USA | 4377 | 8066 | Patients with non-red flag LBP | X-ray, CT or MRI |
| Mafi 2015 | USA | 4018 | 9362 (25%) | Patients with uncomplicated headache (non-red flag | CT and MRI |
| Michaleff 2012 | Australia | 3621 | 3070 (70%) | Patients reporting first time neck pain or LBP (non-specific, non red flag) | Any radiological test |
| Noya 2008 | Israel | N/S | 209 (35%) | Patients who had H.pylori testing | H. pylori test |
| Piccoliori 2013 | Italy | 63 | 475 (43%) | Acute or chronic non-red flag LBP | Any radiological test |
| Piterman 2008 | Australia | 550 | 19219 | Patients with GORD | Endoscopy. Barium Swallow |
| Remedios 2014 | UK | NR | 2026 | Patients who had CTs and/or MRIs | CT and/or MRI |
| Sharp 2015 | USA | 730 | 37,464 | Patient with Acute Sinusitis | CT Sinuses |

| | | | | | |
|---|---|---|---|---|---|
| Schers 2000 | Netherlands | 214 | 1096 (50%) | Patients with non-red flag LBP | X-ray |
| Tahvonen 2017 | Finland | 180 | 18 (35%) | Patients with non-red flag LBP | Lumbar Spine X-ray |
| Van Gurp 2013 | Netherlands | 366 | 155 (38%) | Patients who had Echocardiogram | Echocardiogram |
| Williams 2010 | Australia | 1005 | 1706 (43%) | Patients with non-red flag LBP | All imaging |

*Both men and women

Table 2: Measures of inappropriateness

| Study | Test | Guideline authority and recommendation | Measure of inappropriateness (95%CI) |
|---|---|---|---|
| | | **Under-use** | |
| Girard 2010 | Hepatitis B serology | Ministry of Health (France): Hepatitis serology for suspected acute hepatitis | 100% (82.4 to 100%) |
| Nicholson 2010 | Neisseria Gonorrhoea serology | CDC (US)/British Association for Sexual Health and HIV: Test for N. gonorrhoea for suspected Epididymitis | 99.9% (99.85 to 99.98%) |
| Nicholson 2010 | Chlamydia Trachomatis | CDC (US)/British Association for Sexual Health and HIV: Test for C. Trachomatis for suspected Epididymitis | 97.4% (97.0 to 97.8%) |
| Nicopoullos 2003 | Semen Analysis | Royal College of Obstetricians and Gynaecologists: Semen analysis for Infertility | 96.9% (83.8 to 99.9%) |
| Lipczynska 2012 | Brain Natriuretic Peptide (BNP) | European Society Cardiology: BNP for Heart Failure | 95.7% (89.4 to 98.8%) |
| Musicco 2004 | Collection of laboratory tests | European Federation of Neurological Societies: Collection of laboratory tests to rule out conditions with similar presenting symptoms to dementia | 93.42% (92.1 to 94.6%) |
| Nicholson 2010 | Urethral swabs | CDC (US)/British Association for Sexual Health and HIV: Urethral swabs for suspected epididymitis (Urethral swabs) | 90.7% (89.9 to 91.3%) |
| Moscavitch 2009 | Echocardiogram | Brazilian Society of Cardiology: Echocardiography for Heart Failure | 88.6% (82.8 to 93.0%) |
| Kinouani 2017 | Urine Dipstick | The French Agency for the Safety of Health Products: Urine Dipstick for UTI | 84.4% (80.1 to 88.1%) |
| Majumdar 2003a | Upper Endoscopy | American Gastroenterological Association: Appropriate use of Upper Endoscopy for Dyspepsia | 81.2% (78.8 to 83.4%) |
| Ulrik 2013 | Pulmonary function tests (PFTs) | Danish National Board of Health: PFTs to diagnosis COPD | 78.3 (77.3% to 79.3%) |
| Nicholson 2010 | Mid stream | CDC (US)/British Association for Sexual Health and HIV: Midstream urinalysis for suspected Epididymitis | 78.2 (77.3 to 79.3%) |
| Sokol 2015 | Pulmonary function tests (PFTs) | National Asthma Education and Prevention Program (US): PFTs for asthma | 76.5% (64.6 to 85.9%) |
| Belletti 2013 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 73.0% (70.7 to 75.3%) |

| | | | |
|---|---|---|---|
| Ahmad 2012 | Tuberculosis smear | World Health Organisation: Smear for suspected TB | 72.4% (68.5 to 76.1%) |
| van der Pluijm-Schouten 2017 | Semen Analysis | NHG-Standaard Subfertiliteit: Semen Analysis | 70.4% (61.9 to 77.9%) |
| Droogendijk 2011 | Colonoscopy | Ministry of Health (Netherlands): Colonoscopy for unexplained Iron Deficiency Anaemia | 68.6% (62.9 to 74.0%) |
| Pimlott 2006 | Serum Calcium | Canadian Consensus Conference on Dementia: Serum Calcium for Dementia | 65.0 (57.1 to 72.4%) |
| Gerrits 2008 | Urine dip stick | NICE: Urine dip stick for urinary incontinence | 60.0% (47.1 to 72.0%) |
| Nicopoullos 2003 | Mid-luteal progesterone | Royal College of Obstetricians and Gynaecologists: Mid-luteal progesterone for Infertility | 59.4% (40.6 to 76.3%) |
| Gnani 2004 | Echocardiogram | Department of Health (UK): Echocardiogram for Heart Failure | 57.8% (46.1 to 68.1%) |
| Loo 2009 | Echocardiogram | ACC, AHA, ESC: Echocardiogram to identify causes or complications of atrial fibrillation | 55.7% (46.8 to 64.39%) |
| Ulrik 2010 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 55.0% (52.6 to 57.4%) |
| Lipczynska 2012 | Echocardiogram | European Society Cardiology: Echocardiogram for Heart Failure | 53.8% (43.1 to 64.2%) |
| van der Pluijm-Schouten 2017 | Chlamydia Trachomatis | NHG-Standaard Subfertiliteit: Chlamydia Trachomatis | 57.8% (49.0 to 66.2%) |
| Gnani 2004 | ECG | Department of Health (UK): ECG for Heart Failure | 51.1% (40.4% to 61.8%) |
| Moscavitch 2009 | ECG | Brazilian Society of Cardiology: ECG for Heart Failure | 46.1 (38.4 to 54.0) |
| Moscavitch 2009 | Chest X-ray | Brazilian Society of Cardiology: CXR for Heart Failure | 44.9% (37.2 to 52.8%) |
| Gibbons 2010 | Thyroid function tests | New Zealand Best Practice: Appropriate use of Thyroid Function tests | 44.9% (38.8 to 51.1%) |
| Chavez 2009 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 41.5% (34.6 to 48.7%) |
| Lange 2007 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 40.0% (38.1 to 42.0) |
| Smith 2008 | Pulmonary Function Tests (PFTs) | NICE: PFTs for COPD | 38.1% (37.5 to 38.6%) |
| Pimlott 2006 | Glucose testing | Canadian Consensus Conference on Dementia: Glucose testing for Dementia | 36.9% (29.4% to 44.9%) |
| Gnani 2004 | Chest X-ray | Department of Health (UK): CXR for Heart Failure | 36.7% (26.8 to 47.5%) |

| | | | |
|---|---|---|---|
| Majumdar 2003b | H.pylori | American Gastroenterological Association/American College of Gastroenterology: appropriateness of H.pylori test | 34.4% (28.9 to 40.3%) |
| Pimlott 2006 | Thyroid Stimulating Hormone (TSH) | Canadian Consensus Conference on Dementia: TSH for dementia | 33.1% (25.9 to 41.0%) |
| Lipczynska 2012 | Chest x-ray (CXR) | European Society Cardiology: CXR for Heart Failure | 25.8% (17.3 to 35.9%) |
| Bertella 2013 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 25.6% (21.6 to 30.0%) |
| Pimlott 2006 | Serum electrolytes | Canadian Consensus Conference on Dementia: Serum electrolytes for dementia | 21.9% (15.7 to 29.1%) |
| Pimlott 2006 | Full Blood Count (FBC) | Canadian Consensus Conference on Dementia: FBC for dementia | 18.1% (12.5 to 25.0%) |
| Caplan 2000 | Fine needle aspiration (FNA) of thyroid | American Thyroid Association/American Association of Clinical Endocrinologists: FNA for thyroid nodules | 9.9% (4.4 to 18.5%) |
| | | **Over-use** | |
| Piterman 2008 | Barium Swallow | Gastroenterological Society of Australia: Barium Swallow for GORD | 94.20% (93.9 to 94.5%) |
| Gurzun 2014 | Echocardiogram | American College of Cardiology: Appropriate use of Echocardiography | 92.0% (90.2% to 93.5%) |
| van Gurp 2013 | Echocardiogram | Netherlands Society of Cardiology: Appropriate use of Echocardiography | 76.7% (76.4 to 77.0%) |
| Grover 2007 | Urine cultures | Infectious Disease Society of America: Urine cultures not required for uncomplicated UTI diagnosis | 76.5% (64.6 to 85.9%) |
| Eccles 2001 | Knee x-ray | Royal College of Radiologists: No x-ray for knee pain without restriction of movement | 74.7% (69.6 to 79.3%) |
| Cardin 2005 | H. Pylori breath test | European Society of Primary Care Gastroenterology: Appropriate use of H. pylori | 74.4% (58.8 to 86.5%) |
| Tahvonen 2017 | L spine x-ray | Finish Medical Society: LBP among adults | 68.0% (53.3 to 80.48%) |
| Johnston 2011 | Urine cultures | European Association of Urology: Urinary cultures not required for uncomplicated urinary tract infections | 57.4% (53.8 to 60.9%) |
| Bhatt 2001 | Hip x-ray | Royal College of Radiologists (UK): No hip x-ray for hip pain without restriction of movement | 57.2% (52.5 to 61.8%) |
| Eccles 2001 | Lumbar spine x-ray | Royal College of Radiologists (UK): no x-ray for non-red flag LBP | 56.4% (50.3 to 62.3%) |

| | | | |
|---|---|---|---|
| Piterman 2008 | Upper endoscopy | Gastroenterological Society of Australia: Upper endoscopy for GORD | 53.5% (52.8 to 54.2%) |
| Chan 2006 | Colonoscopy | American Society for Gastrointestinal Endoscopy: Appropriateness of Colonoscopy | 51.9% (32.0 to 71.3%) |
| Heidi Lindbäck 2017 | Urine Culture | Swedish Medicines Agency: Treatment of lower urinary tract infections in women | 47.0% (40.8 to 53.38%) |
| Aljebreen 2013 | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 46.9% (38.7 to 55.3%) |
| Elwyn 2007 | Upper endoscopy | NICE: Appropriate tests for dyspepsia | 45.1% (38.3 to 52.0%) |
| Noya 2008 | H.Pylori | The European Helicobacter Study Group: Appropriate use of H. pylori | 44.5 (37.6 to 51.5%) |
| Cardin 2005 | Upper endoscopy | European Society of Primary Care Gastroenterology: Upper Endoscopy for H.pylori | 44.1% (35.9 to 52.6%) |
| Lin 2016 | L spine x-ray | The George Institute (Aus): LBP | 40.9% (26.3 to 56.8%) |
| Cardin 2007 | Upper endoscopy | European Society of Primary Care Gastroenterology: Upper Endoscopy for H.pylori | 41.9% (38.3 to 45.5%) |
| Fiorenza 2017 | Upper Endoscopy | American College of Gastroenterology: Dyspepsia | 42.4% (36.8 to 48.1%) |
| Cai 2015 | Upper endoscopy | American College of Physicians: Upper endoscopy for GORD | 37.7% (33.8 to 42.0%) |
| Azzam 2015 | Upper endoscopy | American Gastroenterological Association: Upper Endoscopy for Dyspepsia | 36.7 (29.2 to 44.6%) |
| Llor 2011 | Urine cultures | European Association of Urology: Urinary Cultures not required for uncomplicated urinary tract infections | 35.9% (32.2 to 40.0%) |
| Hassan 2007 | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 29.4% (28.0 to 30.9%) |
| Landry 2011 | Carotid ultrasound | Canadian Association of Radiologists 2005 guidelines: Carotid U/S | 25.0% (17.7 to 33.6%) |
| Piccoliori 2013 | Lumbar spine radiology (all) | Ministry of Health (Italy): No imaging for non-red flag LBP | 24.0% (20.2 to 28.1%) |
| Michaleff 2012 | Lumbar spine x-ray | National Health and Medical Research Council (Australia) (NHMRC): No x-ray for non-red flag LBP | 24.0% (22.9 to 25.1%) |
| Williams 2010 | Lumbar spine radiology (all) | National Health and Medical Research Council (Australia) (NHMRC): No imaging for non-red flag LBP | 23.9% (21.9 to 26.0%) |

