In-Depth Literature Review of Downstream Spending and Service Use Following Five Low-Value Services

A report by staff fromRTI International and Harvard Medical School for the Medicare Payment Advisory Commission

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February 2019

January 2019

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Final Report

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RTI Project Number 0215539.002.000.003

RTI INTERNATIONAL

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Executive Summary

ES.1 Background

The Medicare Payment Advisory Commission (MedPAC) seeks to better understand the use of and spending for health care services that occur downstream of a set of previously established low-value services; in other words, health care services or health care spending that occur as a direct result of one of the services of interest. Low-value services are defined as medical services that have little or no clinical benefit or have a risk of harm to patients that outweighs the potential benefit. Experts have estimated that $200 billion is spent on low-value health care in the US health care system annually (Berwick et al., 2012). Downstream service use and spending is often an important part of the definition of low-value care because unnecessary spending or treatments resulting from the low-value service can play a key role in what makes it low-value.

ES.2 Methods

We conducted a systematic review of available literature examining the evidence of downstream service use and spending after five low-value services: (1) prostate-specific antigen (PSA) testing, (2) back imaging for nonspecific low back pain, (3) percutaneous coronary intervention (PCI) for stable coronary disease, (4) stress testing for stable coronary disease, and (5) carotid endarterectomy for asymptomatic patients. We included studies published January 1, 2000, or later. Each included study was examined and categorized by factors such as study design, sample size and sample characteristics (excluding syntheses, which often used population-based datasets), the country where the study was conducted, and the specific downstream services and/or spending examined. Study quality and relevance to our question of downstream service use or spending was then assessed across four domains: study limitations, directness, precision, and suspected reporting bias. Each domain was rated as either high, medium, or low.

ES.3 Results

Our preliminary abstract search identified 91 manuscripts across the five measures of low-value care, and we identified 8 additional manuscripts through our full text review of the original 91 manuscripts. Upon full review, 66 manuscripts were ultimately examined for evidence of downstream service use and spending**.** Thirty-three manuscripts were removed using our exclusion criteria; 33% were excluded for focusing on the wrong population (e.g., PCI for patients with unstable coronary disease), 55% were excluded for not including a downstream outcome of interest, and 12% were excluded for other reasons. Randomized controlled trials constituted 20 of the 66 studies (30%), 18 (27%) were observational studies, and the remaining 28 (42%) were evidence syntheses or economic evaluations. PCI for stable coronary disease was examined in 34 (52%) of the included studies, and 16

(24%) examined PSA testing. The remaining studies examined either stress testing for stable coronary disease (2 studies), imaging for low back pain (9 studies), or carotid endarterectomy for asymptomatic patients (5 studies).

Twenty-one of the 66 studies (32%) had a high level of study quality and applicability to downstream service utilization or spending, and 29 studies (44%) had moderate quality or applicability. In total, 54 of the 66 studies (82%) examined downstream costs of care, and 37 studies (56%) examined downstream service use; 25 studies (38%) examined both downstream costs and service use. However, included studies varied considerably in their estimates of total downstream spending and use, often because of variation in factors such as follow-up time, sample characteristics, and the services and values used in the cost calculations. In addition, some of the included low-value services yielded few studies of interest to this review, and several included studies also examined patient populations that do not strictly meet the criteria of low-value care as defined above. Findings for each of the measures examined include:

PSA Testing: The most common downstream services observed across the included studies were prostate biopsy, radical prostatectomy, radiation therapy, hormone therapy, and active surveillance/conservative management. In general, the cost of the initial PSA test and subsequent biopsy were lower-cost services, whereas subsequent cancer treatment carried more-substantial costs.

Back Imaging for Non-Specific Low Back Pain: Key downstream services examined by these studies were surgery (or referrals), physical therapy (or referrals), additional imaging, and injections, though it is important to note that physical therapy would likely be prescribed even in the absence of the low-value service. Downstream costs for imaging for low back pain were also reported in seven included studies, and four of these reported imaging in a low-value population.