| | | | |
|---|---|---|---|
| Michaleff 2012 | Cervical spine x-ray | Australian National Health and Medical Research Council: No x-ray for neck pain | 22.8% (21.3 to 24.3%) |
| Birk-Urovitz 2017 | Thyroid Stimulating Hormone | The Canadian Task Force on Preventative Health | 22.4% (16.9 to 28.8%) |
| Ip 2014 | Lumbar spine MRI | American College of Physicians/American Pain Society: no MRI for non-red flag LBP | 22.0% (14.3 to 31.4%) |
| Williams 2010 | Lumbar spine x-ray | National Health and Medical Research Council (Australia) (NHMRC): No x-ray for non-red flag LBP | 20.2% (18.3 to 22.2%) |
| Landry 2011 | Thyroid ultrasound | Canadian Association of Radiologists 2005 guidelines: Thyroid U/S | 19.0% (12.1 to 27.0%) |
| Lalude 2014 | Single Photon Emission Computed Tomography | American College of Cardiology: SPECT for chest pain | 18.6% (11.6 to 27.6%) |
| Linder 2006 | Streptococcal throat cultures | American College of Physicians/Infectious Disease Society of America: Pharyngitis | 15.0 (12.9 to 17.2%) |
| 'Mafi 2013 | Lumbar spine x-ray | American College of Physicians/American Pain Society: no x-ray for non-red flag LBP: *2009-2010* | 13.0% (11.1 to 15.1%) |
| | | *2007-2008* | 12.9% (11.1 to 14.9%) |
| | | *2005-2006* | 12.8% (11.0 to 14.8%) |
| | | *2003-2004* | 12.3% (10.7 to 14.0%) |
| | | *2001-2002* | 12.0% (10.3 to 13.8%) |
| | | *1999 - 2000* | 11.8% (10.2 to 13.6%) |
| Landry 2011 | Abdominal ultrasound | Canadian Association of Radiologists 2005 guidelines: Abdominal U/S | 12.1% (6.9 to 19.2%) |
| Mafi 2015 | CT or MRI Brain | The American Headache Society/American Academy of Neurology for Choosing Wisely: No CT or MRI for non-red flag headache *2009 - 2010* | 13.9% (12.2 to 15.7%) |
| | | *2007 – 2008* | 13.5% (11.8 to 15.3%) |
| | | *2005 – 2006* | 9.4% (8.0 to 11.0%) |
| | | *2003 – 2004* | 7.5% (6.3 to 8.9%) |
| | | *2001 – 2002* | 7.1% (5.9 to 8.4%) |
| | | *1999 - 2000* | 6.7% (5.4 to 8.2%) |
| Kovacs 2013 | Lumbar spine radiology tests (all) | NICE, ACP: No imaging for LBP | 12.0% (9.5 to 14.8%) |

| | | | |
|---|---|---|---|
| Chan 2004 | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 10.4% (6.9 to 14.9%) |
| Hughes-Anderson 2002a | Colonoscopy | American Society for Gastrointestinal Endoscopy: Appropriateness of Colonoscopy | 8.2% (5.3 to 12.1%) |
| Hughes-Anderson 2002b | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 7.5% (4.7 to 11.1%) |
| Remedios 2014 | CT (any) | Royal College of Radiologists (UK): CT | 6.9% (5.8 to 8.1%) |
| | MRI (any) | Royal College of Radiologists (UK): MRI | 5.2% (4.1 to 6.5%) |
| Bishop 2003 | Lumbar spine radiology tests (all) | Workers Compensation Board of British Columbia: No imaging for non-red flag LBP | 5.0% (2.1 to 10.1%) |
| Williams 2010 | Lumbar spine CT | National Health and Medical Research Council (Australia) (NHMRC): No CT for non-red flag LBP | 3.7% (2.9 to 4.7%) |
| Schers 2000 | Lumbar spine radiology tests (all) | The Netherlands College of General Practitioners: No imaging for non-red flag LBP | 3.1% (2.2 to 4.3%) |
| Landry 2011 | Soft tissue ultrasound | Canadian Association of Radiologists 2005 guidelines: Soft tissue U/S | 2.4% (0.5 to 6.9% |
| Landry 2011 | Pelvic ultrasound | Canadian Association of Radiologists 2005 guidelines: Pelvic U/S | 1.6% (0.2 to 5.7%) |
| Sharp 2015 | CT Sinuses | American Academy of Otolaryngology: Adult Sinusitis | 0.60% (0.56 to 0.65%) |
| Williams 2010 | Lumbar spine Ultrasound | National Health and Medical Research Council (Australia) (NHMRC): No U/S for non-red flag LBP | 0.59% (0.28 to 1.1%) |
| Williams 2010 | Lumbar spine MRI | National Health and Medical Research Council (Australia) (NHMRC): No MRI for non-red flag LBP | 0.18% (0.04 to 0.5%) |







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## MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

| Reporting Criteria | Reported (Yes/No) | Reported on Page |
|---|---|---|
| **Reporting of Background** | | |
| Problem definition | YES | 4 |
| Hypothesis statement | YES | 4 |
| Description of Study Outcome(s) | YES | 4 |
| Type of exposure or intervention used | N/A | N/A |
| Type of study design used | YES | 5, 6 |
| Study population | YES | 5 |
| **Reporting of Search Strategy** | | |
| Qualifications of searchers (eg, librarians and investigators) | YES | 5 |
| Search strategy, including time period included in the synthesis and keywords | YES | 5, supplementary file |
| Effort to include all available studies, including contact with authors | YES | 5 |
| Databases and registries searched | YES | 5 |
| Search software used, name and version, including special features used (eg, explosion) | YES | 5 |
| Use of hand searching (eg, reference lists of obtained articles) | YES | 5 |
| List of citations located and those excluded, including justification | NO | |
| Method for addressing articles published in languages other than English | NO | |
| Method of handling abstracts and unpublished studies | YES | 5 |
| Description of any contact with authors | N/A | |
| **Reporting of Methods** | | |
| Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | YES | 5,6 |
| Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | YES | 6 |
| Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability) | YES | 6 |
| Assessment of confounding (eg, comparability of cases and controls in studies where appropriate | N/A | N/A |
| Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | YES | 5,6 |
| Assessment of heterogeneity | YES | 6 |

| | | |
|---|---|---|
| Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | YES | 6 |
| Provision of appropriate tables and graphics | YES | Tables 1,2, Figures 2,3,4 |
| **Reporting of Results** | | |
| Table giving descriptive information for each study included | YES | Table 1 and Table 2 |
| Results of sensitivity testing (eg, subgroup analysis) | N/A | 7, 8 |
| Indication of statistical uncertainty of findings | YES | 6,7, 8,9 |
| **Reporting of Discussion** | | |
| Quantitative assessment of bias (eg, publication bias) | YES | 8,9 |
| Justification for exclusion (eg, exclusion of non–English-language citations) | YES | 5 |
| Assessment of quality of included studies | YES | 7, Table 3 |
| **Reporting of Conclusions** | | |
| Consideration of alternative explanations for observed results | YES | 9, 10 |
| Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | YES | 10 |
| Guidelines for future research | YES | 9, 10 |
| Disclosure of funding source | YES | 11 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supplementary file 'Search strategy' |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5 & supplementary figure |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 & 6 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5 & 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5, 6, 7 & supplementary figure |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 5,6 |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis. | 6 |



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 6 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 7 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 7 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 7 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 7, 8 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 7, 8 , 9 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 7 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 7, 8 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 9 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 10 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 10 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 11 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

# PRISMA 2009 Checklist

For more information, visit: **www.prisma-statement.org**.

BMJ Open

# Over and undertesting in primary care: a systematic review and meta-analysis.

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-018557.R2 |
| Article Type: | Research |
| Date Submitted by the Author: | 12-Dec-2017 |
| Complete List of Authors: | O'Sullivan, Jack; Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences<br>Albasri, Ali<br>Nicholson, Brian; University of Oxford,<br>Perera, Rafael; University of Oxford, Primary Health Care<br>Aronson, Jeffrey; University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences<br>Roberts, Nia; University of Oxford, UK, Bodleian Health Care Libraries,<br>Heneghan, Carl; Oxford University, Primary Health Care |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Diagnostics, General practice / Family practice |
| Keywords: | PRIMARY CARE, RADIOLOGY & IMAGING, EPIDEMIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT |
| | |

# Over and undertesting in primary care: a systematic review and meta-analysis.

O'Sullivan JW[1], Albasri A[1], Nicholson B[1], Perera R[1], Aronson J[1], Roberts N[2], Heneghan C[1]

[1] Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Science, University of Oxford, UK

[2] Bodleian Health Care Libraries, University of Oxford.

Jack W O'Sullivan, Clinical Researcher and Doctoral Candidate, jack.osullivan@phc.ox.ac.uk

Ali Albasri, Clinical Researcher and Doctoral Candidate, ali.albasri@gtc.ox.ac.uk

Brian D Nicholson, Clinical Researcher and Doctoral Candidate, brian.nicholson@phc.ox.ac.uk

Rafael Perera, Professor of Medical Statistics, rafael.perera@phc.ox.ac.uk

Jeffrey Aronson, Reader in Evidence-Based Medicine, jeffrey.aronson@phc.ox.ac.uk

Nia Roberts, Medical Librarian, nia.roberts@bodleian.ox.ac.uk

Carl Heneghan, Professor of Evidence-Based Medicine, carl.heneghan@phc.ox.ac.uk

**Correspondence to:** Dr Jack O'Sullivan

Centre for Evidence-Based Medicine

Nuffield Department of Primary Care Health Sciences

Radcliffe Observatory Quarter, Oxford, OX2 6GG

**Abstract**

*Background*

Health systems are currently subject to unprecedented financial strains. Inappropriate test use wastes finite health resources (overuse) and delays diagnoses and treatment (underuse). As most patient care is provided in primary care, it represents an ideal setting to mitigate waste.

*Objective*

To identify over and under use of diagnostic tests in primary care.

*Design*

Systematic review and meta-analysis.

*Data sources and eligibility criteria*

We searched MEDLINE and EMBASE from January 1999 to October 2017 for studies that measured the inappropriateness of any diagnostic test (measured against a national or international guideline) ordered for adult patients in primary care.

*Results*

We included 357,171 patients from 63 studies in 15 countries. We extracted 103 measures of inappropriateness (41 underuse, 62 overuse) from included studies for 47 different diagnostic tests.

The overall rate of inappropriate diagnostic test ordering varied substantially (0.2% to 100%).

17 tests were underused >50% of the time. Of these, echocardiography (n=4 measures) was consistently underused (between 54% and 89%, n=4). There was large variation in the rate of inappropriate underuse of pulmonary function tests (38% to 78%, n = 8).

Eleven tests were inappropriately overused >50% of the time. Echocardiography was consistently overused (77% to 92%), whereas inappropriate overuse of urinary cultures, upper endoscopy and colonoscopy varied widely, from 36% to 77% (n=3), 10% to 54% (n=10) and 8% to 52% (n=2) respectively.

*Conclusions*

There is marked variation in the appropriate use of diagnostic tests in primary care. Specifically, the use of echocardiography (both under and overuse) is consistently poor. There is substantial variation in the rate of inappropriate underuse of pulmonary function tests and the overuse of upper endoscopy, urinary cultures and colonoscopy.

Registration number: PROSPERO Registration ID: CRD42016048832

**Manuscript word count:** 3,531

**Strengths and limitations of this study**

*Strengths*

- Generates rate of under and overtesting for specific diagnostic tests against national or international guidelines
- Only includes data from real clinical encounters rather than surveys or hypothetical clinical vignettes.
- Quantified inappropriate ordering of all types of diagnostic tests, rather than just laboratory.

*Limitations*

- Systematic reviews are restricted to published literature, thus rates of inappropriate ordering are not available for all tests available to primary care physicians.
- Included studies measure appropriateness of testing in a particular health care setting against a particular guideline, thus reflect test ordering in a specific health care setting.

## Introduction

Reaching a diagnosis in primary care is exceedingly complex. The combination of undifferentiated symptoms, a low prevalence of serious disease, a high degree of symptom overlap between serious and benign conditions, patients with multiple complaints, and psychological or social distress manifesting somatically all complicate reaching a diagnosis [1]. In around 40% of primary care consultations a diagnosis cannot be established from the history and physical examination alone [2], and tests are therefore often needed [1,3].

Primary care consultations make up most of the care provided in healthcare systems (90% of consultations in the UK [4], 55% of consultations in the USA[5]) and inappropriate diagnostic testing in primary care therefore has enormous resource implications. Given the calls for £22 billion in efficiency savings from the UK's National Health Service (NHS) [6] and the $660 billion US Medicare deficit predicted by 2023 [7], ensuring the appropriateness of primary care diagnostic testing is crucial to the sustainability of healthcare systems [8].

Inappropriate diagnostic tests in primary care can be both inappropriately underused and overused. Underuse of tests, failure to order a test when indicated, can lead to diagnostic errors and delays in diagnosis and the delivery of effective treatment, leading to adverse patient outcomes and further healthcare costs [9,10]. Overuse of tests, the delivery of tests with no clear benefit or when potential harms outweigh potential benefits, subjects patients to direct harms, such as radiation exposure, as well as potential adverse outcomes (e.g. contrast nephropathy) [11], incidental findings [12], and overdiagnosis [13]. Overuse is also a waste of finite healthcare expenditure, diverting resources from beneficial tests and treatments [14–16].

Many drivers encourage inappropriate under and overuse of diagnostic tests in primary care. Greater access to tests [17], the medicolegal consequences of under-testing [18], few if any disincentives to overinvestigate [14], and clinical performance measures [19] may all contribute to overuse. Increasing primary care workload [4], time constraints [19], and difficulty keeping up-to-date with rapidly increasingly evidence [20] may contribute to both inappropriate underuse and overuse.

Guidelines set the standard of care across most health-care settings [21,22]. Furthermore, they provide a medicolegal framework [23], inform health-care policy, and improve both care outcomes and processes of care [24]. Despite some recognised limitations, including varying quality of guidelines [25–27], guidelines are often used as markers of health-care appropriateness [28–31]. Zhi et al, for instance, used guidelines as a measure of appropriateness to estimate under and overuse of laboratory testing [29]. They estimated that 45% (95%CI 34 – 56%) of secondary care laboratory testing is underused and 21% (95%CI 16 – 25%) is overused.

Despite the increasing use of healthcare resources [32], rising healthcare expenditure [6–8], increasing demands placed on primary care [4], and the apparent drivers of inappropriate testing [1,4,14,17–20], it is not clear how often diagnostic tests are inappropriately overused or underused in primary care. We therefore conducted a systematic review to quantify the frequency of inappropriate ordering of all types of diagnostic tests from primary care in relation to their respective guidelines and identify tests that are frequently over and underused.

## Methods

This study was conducted and is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [33] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) statements [34].

*Protocol and Registration*

The protocol has been published and is available online (open access) via the International prospective register for systematic reviews (PROSPERO) database (Registration ID: CRD42016048832).

*Search Strategy*

We searched EMBASE (OvidSP) and MEDLINE (OvidSP) databases from January 1999 to October 2017 for studies of any design measuring how often diagnostic test guidelines were followed in primary care (Supplementary File 1: Search Strategy). Our search strategy can be summarised as: 'Ambulatory Care AND adherence AND guideline AND diagnostic tests AND inappropriate'. Conference abstracts published after 2015 were also searched for in these databases to capture data not yet published. We also searched the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov, and the reference lists of included studies.

*Eligibility Criteria*

We included studies of any design if they measured the rate of inappropriate ordering (overuse) or not ordering (underuse) of diagnostic tests ordered from primary care against national or international guidelines. We considered all diagnostic tests ordered in adults. We also included studies that measured diagnostic tests ordered from primary care but performed in secondary care (e.g. upper endoscopy). We included the control arms of RCTs if they offered exclusively usual care, and the pre-intervention periods of studies that used interrupted time series designs (before and after studies).

We excluded studies if they met the following criteria: >20% of participants were children (>20% under 18 years old); diagnostic tests not ordered by General Practitioners; screening or monitoring tests, or publication before 1999 (studies after 1999 were considered to ensure that results would more closely reflect current practice). We defined a screening test as a test on an asymptomatic or symptomatic person without signs or symptoms related to that test [35,36]. We defined monitoring tests as 'a test for a patient with an established diagnosis, for which the test is used to measure progression of the disease' [37]. We excluded studies if they did not give a measure of appropriateness or if appropriateness was measured against local guidelines, such as a guideline specific to a hospital or region, rather than international or national guidelines.

*Study selection and data extraction*

Three reviewers (JS and AA or BN) independently screened titles, abstracts, and full texts for eligibility. The same reviewers assessed risks of bias and extracted the following data from included studies: patient demographics, eligibility criteria, name and type of diagnostic test, duration of study (days), guideline name and recommendation, total number of tests performed, and the number of tests ordered when the specific guideline recommended not ordering (inappropriate overuse) or the number of tests not ordered when the guideline recommended ordering it (inappropriate underuse). The last two data points (overuse and underuse) represent 'measures of inappropriateness'. When studies measured inappropriateness of multiple tests we extracted data on each test and presented them as individual measures of inappropriateness. When studies measured tests across different periods we

extracted measures for each time point and considered each one as an individual measure of inappropriateness.

We assessed the quality of included studies using a modified version of the Hoy risk of bias tool [38]. This tool has been validated to assess the internal and external validity of prevalence studies [38]. Our modified version of this tool kept the same domains, but adjusted the wording of the tool to reflect prevalence of inappropriate testing rather than prevalence of disease. Our tool (and results) is available in Supplementary File 2: Risk of Bias.

*Statistical analysis*

The primary outcome was the prevalence of inappropriate diagnostic testing. Inappropriate testing was measured in two ways:

1) Overuse: A diagnostic test was ordered when the relevant guideline recommends not ordering it, for instance, imaging for non-red flag low back pain (LBP).

2) Underuse: A diagnostic test was not ordered when the relevant guideline recommended ordering it, for instance, spirometry to confirm or refute the diagnosis of COPD.

We expressed measures of inappropriateness as percentages (%), where the numerator represents the total number of times a guideline recommendation was not followed and the denominator the total number of times a guideline recommendation could have been followed. For instance, the number of times imaging was inappropriately ordered for non-red flag headache as a percentage of the total number of patients who presented with non-red flag headache. Given these data are percentages, we calculated Clopper-Pearson 95% confidence intervals for each individual measure of appropriateness. We conducted sensitivity analyses with high risk of bias studies excluded.

Where the same guideline and recommendation were used by multiple studies (e.g. five studies measured inappropriate underuse of spirometry testing in patients with COPD [39–43] using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline) we pooled the measures and assessed heterogeneity. We combined measures of inappropriateness using a random-effects meta-analysis with 95% confidence intervals (Clopper-Pearson), for this reason each measure of appropriateness contributed relatively evenly to pooled estimates. We performed double arcsine transformation on prevalence data to stabilize the variance [44], and pooled the data using the inverse variance method [45]. We assessed heterogeneity using the $I^2$ statistic [46]. We did not combine measures of overuse and underuse, as they have different denominators: overuse involves the total number of tests ordered, whereas underuse involves the total number of times a test should have been ordered. We performed analyses using R version 3.3.2 (R project).

## Results

*Study selection and characteristics*

We included 63 studies from 14,716 references identified from independent searches by two authors (JOS and AA or BN) (see Figure 1). Of the 63 included studies, 55 were observational studies, 6 were before and after studies and 2 were RCTs. The two RCTs investigated the effect of implementing an intervention to reduce inappropriate testing. These studies were conducted in 15 countries and included 357,171 patients (Supplementary File 3: Table 1). Table 1 (Supplementary File 4: Table 1) shows the 103 measures of inappropriateness extracted from included studies for 47 different diagnostic tests measured against 77 guideline recommendations (41 measured underuse and 62 measured overuse). Guideline recommendations came from 42 different guideline organisations from 15 countries.

Fourteen studies measured inappropriateness of more than one diagnostic tests for the same condition (e.g. chest x-ray (CXR), electrocardiography (ECG), and transthoracic echocardiography (TTE) to confirm or refute a diagnosis of heart failure). Two studies [47,48] measured inappropriateness across multiple time periods. No studies measured both under and overuse of the same test.

Included studies measured inappropriateness in one of three ways:

1. Patients with specific symptoms were assessed (prospectively or retrospectively) to see if they had received an inappropriate diagnostic test (overuse) or hadn't received the appropriate diagnostic test (underuse) in line with the relevant guideline recommendation (e.g. records for patients with non-red flag LBP to see if they received imaging [49]). 18 studies used this method.

2. Patients who had undergone a diagnostic test were identified (via hospital or national databases) and an assessment of whether the test was inappropriate (as per the defined guideline recommendations) via individual patient data was made (overuse). For instance, patients who had an upper endoscopy[50]). 22 studies used this method.

3. Patients with a diagnosis were identified via hospital or national databases and assessed to see whether they had received the appropriate diagnostic test (as per the defined guideline) to confirm or refute the diagnosis via individual patient data (underuse). For instance, assessing if patients with a diagnosis of COPD had spirometry to confirm or refute the diagnosis [39]). 23 studies used this method.

*Risk of bias*

Two thirds of the studies (n=44) were graded as being at low risk of bias, 15 (24%) at moderate risk, and 4 (6%) at high risk (Supplementary File 2 Risk of Bias). Moderate or high risk studies were at an increased risk of non-response bias (>20%), non-objective collection of data, and/or unclear intervals between symptom onset and diagnostic test use. Supplementary File 2 Risk of Bias outlines risk of bias scores in detail.

*Percentage of diagnostic tests ordered in line with specific guideline recommendations*

There was large variation in the rate of inappropriate diagnostic test ordering. The 103 diagnostic test guideline recommendations were not followed 0.2 - 100% of the time (Supplementary File 4 Table 1), wide variation was largely sustained (0.2 – 99.94%) when a further analysis was conducted excluding studies judged to be of high risk of bias. The prevalence of underuse varied 8.2% to 100%, whereas overuse varied between 0.2% and 94.2%. Similarly, this variation was essentially maintained upon exclusion of high risk studies (under use 9.8% - 99.9%, overuse 0.2 – 94.2%).