PCI for Stable Coronary Disease: Key downstream services examined by these studies include coronary artery bypass surgery (CABG), repeat PCI, any revascularization (PCI or CABG), target lesion revascularization, target vessel revascularization, coronary angiograph, hospitalizations, and outpatient visits. The rates of these outcomes varied widely from study to study, ranging from less than one percent for CABG within 1 year, to 55.7% for outpatient visits within 1 year. Costs per patient varied, largely dependent on the length of the follow-up.

Stress Testing for Stable Coronary Disease: Two studies reported downstream use of PCI and CABG in their respective populations. One study examined downstream costs within 3 years of follow-up for patients with known or suspected coronary disease; the other examined lifetime costs per patient with known or suspected coronary disease.

Carotid Endarterectomy for Asymptomatic Patients: One study reported downstream costs among asymptomatic patients after two years of follow-up. The remaining studies reported lifetime costs broken down by age, gender, or percent stenosis. Only one study, Wallaert et al. (2016), examined downstream services, specifically readmission and reintervention at 2 years.

ES.4 Conclusions

Downstream service use and spending are important aspects of what makes these health care services potentially low value. Therefore, understanding their likelihood and magnitude is essential to adequately assessing the value of health care delivered to patients. Although the evidence varies by low-value measure, this review suggests that there is substantial downstream service use and spending. However, literature examining downstream spending and service use remains limited for included measures of low-value care, making this an important area for future research to maximize the value of the health care that is delivered to patients.

1. Introduction

1.1 Overview and Objective

Low-value services are defined as medical services that have little or no clinical benefit or that have a risk of harm to patients that outweighs the potential benefit. Experts have estimated that $200 billion is spent on low-value health care (i.e., overtreatment) annually in the U.S. health care system (Berwick et al., 2012). The Medicare Payment Advisory Commission (MedPAC) seeks to better understand the use of and spending for health care services that occur downstream of a set of previously established low-value services; in other words, health care service use or health care spending that occur as a direct result of one of the services of interest. To that end, we conducted a systematic review of available literature examining the evidence of effects on downstream service use and spending after five low-value services: (1) prostate-specific antigen (PSA) testing, (2) back imaging for nonspecific low back pain, (3) percutaneous coronary intervention (PCI) for stable coronary disease, (4) stress testing for stable coronary disease, and (5) carotid endarterectomy for asymptomatic patients.

In the first phase of this project, we reviewed the peer-reviewed, government, and grey literature surrounding 10 measures of low-value care identified by MedPAC.[1] The purpose of the initial review was to develop a general understanding of the scope of the literature available for each of these measures and to identify and recommend a subset of the measures for the more-thorough assessment. Specifically, we identified available literature examining health care service use and spending occurring downstream of at least one of the low-value health care services of interest to determine which measures have sufficient published evidence to benefit from an in-depth review. Ultimately, five measures of low-value health care were selected. This report presents the results of that review.

The remainder of the introduction describes the challenges associated with defining low-value services, the measures of interest in this review, and how we have conceptualized downstream service use and health care spending in this analysis. The methods section describes our initial search strategy, study selection, data review, abstraction, and study comparison strategies. The results section presents an overview of studies included in the in-depth review and findings organized by low-value service. Finally, the discussion section summarizes the findings of this review and explores areas where gaps appear to exist in the literature and future study is warranted.

[1] The 10 low-value measures included in the initial abstract review were: PSA testing, hypercoagulability testing for patients with deep vein thrombosis (DVT), preoperative chest radiography, back imaging for patients with nonspecific low back pain, screening for carotid artery disease in asymptomatic adults, screening for carotid artery disease for syncope, stress testing for stable coronary disease, PCI with balloon angioplasty or stent placement for stable coronary disease, renal artery angioplasty or stenting, and carotid endarterectomy for asymptomatic adults.

1.2 Current State of the Literature

Propelled by the 2010 Institute of Medicine report "The Healthcare Imperative" and initiatives like Choosing Wisely® to reduce waste and inefficiencies in care, numerous researchers and organizations have identified and measured low-value services use among different populations, including children, elderly adults, and adults with commercial insurance (Barnett et al., 2017; Carter et al., 2017; Choosing Wisely, 2018; Chua et al., 2016; Colla et al., 2018; Mafi et al., 2016; Schwartz et al., 2014; Segal et al., 2015; Yong et al., 2010).