*Underused tests*

Table 1 (Supplementary File 4) shows that 17 tests were underused more than 50% of the time. Echocardiography was the most frequently studied (n=4 measures in Poland, UK (2), Brazil). In patients with heart failure, echocardiography was underused between 54% and 89% (n=3) of the time and in atrial fibrillation 56% (n=1).

For some tests there was large variation in the rate of underuse (Figure 2). Underuse of pulmonary function tests (PFTs) to confirm or refute COPD, measured against the Global Initiative for Chronic Obstructive Lung Disease (GOLD), NICE (UK) and Danish National Board of Health guidelines, varied from 26% to 78% (n=8). None of the studies that studied echocardiography, or PFTs were considered high risk of bias and thus results didn't change upon further analysis excluding high risk studies.

*Overused tests*

Eleven tests were overused more than 50% of the time (Figure 3). Echocardiography was consistently overused, for instance in 'routine perioperative evaluation of ventricular function with no symptoms or signs of cardiovascular disease', whereas other tests (urinary cultures, upper endoscopy and colonoscopy) were overused at varying rates. The over use of echocardiography was studied in the UK [51] and the Netherlands [52]. The rates of overuse varied between the two settings: between 77% (Netherlands) and 92% (UK). Overuse of urinary cultures for uncomplicated urinary tract infections was studied in the USA [53,54], Spain [55] and Sweden [56] the rate varied from 57% to 77% in the USA, was around 50% in Sweden and was as low as 36% in Spain. Overuse of upper endoscopy was studied widely (n=11); in Australia [57,58], Saudi Arabia [59,60], UK [61], Italy [62–64], USA [50,65], and Malaysia [66]. The overuse varied markedly, from 7.5% to 54% (n=11) respectively (Figure 3, Supplementary File 4 Table 1). Similarly, the inappropriate over-use of colonoscopy varied substantially; from 8% in Australia [58] to 52% in Malaysia [67]. None of the above studies were considered high risk of bias and thus results didn't change upon further analysis excluding high risk studies.

Our results also suggest that the inappropriate overuse of CT and MRI scans for non-red flag headache (a headache without symptoms suggesting a malignant underlying pathology) has more than doubled in the last ten years in the USA (*2000*: 6.7% (95%CI: 5.4 to 8.2%, *2010*: 14% (95%CI 12. to 16%) (Supplementary File 4 Table 1) [48]. Conversely, the rate of inappropriate overuse of radiology tests for non-red flag low back pain was consistently low, with all (n=18 measures) but two measure showing inappropriate overuse less than 25% of the time (Supplementary File 4 Table 1). One of these studies [68] estimated overuse to be about 50%, but was conducted in 2001 and thus may reflect improvements over time. The other study is current, but used a small sample size [69]. None of these studies were considered high risk of bias and thus results didn't change upon further analysis excluding high risk studies.

*Variation of inappropriateness against the same guideline recommendation*

Eleven different guideline recommendations were studied more than once. There was significant heterogeneity ($I^2$ >50%) in nine of these pooled measures. Significant heterogeneity may have occurred for several reasons: 1) vastly different populations (for instance, one study measured the inappropriateness of upper endoscopy in Saudi Arabia [60] using the American Gastroenterological Association recommendations, whereas another study used the same recommendations in the USA [70]; 2) Contrasting healthcare systems [71,72]; 3) Relevance and applicability of one country's national guideline to another country [73]; 4) A low number of measures for meta-analysis [46] and/or 5) Significant heterogeneity, reflecting significant variation in inappropriate ordering.

## Discussion

There is marked variation in the rate of underuse and overuse of diagnostic tests from many primary care settings across the world. This variation suggests improvement can be made in the rate of appropriate diagnostic test ordering.

Primary care use of echocardiography is consistently poor. Echocardiography is inappropriately underused for some clinical situations, e.g. confirming a diagnosis of heart failure, and inappropriately overused in others, e.g. perioperative assessment. This was consistent across the countries where appropriateness of echocardiogram has been studied. This is of concern, given the expertise and resource requirements to perform the test and the increasing availability of direct access ordering for primary care physicians.

For four tests we found marked variation in the rate of inappropriate use. Underuse of pulmonary function tests varied by >50% , whereas overuse of urinary cultures, upper endoscopy and colonoscopy all varied by around 40%.

Radiology tests for both non-red flag low back pain and non-red flag headache were frequently ***not*** overused, but the rate of overuse of imaging for non-red flag headache showed concerning trends, more than doubling from 2000 to 2010 (Supplementary File 4 Table 1).

*Implications and future research*

Two principle conclusions can be drawn from our results: 1.Ordering of echocardiograms from primary care appears to require improvement, 2. Markedly varying rates of inappropriate use for pulmonary function tests (underuse), colonoscopy (overuse), upper endoscopy (overuse), and urinary cultures (overuse) suggests that ordering can be improved.

Future research should focus on: Determining the reasons for deviation from guidelines, assessing the quality of guidelines supporting diagnostic test use and systematic reviews quantifying inappropriate screening and monitoring tests. Further, investigators wishing to undertake primary studies measuring inappropriate use should focus on developing objective data extraction methods for assessing patient notes and define clearly the interval they (investigators) will consider a test ordered for a particular symptom or disease.

*Strengths in relation to other studies*

Compared with other studies of inappropriate use of healthcare resources, we used data from real clinical encounters. This allowed a more robust assessment of diagnostic test inappropriateness, where other studies used surveys and hypothetical clinical vignettes [19,74,75]. Furthermore, we quantified the appropriateness of all types of diagnostic tests, rather than focusing on a specific test or specific disease (such as only laboratory tests [29]). Our paper is the first systematic review of studies that measured inappropriateness of all diagnostic tests ordered from primary care. Zhi et al [29] quantified the mean rates of overuse and underuse of laboratory tests in secondary care and focused on quantifying an overall rate of over and under use. They estimated that over and underuse of laboratory tests was around 21% and 45% respectively [29]. We choose not to quantify an overall rate of over and under use because we feel the results would not be representative; we would be combining data from multiple different health care settings and data captured only the studied selection of diagnostic tests available in primary care.

Our use of guideline recommendations as the metric of appropriateness allowed a direct measure of diagnostic test appropriateness. Other studies that have assessed temporal and geographical variation in the use of diagnostic tests [76,77] have noted substantial differences in diagnostic practices across

different regions, irrespective of disease prevalence and patient characteristics [77]. These studies, however, could not quantify what percentage of the temporal increase in the use of a diagnostic test is inappropriate and what percentage of variation between regions is inappropriate. We have quantified the percentage of inappropriate testing.

Although beyond the scope of our review, ultimately, interventions should be implemented to improve test use. A 2015 systematic review [78] concluded that 'Interventions such as educational strategies, feedback and changing test order forms may improve the efficient use of laboratory tests in primary care'. Thus, doctors, academics and policy makers can use our results to identify diagnostic tests in their particular health care settings which may benefit from intervention.

*Limitations*

The use of guidelines to quantify appropriateness of diagnostic tests could be considered a limitation of this study. Guidelines are often criticised for varying quality [25–27,79] and panel members' conflicts of interests [80]. However, clinical practice guidelines have been shown to improve both care outcomes and processes of care [24], allow assessment of care on a population level, inform health policy [81,82], set the standard of care across many health care settings [21,22], and provide a medicolegal framework [23]. One major medical insurance company advises that 'doctors must be prepared to explain and justify their decisions and actions, especially if they depart from guidelines produced by a nationally recognised body' [23]. Furthermore, guidelines have been used to measure appropriateness of the use of tests in other published peer-review studies [29]. There will always be times when it is appropriate to depart from guidelines, but dramatic, consistent variation from guidelines requires investigation and is unlikely to be caused entirely by the quality of guidelines.

Furthermore, our study includes only a selection of diagnostic tests and is thus not an all-encompassing reflection of clinical practice. The data reflects the use of a specific test, sometimes for a particular clinical situation, in a particular country's health care system. Thus, policy makers and those interested in improving the quality of primary care diagnostic test use, can use our results as a resource to identify tests in their healthcare setting that require improvement and/or investigation to decipher why such deviation from guidelines exists. Our conclusions from this paper, however, are not generalisable to all primary care settings nor all primary care diagnostic tests.

Lastly, caution must be taken when comparing results that measured inappropriateness using different denominators. The results from studies that measured inappropriateness using patients who had undergone a diagnostic test as a denominator should be interpreted differently to studies that used patients with a diagnosis or symptoms as a denominator (and vice versa).

*Conclusion*

There is marked variation in under and overuse of appropriate diagnostic test use in primary care across the world. From the available data, echocardiograms are ordered particularly poorly, while the substantial variation in appropriate ordering of pulmonary function tests, colonoscopy, upper endoscopy, and urinary cultures suggest a need for improvement.

**Acknowledgements**

We thank Kate Roche and Jason Hendry for comments on the draft and figures. We also thank the peer reviewers for their constructive feedback.

**Funding:**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

All author declare no conflicts of interests.

**Ethical approval:** Not required

**Data sharing:** Data extracted from the included studies in this review are available on request from the corresponding author.

**Registration:** PROSPERO protocol Registration ID: CRD42016048832 (https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016048832)

**Competing interest statement.**

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and jointly declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

**Contribution statement:**

Conception and design: Jack O'Sullivan, Rafael Perera and Carl Heneghan

Search Strategy: Nia Roberts and Jack O'Sullivan

Screening, extraction and risk of bias: Jack O'Sullivan, Ali Albasri and Brian Nicholson.

Analysis and interpretation of the data: Jack O'Sullivan, Rafael Perera, Jeffrey Aronson and Carl Heneghan.

Drafting of the article: Jack O'Sullivan (all authors critically reviewed and approved manuscript)

Statistical expertise: Rafael Perera

Clinical expertise: Jack O'Sullivan, Brian Nicholson, Jeffrey Aronson and Carl Heneghan

Jack O'Sullivan is the guarantor.

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Figure legends

Figure 1: PRISMA Flow Diagram

Figure 2: Rates of underuse. FNA=Fine needle aspiration, FBC=Full Blood Count, TSH=Thyroid Stimulating Hormone, PFTs=Pulmonary function tests, CXR=Chest x-ray, ECG= Electrocardiogram,

AFib= Atrial Fibrillation, TB=Tuberculosis, ACC=American College of Cardiology, AHA=American Heart Association, ESC: European Society of Cardiology.

Figure 3: Rates of overuse. NHMRC= National Health and Medical Research Council, U/S=Ultrasound

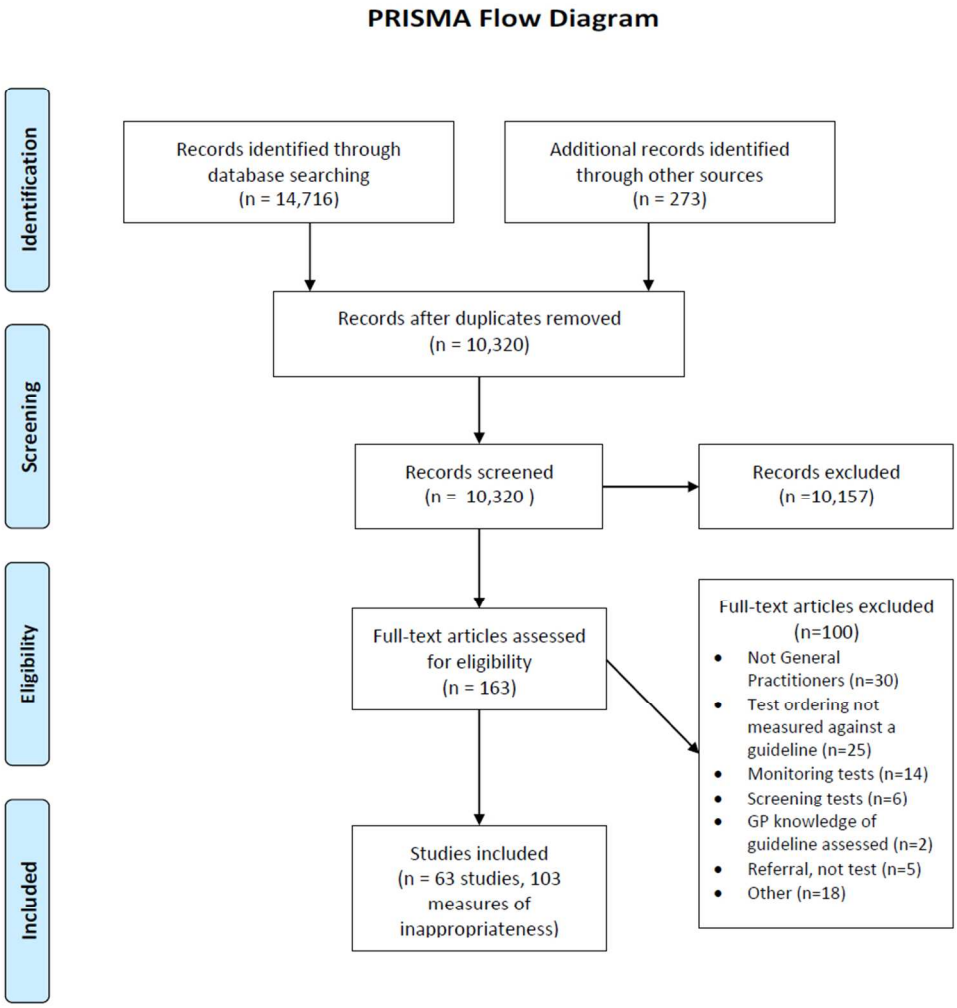


Figure 1: PRISMA Flow Diagram

86x87mm (300 x 300 DPI)

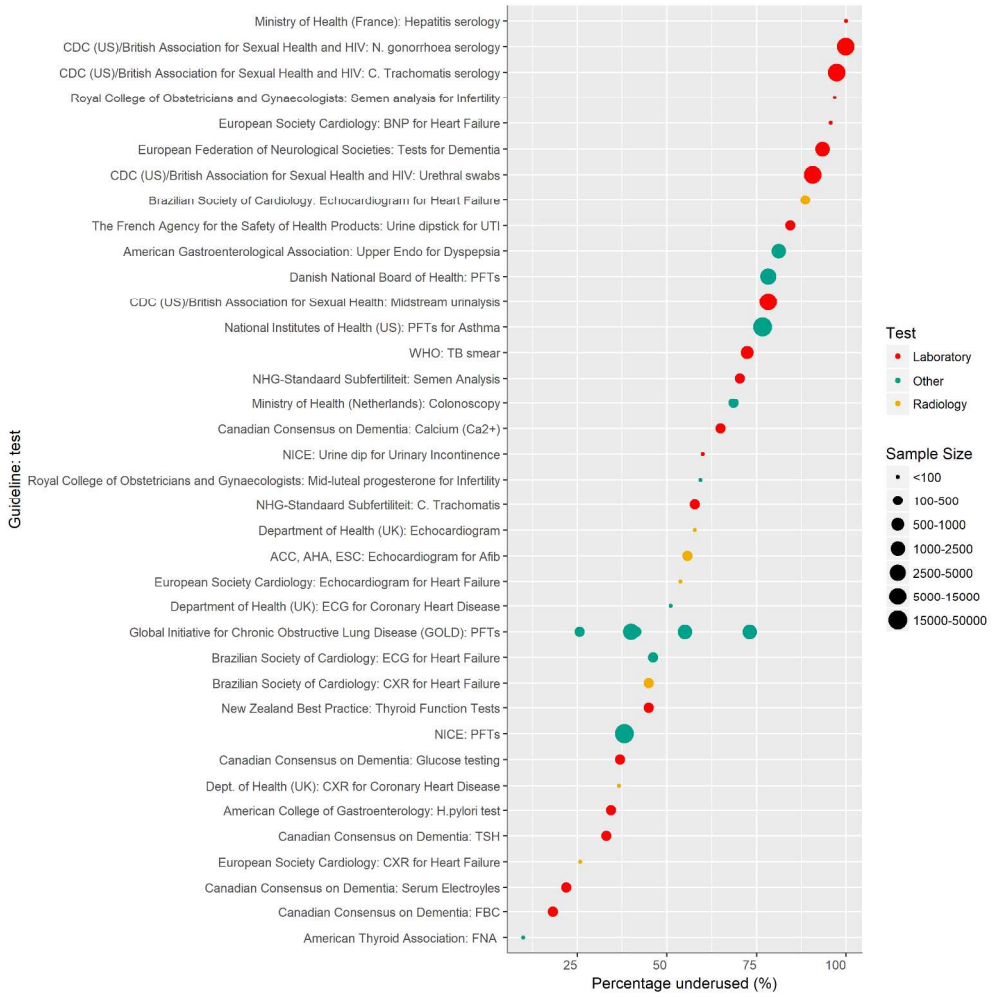


Figure 2: Rates of underuse. FNA: Fine needle aspiration, FBC: Full Blood Count, TSH: Thyroid Stimulating Hormone, PFTs: Pulmonary function tests, CXR: Chest x-ray, ECG:Electrocardiogram, AFib: Atrial Fibrillation, TB: Tuberculosis, ACC: American College of Cardiology, AHA: American Heart Association, ESC: European Society of Cardiology, UTI: Urinary Tract Infection.

254x254mm (300 x 300 DPI)


Figure 3: Rates of overuse. NHMRC: National Health and Medical Research Council, U/S: Ultrasound, TSH: Thyroid Stimulating Hormone, GORD: gastro-oesophageal reflux disease, UTI: Urinary Tract Infection.

254x254mm (300 x 300 DPI)

**MEDLINE Search Strategy**

1. Ambulatory Care/
2. exp Ambulatory Care Facilities/
3. general practice/ or family practice/
4. general practitioners/ or physicians, family/ or physicians, primary care/
5. Primary Health Care/
6. Office visits/
7. Academic Medical Centers/
8. (ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
9. ((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.
10. (primary care or primary health care or primary healthcare or family medicine or community medicine or community health).ti,ab.
11. (gp or gps).ti,ab.
12. (after hour? or afterhour? or "out of hour?" or ooh).ti,ab.
13. (clinic? or visit?).ti,ab.
14. ((health* or medical) adj2 (center? or centre?)).ti,ab.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp Emergency Service, Hospital/
17. Emergency Medical Services/
18. (emergency adj3 (care or setting? or facilit* or ward? or department? or service? or room?)).ti,ab.
19. (emergency medicine or ed or er or a&e).ti,ab.
20. 16 or 17 or 18 or 19
21. 15 or 20
22. guidelines as topic/ or practice guidelines as topic/
23. (guideline? or guidance?).ti,ab.
24. 22 or 23
25. (adhere* or non-adhere* or nonadhere* or concord* or non-concord* or nonconcord* or discord* or comply or complian* or non-complian* or noncomplian* or align* or nonalign* or nonalign* or congruen* or incongruen* or consisten* or inconsisten* or contradict*).ti,ab.
26. ((does or "does not" or doesn?t or did or "did not" or didn?t or "not" or fail*) adj3 (follow* or met or meet or meeting or match or matching or "in line with")).ti,ab.
27. ((follow* or met or meet or meeting or match or matching or "in line with" or keep or kept or keeping or utili?ation or utile?e? or change?) adj5 (criteria or recommend* or guideline? or guidance)).ti,ab.
28. Physician's Practice Patterns/
29. clinical competence/ or nursing competence/
30. 25 or 26 or 27 or 28 or 29
31. 24 and 30
32. Guideline Adherence/
33. 31 or 32
34. exp *"diagnostic techniques and procedures"/
35. exp "diagnostic techniques and procedures"/ut
36. (diagnos* or detect* or test* or screen* or manag*).ti.

37. (imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra*).ti,ab.
38. ((medical or clinical or diagnos* or screening or routine or laboratory) adj5 (test* or investigation?)).ti,ab.
39. ((h?ematolog* or blood or urin* or saliva*) adj5 test*).ti,ab.
40. ((stress* or physical or function*) adj5 test*).ti,ab.
41. 34 or 35 or 36 or 37 or 38 or 39 or 40
42. 21 and 33 and 41
43. ((necessary or unnecessary or appropriate* or inappropriate* or waste* or utili?ation or indicated or excess* or less or more or increas* or decreas*) adj10 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
44. ((order* or request*) adj5 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
45. Unnecessary Procedures/
46. 43 or 44 or 45
47. 21 and 24 and 46
48. 21 and 41 and 45
49. 42 or 47 or 48
50. limit 49 to yr="1999 -Current"
51. limit 50 to english language
52. exp animals/ not humans.sh.
53. 51 not 52

**EMBASE Search Strategy**

1. Ambulatory Care/
2. general practice/
3. general practitioners/
4. Primary Health Care/
5. (ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
6. ((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.
7. (primary care or primary health care or primary healthcare or family medicine or community medicine or community health).ti,ab.
8. (gp or gps).ti,ab.
9. (after hour? or afterhour? or "out of hour?" or ooh).ti,ab.
10. (clinic? or visit?).ti,ab.
11. ((health* or medical) adj2 (center? or centre?)).ti,ab.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Emergency Ward/
14. (emergency adj3 (care or setting? or facilit* or ward? or department? or service? or room?)).ti,ab.
15. (emergency medicine or ed or er or a&e).ti,ab.
16. 13 or 14 or 15
17. 12 or 16
18. *practice guideline/

19. (guideline? or guidance?).ti,ab.
20. 18 or 19
21. (adhere* or non-adhere* or nonadhere* or concord* or non-concord* or nonconcord* or discord* or comply or complian* or non-complian* or noncomplian* or align* or nonalign* or nonalign* or congruen* or incongruen* or consisten* or inconsisten* or contradict*).ti,ab.
22. ((does or "does not" or doesn?t or did or "did not" or didn?t or "not" or fail*) adj3 (follow* or met or meet or meeting or match or matching or "in line with")).ti,ab.
23. ((follow* or met or meet or meeting or match or matching or "in line with" or keep or kept or keeping or utili?ation or utile?e? or change?) adj5 (criteria or recommend* or guideline? or guidance)).ti,ab.
24. clinical competence/ or nursing competence/
25. 21 or 22 or 23 or 24
26. 20 and 25
27. diagnostic procedure/ or exp blood examination/ or exp cardiovascular system examination/ or exp digestive system examination/ or exp endocrine system examination/ or exp neurologic examination/ or exp respiratory tract examination/ or exp urogenital system examination/
28. (diagnos* or detect* or test* or screen* or manag*).ti.
29. (imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra*).ti,ab.
30. ((medical or clinical or diagnos* or screening or routine or laboratory) adj5 (test* or investigation?)).ti,ab.
31. ((h?ematolog* or blood or urin* or saliva*) adj5 test*).ti,ab.
32. ((stress* or physical or function*) adj5 test*).ti,ab.
33. 27 or 28 or 29 or 30 or 31 or 32
34. 17 and 26 and 33
35. ((necessary or unnecessary or appropriate* or inappropriate* or waste* or utili?ation or indicated or excess* or less or more or increas* or decreas*) adj10 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
36. ((order* or request*) adj5 (test* or imaging or radiolog* or tomogra* or ct scan* or pet scan* or echocardiogra* or angiogra* or ultrasound* or ultrasonogra* or investigation?)).ti,ab.
37. Unnecessary Procedures/
38. 35 or 36 or 37
39. 17 and 20 and 38
40. 17 and 33 and 37
41. 34 or 39 or 40
42. limit 41 to yr="1999 -Current"
43. limit 42 to english language
44. (exp animals/ or nonhuman/) not human/
45. 43 not 44
46. conference*.pt.
47. 45 and 46
48. 45 not 46
49. exp child/ not (exp Child/ and exp Adult/)