Using 31 measures of low-value service use identified by Schwartz et al. (2014, 2015), MedPAC estimated the total cost of low-value health care services to Medicare in 2014 to be between $2.4 and $6.5 billion; 23 to 37 percent of beneficiaries received at least one of these low-value services (MedPAC, 2017). Among these measures, the highest-spending categories of low-value service use were cardiovascular tests/procedures, other surgical procedures, and imaging, while the highest-volume categories were imaging, cancer screening, and diagnostic and preventive testing. However, as MedPAC and others have noted, in addition to being restricted to low-value services that can be measured using claims data, these estimates likely understate the spending on and impact of low-value service use because they do not include spending on downstream services that might result from undergoing a low-value test or procedure.

Many low-value services have low or very low upfront costs to administer and cause little direct harm to patients (Mafi et al., 2017). However, these tests may result in unnecessary anxiety and a cascade of follow-up tests and procedures that harm the patient and increase health care spending. For example, cost-effectiveness research suggests that the PSA screening test for prostate cancer (which costs $144 on average) accounts for a mere 2% of the total lifetime costs related to PSA testing (Mafi et al., 2017; Shteynshlyuger et al., 2011). Understanding the health care costs and patient outcomes of subsequent services that arise from the initial low-value service is essential to quantifying the magnitude of savings that can be achieved by reducing these services. Developing policy recommendations around low-value care services will require careful consideration of the impact on volume and spending. Averting these unnecessary costs and potential adverse sequalae on patients would be an important development for Medicare, the U.S. health care system, and patients.

1.3 Defining Downstream Service Use and Health Care Spending

Downstream service use and spending is often an important part of the definition of low-value care because unnecessary spending or treatments resulting from the low-value service can play a key role in what makes it low-value. In this review, we conceptualized downstream as a health care service or health care spending that occurs as a direct result of one of the low-value health care services of interest. For example, downstream service use

and spending from a positive PSA test would include a biopsy used to confirm the diagnosis, and a confirmed diagnosis would likely result in additional cancer treatments even if they would do little to change the long-term prognosis.

In this review, we identified downstream service use and spending as follows. First, we examined whether the service or spending was a result of or in any way affected by the low-value health care service of interest. For example, a study examining prostate biopsy and cancer treatment costs after PSA testing would be considered downstream. We then considered whether the downstream service was simply a repeat of the same low-value service. A key example of this is studies that examine the likelihood of repeat stenting after PCI in patients with stable coronary disease. If the patient continues to be stable, a second stenting procedure may be of equally low value and may not be any more useful than the initial procedure. However, restenosis is a commonly examined outcome of PCI warranting reintervention of the target vessel in a way that would not necessarily be of low value and would therefore count as downstream. Such cases were distinguished subjectively on a case-by-case basis using information available in each study. Studies that did not examine downstream service use or spending were excluded from this review.

2. Methods

2.1 Low-Value Services Included in this Review

Among the 31 low-value services identified by (Schwartz et al., 2014, 2015), MedPAC selected 10 services for preliminary abstract review of downstream spending or use in peer-reviewed, government, and grey literature (Table 2-1). After a preliminary review of titles and abstracts (See Appendix 1 for additional details), MedPAC staff selected five measures with a sufficient number of studies for in-depth review:(1) PSA testing, (2) back imaging for nonspecific low back pain, (3) PCI for stable coronary disease, (4) stress testing for stable coronary disease, and (5) carotid endarterectomy for asymptomatic adults. We obtained and reviewed the full text of manuscripts selected for inclusion from our preliminary review for each of these five measures.

Table 2-1. Low-Value Services Identified by MedPAC Recommended for Preliminary Review

Service	Population	Selected for Full Review
PSA testing	Male patients ≥ 75 years	Yes
Hypercoagulability testing for patients with deep vein thrombosis (DVT)	Patients with DVT	No
Preoperative chest radiography	Patients undergoing non-cardiothoracic surgeries	No
Back imaging for patients with nonspecific low back pain	All patients	Yes
Screening for carotid artery disease in asymptomatic adults	All patients	No
Screening for carotid artery disease for syncope	Syncope patients	No
Stress testing for stable coronary disease	Patients with ischemic heart disease	Yes
PCI with balloon angioplasty or stent placement for stable coronary disease	Patients with ischemic heart disease	Yes
Renal artery angioplasty or stenting	Patients with hypertension	No
Carotid endarterectomy for asymptomatic adults	All patients	Yes

2.2 Review of Search Strategy and Study Selection Criteria for Preliminary Abstract Review

To identify relevant full-text manuscripts, we searched PubMed®, CINAHL, the Cochrane Library, and the New York Academy of Medicine Grey Literature Database for English-language articles published between January 1, 2000, and August 3, 2018. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing

on terms to describe relevant populations, measures, and outcomes. We also conducted targeted searches for published and unpublished literature by searching the websites of Choosing Wisely®, the U.S. Preventive Services Task Force (USPSTF), the Centers for Medicare & Medicaid Services, the American Academy of Family Physicians, Great Britain's National Institute for Health and Care Excellence (NICE), the Patient-Centered Outcomes Research Institute, and Massachusetts Blue Cross Blue Shield. Finally, to supplement our electronic searches, we manually reviewed the reference lists of pertinent systematic review articles and added all previously unidentified relevant articles to our database. See Appendix 1 for additional details on our search strategy and study selection criteria.

2.3 Study Selection for Preliminary Abstract Review

We selected studies for inclusion in the preliminary abstract review using the criteria presented in Table 2-2. Included studies must have been published in the year 2000 or later, must examine at least one of the 10 low-value health care services of interest, must not exclude the examination of either service use or spending that occurs downstream of the low-value service, must examine adults (age 18 or older), must have a sample size of greater than 20, and must have been published in English. Systematic literature reviews that did not derive their own estimates of one of the measures of interest were excluded, but their reference lists were manually reviewed for studies not picked up in our searches, as noted above.

Table 2-2. Inclusion Criteria from Initial Review

	Inclusion Criteria	Rationale
Measure	Examines one of the 10 low-value services of interest	General conceptual studies are not of interest in this review. Only studies that contain one of the 10 low-value services of interest will be included.
Outcome	Does not exclude examination of downstream service use or spending	Studies that do not examine health care spending or service use downstream of the low-value service of interest are not of interest in this review. However, studies that examined spending or use but did not explicitly exclude downstream spending or use were included initially.
Study population	Study population includes adults (exclude studies of children only)	The Medicare population is primarily composed of elderly individuals. Many of the low-value services pertain to adult or elderly populations.
	Sample size of 20 or more	Case studies and studies of smaller samples lack the statistical power necessary for generalizable results.
Study design	Randomized controlled trial (RCT), observational, or synthesis	Systematic literature reviews do not generate independent estimates of downstream service use or costs.
Language	Published in English	

Two team members independently reviewed titles and abstracts for inclusion criteria. Studies that met the inclusion criteria after title/abstract review were retained for subsequent full-text review. A consensus process was used to resolve disagreements, and a third team member resolved any remaining differences between the reviews. From this preliminary review of abstracts, MedPAC staff selected five measures of low-value care with enough studies for an in-depth literature review

2.4 Data Extraction for In-Depth Review: What Factors Were Identified for Each Type of Study

For the in-depth literature review of five measures of low-value care, each included study was examined and categorized by the following factors: study design (randomized controlled trial [RCT], observational, or economic evaluation/evidence synthesis), sample size and sample characteristics (excluding syntheses), the country where the study was conducted, and the operational definition of the low-value health care service of interest. Studies were identified as an RCT if specified as such in the methods or if investigators randomly applied a treatment or experiment on the study population, observational if investigators observed the study population and measured the outcome without assigning treatments, or economic evaluation/evidence synthesis if a decision or simulation model (e.g., meta-analysis, Markov, microsimulation, cost-effectiveness) was used to estimate downstream service use or costs (Kuntz et al., 2013). Meta-analyses, or studies that create a pooled estimate using data from multiple studies, were categorized as evidence syntheses. It is important to note that study types were unclear at times and were inferred as needed based on the manuscript content.

Studies examined downstream service use, downstream spending, or both. In studies examining downstream service use, we identified the specific downstream services examined, how use of those services was measured operationally (e.g., claims, RCT data), the length of the follow-up period examined for this utilization, the statistical methods used to quantify the likelihood and/or magnitude of the utilization, and the study findings associated with the downstream service. All services downstream of the low-value service of interest were extracted and reported, regardless of whether the use of the downstream service was directly affected by the low-value service.