50. 48 not 49
51. 48 not 49
52. limit 47 to yr="2015 -Current"

| | Was the study"s target population a close representation of the national population in relation to relevant variables? | Does the inclusion criteria match the target population of guideline? | Were all eligible participants included in the study? | Was the likelihood of non-response bias <20? | Was an acceptable disease, test or symptom definition used? | Was data extracted/collected in an objective way? | Was the interval from symptoms to test clinically appropriate for the diagnosis of interest? | Did they report extractable measures? | Other bias? |
|---|---|---|---|---|---|---|---|---|---|
| Ahmad2012 | Low | Unclear | Low | Unclear | Low | Unclear | Unclear | Low | Low |
| Aljebreen 2013 | Low | Low | Low | Low | Unclear | Unclear | Low | Low | High |
| Azzam 2015 | Low | Low | Unclear | High | Low | Unclear | Low | Low | Low |
| Belletti2013 | Low | Unclear | Unclear | Unclear | Low | Low | Low | Low | Low |
| Bertella 2013 | Low | Low | Low | Low | Unclear | Low | Unclear | Low | Low |
| Bhatt 2001 | Low | Low | Low | High | High | Unclear | Unclear | Low | High |
| Birk-Urovitz 2017 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Bishop 2003 | High | Low | Low | Low | Low | Low | Low | Low | Low |
| Cai 2015 | Low | Low | Unclear | Low | Unclear | Unclear | Unclear | Low | Low |
| Caplan 2000 | Low | Low | Low | Low | Unclear | Unclear | Unclear | Low | Low |
| Cardin 2005 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Cardin 2007 | Low | Low | Low | Unclear | Low | Low | Low | Low | Low |
| Chan 2004 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Chan 2006 | Low | Low | Low | High | Unclear | Low | Unclear | Low | Low |
| Chavez 2009 | Low | Low | Low | Low | Low | Low | High | Low | High |
| Droogendijk 2011 | Unclear | Low | High | Unclear | Low | Unclear | Low | Low | Low |
| Eccles 2001 | Low | Low | Low | Low | Unclear | Unclear | Unclear | Low | Low |
| Elwyn 2007 | Low | Low | Unclear | Unclear | Unclear | Low | Low | High | High |

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|---|---|---|---|---|---|---|---|---|---|
| Fiorenza 2017 | Low | Low | Low | Unclear | Low | Low | Unclear | Low | Low |
| Gerrits2008 | Low | Unclear | High | Low | Low | Low | Unclear | Low | Low |
| Gibbons 2010c | Low | Low | Low | Low | Low | High | Low | Low | Low |
| Girard 2010 | High | Low | Unclear | High | Unclear | High | Unclear | Low | High |
| Gnani 2004 | Low | Low | Unclear | Low | Unclear | Low | Unclear | Low | Low |
| Grover 2007 | Low | Low | Unclear | Low | Low | High | Unclear | Low | Low |
| Gurzun 2014 | Low | Low | High | Low | High | Low | Unclear | Low | High |
| Hassan 2007 | Low | Low | Low | High | Unclear | Low | Unclear | Low | Low |
| Heidi Lindbäck 2017 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Hughes-Anderson 2002 | High | Low | Unclear | Low | Unclear | Unclear | unclear | Low | Low |
| Ip2014 | Low | Low | High | Unclear | Low | Unclear | Unclear | Low | High |
| Johnson 2011 | Low | Unclear | Unclear | Low | High | Low | Low | Low | Low |
| Kinouani 2017 | Low | Low | low | Low | Unclear | Yes | Unclear | Low | Low |
| Kovacs 2013 | Low | Unclear | High | Low | Low | Low | Unclear | Low | High |
| Lalude 2014 | Low | Low | Low | Low | High | Low | Unclear | Low | High |
| Landry 2011 | Low | Unclear | Low | Low | Unclear | Unclear | Unclear | Low | Low |
| Lange 2007 | Low | Low | Unclear | Low | Unclear | Unclear | Unclear | Low | Low |
| Lin 2016 | Low | Low | Unclear | Unclear | Low | Low | Unclear | Low | Low |
| Linder 2006 | Low | High | Unclear | Low | Low | Low | Low | Unclear | Low |
| Lipczynska 2012 | High | High | Unclear | Low | Low | Unclear | Low | Low | High |
| Llor 2011 | Low | Low | Low | High | Low | Low | Low | Low | Low |

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|---|---|---|---|---|---|---|---|---|---|
| Loo 2009 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low |
| Mafi2013 | Low | Low | Unclear | Unclear | Low | Low | Unclear | Low | Low |
| Mafi2015 | Low | Low | Unclear | Unclear | Low | Low | Unclear | Low | Low |
| Majumdar 2003 | Low | Low | Unclear | Low | Low | Low | Unclear | Low | Low |
| Michaleff 2012 | Low | Low | Low | Unclear | High | Low | Unclear | Low | Low |
| Moscavitch 2009 | Low | Low | Unclear | Low | Low | Unclear | Low | Low | Low |
| Musicco 2004 | High | Low | Low | Unclear | Unclear | Unclear | Unclear | High | High |
| Nicholson 2010 | Low | Low | Low | Low | Unclear | Low | Low | Low | Low |
| Nicopoullos 2003 | High | High | Low | High | Low | Unclear | Unclear | Low | High |
| Noya 2008 | Low | Low | Low | Low | Unclear | Unclear | Unclear | Low | High |
| Piccoliori 2013 | Low | Low | Low | Low | Low | Unclear | Low | Low | High |
| Pimlott 2006 | Low | Low | Unclear | High | Unclear | Unclear | Unclear | Low | Low |
| Piterman 2008 | Low | Unclear | Low | Unclear | Unclear | Low | Unclear | High | High |
| Remedios 2014 | Low | Unclear | Low | High | Unclear | Low | Unclear | Low | High |
| Schers 2000 | Low | Low | Low | Unclear | Unclear | Low | Unclear | Low | Low |
| Smith 2008 | Low | Low | Low | Low | Unclear | Low | Unclear | Low | Low |
| Sokol 2015 | Low | Low | Low | Low | Low | Low | High | Low | High |
| Tahvonen 2017 | Low | Low | High | Low | Low | Low | Unclear | Low | Low |
| Ulrik 2010 | Low | Low | Low | High | Low | Low | unclear | Low | High |
| Ulrik 2013 | Low | Low | Low | High | Low | Low | unclear | Low | Low |
| van der Pluijm-Schouten 2017 | Low | Low | Low | Unclear | Low | Unclear | Unclear | Low | Low |

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|---|---|---|---|---|---|---|---|---|---|
| van Gurp 2013 | Low | Low | Low | Low | Unclear | Low | Unclear | Low | Low |
| Williams 2010 | Low | Low | Unclear | Low | Low | Unclear | Unclear | Low | Low |

Table 1: Study Characteristics

| Study | Country | Study length (days) | N (men%) | Population | Test |
|---|---|---|---|---|---|
| **Under-use** | | | | | |
| Ahmad 2012 | Indonesia | 181 | 554 (41%) | Patients registered at health clinics where TB was suspected | Sputum smear microscopy |
| Belletti 2013 | USA | N/S | 1517 (46%) | Patients with COPD | Pulmonary function tests (PFT) |
| Bertella 2013 | Italy | 1765 | 437 (286) | Patients with COPD | PFTs |
| Caplan 2000 | USA | 365 | 81 | Patients with a thyroid nodule | FNA of thyroid |
| Chavez 2009 | USA | 2920 | 200 (48%) | Patients with COPD | PFT |
| Droogendijk 2011 | Netherlands | 730 | 287 (45%) | Women >50yrs and men >18 years with Iron Deficiency Anaemia | Upper endoscopy and colonoscopy |
| Gerrits 2008 | Netherlands | 2556 | 65 (0%) | Women aged 18 – 65 yrs with newly diagnosed urinary incontinence | Urine dipstick |
| Gibbons 2010 | New Zealand | 364 | 265 | Patients with subclinical hypothyroidism | Free T4 |
| Gnani 2004 | UK | 365 | 90 (53%) | Patients with heart failure | CXR, ECG and Echocardiogram |
| Girard 2010 | France | 28 | 19 (37%) | Patients with acute hepatitis | Hepatitis serology (HBs antigens, anti-HBc anitbodies) |
| Kinuoani 2017 | France | 150 | 61 (18%) | Patients with urinary tract infections | Urine Dipstick |
| Lange 2007 | Denmark | 91 | 2549 (44%) | Patients with COPD | PFTs |
| Lipczynska 2012 | Poland | 61 | 93 | Aged ≥ 55 with Heart Failure (HF) or HF risk factors | Echocardiogram, BNP, CXR |
| Loo 2009 | UK | 364 | 131 (50%) | Patients with Atrial Fibrillation | Echocardiogram |
| Majumdar 2003a | USA | 2371 | 531 (47%) | Patients >50 years, on Proton Pump Inhibitors with persistent dyspepsia | Upper endoscopy |
| Majumdar 2003b | USA | 2371 | 132 (47%) | Patients with peptic ulcer disease (PUD) | H.pylori |
| Moscavitch 2009 | Brazil | 61 | 167 (43%) | Patients with Heart Failure | ECG, CXR, Echocardiogram |
| Musicco 2004 | Italy | NR | 1549 (38%) | Patients being assessed for Dementia | Collection of laboratory tests to rule out conditions with similar presenting symptoms to dementia |

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|---|---|---|---|---|---|
| Nicholson 2010 | UK | 1827 | 6943 (100%) | Men with epididymo-orchtitis | C. trachomatis, N. gonorrhoeae, urethral swabs and midstream urinalysis. |
| Nicopoullos 2003 | UK | 242 | 32 | Patients with subfertility | Mid-luteal progesterone and semen analysis |
| Pimlott 2006 | Canada | 1611 | 160 (34%) | Patients with Dementia | FBC, TSH, serum electrolytes, serum calcium, glucose |
| Smith 2008 | UK | 731 | 29870 (52%) | Patients with COPD | PFT |
| Sokol 2015 | USA | 3652 | 75902 (23%) | Patients with Asthma | PFT |
| Ulrik 2010 | Denmark | 121 | 1716 (44%) | Patients with COPD | PFT |
| Ulrik 2013 | Denmark | 731 | 4058 | Patients with COPD | PFT |
| van der Pluijm-Schouten 2017 | Netherlands | 840 | 100%* | Patients (couples) referred to IVF clinics | Chlamydia Antibody Titre and Semen Analysis |
| **Over-use** | | | | | |
| Aljebreen 2013 | Saudi Arabia | 365 | 147 (51%) | Patients who had upper endoscopy | Upper endoscopy |
| Azzam 2015 | Saudi Arabia | 121 | 161 (30%) | Dyspeptic patients who had upper endoscopy | Upper endoscopy |
| Bhatt 2001 | UK | 504 | 437 (65%) | Patients referred for pelvis x-rays | Pelvis x-ray |
| Birk-Urovitz 2017 | Canada | 1538 | 77 (38%) | Patients that had a Thyroid Stimulating Hormone (TSH) test | TSH |
| Bishop 2003 | Canada | 28 | 139 | Patients with non-red flag LBP | Advanced imaging (CT, MRI or bone scan) |
| Cai 2015 | USA | 121 | 550 (46%) | Patients who under went upper endoscopy | Upper endoscopy |
| Chan 2004 | Malaysia | 153 | 250 (45%) | Patients who under went upper endoscopy | Upper endoscopy |
| Chan 2006 | Malaysia | 184 | 27 (63%) | Patients who underwent 'diagnostic colonoscopies' | Colonoscopy |
| Cardin 2005 | Italy | 151 | 1678 | Patients who had upper endoscopy | Upper endoscopy |
| Cardin 2007 | Italy | 182 | NR | Dyspeptic patients who had upper endoscopy | Upper endoscopy |
| Eccles 2001 | UK | 182 | 275 | Patients who had knee or lumbar x-ray | Lumbar or knee x-ray |
| Elwyn 2007 | UK | 184 | 215 | Patients who under went upper endoscopy | Upper endoscopy |
| Fiorenza 2017 | USA | 456 | 45 (34%) | Patients who under went upper endoscopy | Upper Endoscopy |

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|---|---|---|---|---|---|
| Grover 2007 | USA | 364 | 68 (0%) | Patients with uncomplicated UTI | Urine culture and sensitivity analysis |
| Gurzun 2014 | UK | 7 | 1070 (54%) | Patients who underwent an echocardiogram | Echocardiogram |
| Hassan 2007 | Italy | 30 | 3769 (46%) | Patients who underwent upper endoscopy | Upper endoscopy |
| Hughes-Anderson 2002a | Australia | 1613 | 154 (55%) | Patients who had colonoscopy | Colonoscopy |
| Hughes-Anderson 2002b | Australia | 1613 | 162 (55%) | Patients who had upper endoscopy, | Upper endoscopy |
| Ip 2014 | USA | 1096 | 100 (43%) | Patients with non-red flag LBP | MRI lumbar spine |
| Johnson 2011 | USA | 510 | 779 (0%) | Patients with uncomplicated UTI | Urine culture |
| Kovacs 2013 | Spain | 183 | 602 (48%) | Patients with non-red flag LBP | MRI lumbar spine |
| Lalude 2014 | USA | 121 | 102 | Patients who had SPECT Myocardial perfusion imaging (MPI) studies | Single Photon Emission CT (SPECT) MPI |
| Landry 2011 | USA | 272 | 124 | Patients who had U/S of thyroid, pelvis, abdo, carotid or soft tissue | Thyroid, pelvis, abdomen, carotid or soft tissue ultrasound |
| Lin 2016 | Australia | NR | NR | Patients with non-red flag LBP | Lumbar Spine X-ray |
| Lindbäck 2017 | Sweden | 59 | 0 | Patients that had urinary cultures | Urinary Culture |
| Linder 2006 | USA | 608 | 1076 (19%) | Patients with pharyngitis | Strep testing (rapid antigen detection test, throat culture) |
| Llor 2011 | Spain | 122 | 658 (0%) | Women with UTI | Urine cultures |
| Mafi 2013 | USA | 4377 | 8066 | Patients with non-red flag LBP | X-ray, CT or MRI |
| Mafi 2015 | USA | 4018 | 9362 (25%) | Patients with uncomplicated headache (non-red flag | CT and MRI |
| Michaleff 2012 | Australia | 3621 | 3070 (70%) | Patients reporting first time neck pain or LBP (non-specific, non red flag) | Any radiological test |
| Noya 2008 | Israel | N/S | 209 (35%) | Patients who had H.pylori testing | H. pylori test |
| Piccoliori 2013 | Italy | 63 | 475 (43%) | Acute or chronic non-red flag LBP | Any radiological test |
| Piterman 2008 | Australia | 550 | 19219 | Patients with GORD | Endoscopy. Barium Swallow |
| Remedios 2014 | UK | NR | 2026 | Patients who had CTs and/or MRIs | CT and/or MRI |
| Sharp 2015 | USA | 730 | 37,464 | Patient with Acute Sinusitis | CT Sinuses |

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|---|---|---|---|---|---|
| Schers 2000 | Netherlands | 214 | 1096 (50%) | Patients with non-red flag LBP | X-ray |
| Tahvonen 2017 | Finland | 180 | 18 (35%) | Patients with non-red flag LBP | Lumbar Spine X-ray |
| Van Gurp 2013 | Netherlands | 366 | 155 (38%) | Patients who had Echocardiogram | Echocardiogram |
| Williams 2010 | Australia | 1005 | 1706 (43%) | Patients with non-red flag LBP | All imaging |

*Both men and women

Table 1: Measures of inappropriateness

| Study | Test | Guideline authority and recommendation | Measure of inappropriateness (95%CI) |
|---|---|---|---|
| | | **Under-use** | |
| Girard 2010 | Hepatitis B serology | Ministry of Health (France): Hepatitis serology for suspected acute hepatitis | 100% (82.4 to 100%) |
| Nicholson 2010 | Neisseria Gonorrhoea serology | CDC (US)/British Association for Sexual Health and HIV: Test for N. gonorrhoea for suspected Epididymitis | 99.9% (99.85 to 99.98%) |
| Nicholson 2010 | Chlamydia Trachomatis | CDC (US)/British Association for Sexual Health and HIV: Test for C. Trachomatis for suspected Epididymitis | 97.4% (97.0 to 97.8%) |
| Nicopoullos 2003 | Semen Analysis | Royal College of Obstetricians and Gynaecologists: Semen analysis for Infertility | 96.9% (83.8 to 99.9%) |
| Lipczynska 2012 | Brain Natriuretic Peptide (BNP) | European Society Cardiology: BNP for Heart Failure | 95.7% (89.4 to 98.8%) |
| Musicco 2004 | Collection of laboratory tests | European Federation of Neurological Societies: Collection of laboratory tests to rule out conditions with similar presenting symptoms to dementia | 93.42% (92.1 to 94.6%) |
| Nicholson 2010 | Urethral swabs | CDC (US)/British Association for Sexual Health and HIV: Urethral swabs for suspected epididymitis (Urethral swabs) | 90.7% (89.9 to 91.3%) |
| Moscavitch 2009 | Echocardiogram | Brazilian Society of Cardiology: Echocardiography for Heart Failure | 88.6% (82.8 to 93.0%) |
| Kinouani 2017 | Urine Dipstick | The French Agency for the Safety of Health Products: Urine Dipstick for UTI | 84.4% (80.1 to 88.1%) |
| Majumdar 2003a | Upper Endoscopy | American Gastroenterological Association: Appropriate use of Upper Endoscopy for Dyspepsia | 81.2% (78.8 to 83.4%) |
| Ulrik 2013 | Pulmonary function tests (PFTs) | Danish National Board of Health: PFTs to diagnosis COPD | 78.3 (77.3% to 79.3%) |
| Nicholson 2010 | Mid stream | CDC (US)/British Association for Sexual Health and HIV: Midstream urinalysis for suspected Epididymitis | 78.2 (77.3 to 79.3%) |
| Sokol 2015 | Pulmonary function tests (PFTs) | National Asthma Education and Prevention Program (US): PFTs for asthma | 76.5% (64.6 to 85.9%) |
| Belletti 2013 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 73.0% (70.7 to 75.3%) |

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|---|---|---|---|
| Ahmad 2012 | Tuberculosis smear | World Health Organisation: Smear for suspected TB | 72.4% (68.5 to 76.1%) |
| van der Pluijm-Schouten 2017 | Semen Analysis | NHG-Standaard Subfertiliteit: Semen Analysis | 70.4% (61.9 to 77.9%) |
| Droogendijk 2011 | Colonoscopy | Ministry of Health (Netherlands): Colonoscopy for unexplained Iron Deficiency Anaemia | 68.6% (62.9 to 74.0%) |
| Pimlott 2006 | Serum Calcium | Canadian Consensus Conference on Dementia: Serum Calcium for Dementia | 65.0 (57.1 to 72.4%) |
| Gerrits 2008 | Urine dip stick | NICE: Urine dip stick for urinary incontinence | 60.0% (47.1 to 72.0%) |
| Nicopoullos 2003 | Mid-luteal progesterone | Royal College of Obstetricians and Gynaecologists: Mid-luteal progesterone for Infertility | 59.4% (40.6 to 76.3%) |
| Gnani 2004 | Echocardiogram | Department of Health (UK): Echocardiogram for Heart Failure | 57.8% (46.1 to 68.1%) |
| Loo 2009 | Echocardiogram | ACC, AHA, ESC: Echocardiogram to identify causes or complications of atrial fibrillation | 55.7% (46.8 to 64.39%) |
| Ulrik 2010 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 55.0% (52.6 to 57.4%) |
| Lipczynska 2012 | Echocardiogram | European Society Cardiology: Echocardiogram for Heart Failure | 53.8% (43.1 to 64.2%) |
| van der Pluijm-Schouten 2017 | Chlamydia Trachomatis | NHG-Standaard Subfertiliteit: Chlamydia Trachomatis | 57.8% (49.0 to 66.2%) |
| Gnani 2004 | ECG | Department of Health (UK): ECG for Heart Failure | 51.1% (40.4% to 61.8%) |
| Moscavitch 2009 | ECG | Brazilian Society of Cardiology: ECG for Heart Failure | 46.1 (38.4 to 54.0) |
| Moscavitch 2009 | Chest X-ray | Brazilian Society of Cardiology: CXR for Heart Failure | 44.9% (37.2 to 52.8%) |
| Gibbons 2010 | Thyroid function tests | New Zealand Best Practice: Appropriate use of Thyroid Function tests | 44.9% (38.8 to 51.1%) |
| Chavez 2009 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 41.5% (34.6 to 48.7%) |
| Lange 2007 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 40.0% (38.1 to 42.0) |
| Smith 2008 | Pulmonary Function Tests (PFTs) | NICE: PFTs for COPD | 38.1% (37.5 to 38.6%) |
| Pimlott 2006 | Glucose testing | Canadian Consensus Conference on Dementia: Glucose testing for Dementia | 36.9% (29.4% to 44.9%) |
| Gnani 2004 | Chest X-ray | Department of Health (UK): CXR for Heart Failure | 36.7% (26.8 to 47.5%) |

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|---|---|---|---|
| Majumdar 2003b | H.pylori | American Gastroenterological Association/American College of Gastroenterology: appropriateness of H.pylori test | 34.4% (28.9 to 40.3%) |
| Pimlott 2006 | Thyroid Stimulating Hormone (TSH) | Canadian Consensus Conference on Dementia: TSH for dementia | 33.1% (25.9 to 41.0%) |
| Lipczynska 2012 | Chest x-ray (CXR) | European Society Cardiology: CXR for Heart Failure | 25.8% (17.3 to 35.9%) |
| Bertella 2013 | Pulmonary function tests (PFTs) | Global Initiative for Chronic Obstructive Lung Disease (GOLD): PFTs for COPD | 25.6% (21.6 to 30.0%) |
| Pimlott 2006 | Serum electrolytes | Canadian Consensus Conference on Dementia: Serum electrolytes for dementia | 21.9% (15.7 to 29.1%) |
| Pimlott 2006 | Full Blood Count (FBC) | Canadian Consensus Conference on Dementia: FBC for dementia | 18.1% (12.5 to 25.0%) |
| Caplan 2000 | Fine needle aspiration (FNA) of thyroid | American Thyroid Association/American Association of Clinical Endocrinologists: FNA for thyroid nodules | 9.9% (4.4 to 18.5%) |
| | | **Over-use** | |
| Piterman 2008 | Barium Swallow | Gastroenterological Society of Australia: Barium Swallow for GORD | 94.20% (93.9 to 94.5%) |
| Gurzun 2014 | Echocardiogram | American College of Cardiology: Appropriate use of Echocardiography | 92.0% (90.2% to 93.5%) |
| Linder 2006 | Streptococcal throat cultures | American College of Physicians/Infectious Disease Society of America: Do not order strept test for centor criteria 0 or 1 in pharyngitis | 91.5% (89.7 to 93.1%) |
| van Gurp 2013 | Echocardiogram | Netherlands Society of Cardiology: Appropriate use of Echocardiography | 76.7% (76.4 to 77.0%) |
| Grover 2007 | Urine cultures | Infectious Disease Society of America: Urine cultures not required for uncomplicated UTI diagnosis | 76.5% (64.6 to 85.9%) |
| Eccles 2001 | Knee x-ray | Royal College of Radiologists: No x-ray for knee pain without restriction of movement | 74.7% (69.6 to 79.3%) |
| Cardin 2005 | H. Pylori breath test | European Society of Primary Care Gastroenterology: Appropriate use of H. pylori | 74.4% (58.8 to 86.5%) |
| Tahvonen 2017 | L spine x-ray | Finish Medical Society: LBP among adults | 68.0% (53.3 to 80.48%) |
| Johnston 2011 | Urine cultures | European Association of Urology: Urinary cultures not required for uncomplicated urinary tract infections | 57.4% (53.8 to 60.9%) |
| Bhatt 2001 | Hip x-ray | Royal College of Radiologists (UK): No hip x-ray for hip pain without restriction of movement | 57.2% (52.5 to 61.8%) |

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| Eccles 2001 | Lumbar spine x-ray | Royal College of Radiologists (UK): no x-ray for non-red flag LBP | 56.4% (50.3 to 62.3%) |
| Piterman 2008 | Upper endoscopy | Gastroenterological Society of Australia: Upper endoscopy for GORD | 53.5% (52.8 to 54.2%) |
| Chan 2006 | Colonoscopy | American Society for Gastrointestinal Endoscopy: Appropriateness of Colonoscopy | 51.9% (32.0 to 71.3%) |
| Heidi Lindbäck 2017 | Urine Culture | Swedish Medicines Agency: Treatment of lower urinary tract infections in women | 47.0% (40.8 to 53.38%) |
| Aljebreen 2013 | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 46.9% (38.7 to 55.3%) |
| Elwyn 2007 | Upper endoscopy | NICE: Appropriate tests for dyspepsia | 45.1% (38.3 to 52.0%) |
| Noya 2008 | H.Pylori | The European Helicobacter Study Group: Appropriate use of H. pylori | 44.5 (37.6 to 51.5%) |
| Cardin 2005 | Upper endoscopy | European Society of Primary Care Gastroenterology: Upper Endoscopy for H.pylori | 44.1% (35.9 to 52.6%) |
| Lin 2016 | L spine x-ray | The George Institute (Aus): LBP | 40.9% (26.3 to 56.8%) |
| Cardin 2007 | Upper endoscopy | European Society of Primary Care Gastroenterology: Upper Endoscopy for H.pylori | 41.9% (38.3 to 45.5%) |
| Fiorenza 2017 | Upper Endoscopy | American College of Gastroenterology: Dyspepsia | 42.4% (36.8 to 48.1%) |
| Cai 2015 | Upper endoscopy | American College of Physicians: Upper endoscopy for GORD | 37.7% (33.8 to 42.0%) |
| Azzam 2015 | Upper endoscopy | American Gastroenterological Association: Upper Endoscopy for Dyspepsia | 36.7 (29.2 to 44.6%) |
| Llor 2011 | Urine cultures | European Association of Urology: Urinary cultures not required for uncomplicated urinary tract infections | 35.9% (32.2 to 40.0%) |
| Hassan 2007 | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 29.4% (28.0 to 30.9%) |
| Landry 2011 | Carotid ultrasound | Canadian Association of Radiologists 2005 guidelines: Carotid U/S | 25.0% (17.7 to 33.6%) |
| Piccoliori 2013 | Lumbar spine radiology (all) | Ministry of Health (Italy): No imaging for non-red flag LBP | 24.0% (20.2 to 28.1%) |
| Michaleff 2012 | Lumbar spine x-ray | National Health and Medical Research Council (Australia) (NHMRC): No x-ray for non-red flag LBP | 24.0% (22.9 to 25.1%) |

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| Williams 2010 | Lumbar spine radiology (all) | National Health and Medical Research Council (Australia) (NHMRC): No imaging for non-red flag LBP | 23.9% (21.9 to 26.0%) |
| Michaleff 2012 | Cervical spine x-ray | Australian National Health and Medical Research Council: No x-ray for neck pain | 22.8% (21.3 to 24.3%) |
| Birk-Urovitz 2017 | Thyroid Stimulating Hormone | The Canadian Task Force on Preventative Health | 22.4% (16.9 to 28.8%) |
| Ip 2014 | Lumbar spine MRI | American College of Physicians/American Pain Society: no MRI for non-red flag LBP | 22.0% (14.3 to 31.4%) |
| Williams 2010 | Lumbar spine x-ray | National Health and Medical Research Council (Australia) (NHMRC): No x-ray for non-red flag LBP | 20.2% (18.3 to 22.2%) |
| Landry 2011 | Thyroid ultrasound | Canadian Association of Radiologists 2005 guidelines: Thyroid U/S | 19.0% (12.1 to 27.0%) |
| Lalude 2014 | Single Photon Emission Computed Tomography | American College of Cardiology: SPECT for chest pain | 18.6% (11.6 to 27.6%) |
| 'Mafi 2013 | Lumbar spine x-ray | American College of Physicians/American Pain Society: no x-ray for non-red flag LBP: *2009-2010* | 13.0% (11.1 to 15.1%) |
| | | *2007-2008* | 12.9% (11.1 to 14.9%) |
| | | *2005-2006* | 12.8% (11.0 to 14.8%) |
| | | *2003-2004* | 12.3% (10.7 to 14.0%) |
| | | *2001-2002* | 12.0% (10.3 to 13.8%) |
| | | *1999 - 2000* | 11.8% (10.2 to 13.6%) |
| Landry 2011 | Abdominal ultrasound | Canadian Association of Radiologists 2005 guidelines: Abdominal U/S | 12.1% (6.9 to 19.2%) |
| Mafi 2015 | CT or MRI Brain | The American Headache Society/American Academy of Neurology for Choosing Wisely: No CT or MRI for non-red flag headache *2009 - 2011* | 13.9% (12.2 to 15.7%) |
| | | *2007 – 2008* | 13.5% (11.8 to 15.3%) |
| | | *2005 – 2006* | 9.4% (8.0 to 11.0%) |
| | | *2003 – 2004* | 7.5% (6.3 to 8.9%) |
| | | *2001 – 2002* | 7.1% (5.9 to 8.4%) |
| | | *1999 - 2000* | 6.7% (5.4 to 8.2%) |

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| Kovacs 2013 | Lumbar spine radiology tests (all) | NICE, ACP: No imaging for LBP | 12.0% (9.5 to 14.8%) |
| Chan 2004 | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 10.4% (6.9 to 14.9%) |
| Hughes-Anderson 2002a | Colonoscopy | American Society for Gastrointestinal Endoscopy: Appropriateness of Colonoscopy | 8.2% (5.3 to 12.1%) |
| Hughes-Anderson 2002b | Upper endoscopy | The American Society for Gastrointestinal Endoscopy: Appropriateness of Upper Endoscopy | 7.5% (4.7 to 11.1%) |
| Remedios 2014 | CT (any) | Royal College of Radiologists (UK): CT | 6.9% (5.8 to 8.1%) |
| | MRI (any) | Royal College of Radiologists (UK): MRI | 5.2% (4.1 to 6.5%) |
| Bishop 2003 | Lumbar spine radiology tests (all) | Workers Compensation Board of British Columbia: No imaging for non-red flag LBP | 5.0% (2.1 to 10.1%) |
| Williams 2010 | Lumbar spine CT | National Health and Medical Research Council (Australia) (NHMRC): No CT for non-red flag LBP | 3.7% (2.9 to 4.7%) |
| Schers 2000 | Lumbar spine radiology tests (all) | The Netherlands College of General Practitioners: No imaging for non-red flag LBP | 3.1% (2.2 to 4.3%) |
| Landry 2011 | Soft tissue ultrasound | Canadian Association of Radiologists 2005 guidelines: Soft tissue U/S | 2.4% (0.5 to 6.9% |
| Landry 2011 | Pelvic ultrasound | Canadian Association of Radiologists 2005 guidelines: Pelvic U/S | 1.6% (0.2 to 5.7%) |
| Sharp 2015 | CT Sinuses | American Academy of Otolaryngology: Adult Sinusitis | 0.60% (0.56 to 0.65%) |
| Williams 2010 | Lumbar spine Ultrasound | National Health and Medical Research Council (Australia) (NHMRC): No U/S for non-red flag LBP | 0.59% (0.28 to 1.1%) |
| Williams 2010 | Lumbar spine MRI | National Health and Medical Research Council (Australia) (NHMRC): No MRI for non-red flag LBP | 0.18% (0.04 to 0.5%) |

## MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

| Reporting Criteria | Reported (Yes/No) | Reported on Page |
|---|---|---|
| **Reporting of Background** | | |
| Problem definition | YES | 4 |
| Hypothesis statement | YES | 4 |
| Description of Study Outcome(s) | YES | 4 |
| Type of exposure or intervention used | N/A | N/A |
| Type of study design used | YES | 5, 6 |
| Study population | YES | 5 |
| **Reporting of Search Strategy** | | |
| Qualifications of searchers (eg, librarians and investigators) | YES | 5 |
| Search strategy, including time period included in the synthesis and keywords | YES | 5, supplementary file |
| Effort to include all available studies, including contact with authors | YES | 5 |
| Databases and registries searched | YES | 5 |
| Search software used, name and version, including special features used (eg, explosion) | YES | 5 |
| Use of hand searching (eg, reference lists of obtained articles) | YES | 5 |
| List of citations located and those excluded, including justification | NO | |
| Method for addressing articles published in languages other than English | NO | |
| Method of handling abstracts and unpublished studies | YES | 5 |
| Description of any contact with authors | N/A | |
| **Reporting of Methods** | | |
| Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | YES | 5,6 |
| Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | YES | 6 |
| Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability) | YES | 6 |
| Assessment of confounding (eg, comparability of cases and controls in studies where appropriate | N/A | N/A |
| Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | YES | 5,6 |
| Assessment of heterogeneity | YES | 6 |

| | | |
|---|---|---|
| Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | YES | 6 |
| Provision of appropriate tables and graphics | YES | Tables 1,2, Figures 2,3,4 |
| **Reporting of Results** | | |
| Table giving descriptive information for each study included | YES | Table 1 and Table 2 |
| Results of sensitivity testing (eg, subgroup analysis) | N/A | 7, 8 |
| Indication of statistical uncertainty of findings | YES | 6,7, 8,9 |
| **Reporting of Discussion** | | |
| Quantitative assessment of bias (eg, publication bias) | YES | 8,9 |
| Justification for exclusion (eg, exclusion of non–English-language citations) | YES | 5 |
| Assessment of quality of included studies | YES | 7, Table 3 |
| **Reporting of Conclusions** | | |
| Consideration of alternative explanations for observed results | YES | 9, 10 |
| Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | YES | 10 |
| Guidelines for future research | YES | 9, 10 |
| Disclosure of funding source | YES | 11 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supplementary file 'Search strategy' |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5 & supplementary figure |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 & 6 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5 & 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5, 6, 7 & supplementary figure |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 5,6 |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis. | 6 |



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 6 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 7 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 7 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 7 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 7, 8 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 7, 8 , 9 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 7 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 7, 8 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 9 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 10 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 10 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 11 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

# PRISMA 2009 Checklist

For more information, visit: **www.prisma-statement.org**.