Studies examining downstream spending varied more widely in their design. RCTs and observational studies tended to examine the spending of a certain cohort for a specified period following the low-value service, whereas evidence syntheses typically examined a broader population for a longer period (e.g., lifetime spending). Therefore, we began our examination of each study that looked at downstream spending by identifying the perspective of the cost calculation (i.e., hospital, payer, societal, not specified), whether costs were derived from a single study or modeled from multiple sources, and the period the spending represented. We then identified the specific costs incorporated into the cost

calculation (where specified), including whether the initial service was included in the cost calculation, what services were included and how the cost of those services was determined (e.g., published prices, claims data), whether indirect costs were included, the currency and year of the costs, whether any discounting was applied over extended periods of time, and the statistical methods used to quantify the likelihood and/or magnitude of the spending. We then identified any sensitivity analyses conducted to quantify the uncertainty of the estimates, underlying assumptions and limitations identified by the authors, and the funding source for the study (where applicable). Finally, we extracted the study estimation of downstream cost.

2.5 Data Synthesis and Reporting

For the downstream service use outcomes, we abstracted all outcomes and aggregated outcomes that were reported in more than one included study. When possible, we summarized study outcomes as frequencies (e.g., the prevalence of an outcome per individual in the study sample/population). These frequencies were either abstracted directly from the manuscript or calculated as the frequency of event divided by the relevant population when possible. Frequencies calculated for this report are *italicized*. When frequencies could not be reliably calculated from the manuscript, the original value and its units were reported separately.

All costs were compared and reported using 2018 U.S. dollars. Costs were inflation-adjusted to 2018 dollars using an average inflation rate of 2.29% per year (OECD, 2018) and then converted to U.S. dollars using Google Currency Conversion (exchange rates as of the week of November 5, 2018) (City of Lincoln Nebraska). The average inflation rate of 2.29% was calculated from the average of inflation rates of Organisation for Economic Co-operation and Development (OECD) countries ("OECD – Total") from 2000 to 2016 (OECD, 2018). When the year of the reported costs were not specified in the study, we assumed the year of the costs was the last year of the study period or the publication year.

We report the estimated total costs and prevalence of each downstream service for all studies examining them, stratified by the type of cost or service, type of study, and population examined (if important for the measure). For example, prostate biopsy and cancer treatment are reported separately following PSA testing, and studies examining different age ranges were differentiated in our results. Within the ranges, we report the lowest and highest value, regardless of length of follow-up. When possible, the estimate for the low-value population is reported separately for each measure and downstream outcome.

2.6 Rating Study Quality and Applicability

We rated each study on a 10-point scale based on its study limitations, directness, precision, and suspected reporting bias. These domains were adapted from the strength of evidence work from Berkman and colleagues (2015), Brunetti and colleagues (2013), and

the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Collaboration, 2008). We developed questions to assess each domain by study type; these questions were adapted from The National Institutes of Health "Quality Assessment Tools" (National Institute of Health, 2018) and the ISPOR CHEERS Checklist (Husereau et al., 2013) and can be found in Appendix 3. Our rating system emphasized both overall study quality and applicability of the study question to this review. For example, several studies included in this review compare the downstream costs and outcomes of beneficiaries receiving different types of stents (e.g., bare metal vs. drug-eluting). Although such studies yield important insights into use and spending downstream of a low-value service, their contribution to this review, specifically in the areas of precision and study limitations, would be more limited because they do not include a control group that did not receive PCI. More detail on these considerations is presented below and in Appendix 3.

Each study was assessed on its study limitations, directness, precision, and suspected reporting bias, as described below. Ratings were based on reviewers' judgment of the overall study quality and applicability using these criteria.

Study limitations were a summary judgement of how well the study could provide an accurate, unbiased estimates of the true effect. This assessment defined study limitations based on the type of study and the specific way it was executed. Our rating system considered both methodological quality and applicability to this review. Important considerations included a clearly defined study objective and methodology, a clear discussion of study limitations, and study objectives that include examining either spending or service use downstream of one of the low-value services of interest. Studies were scored as a 3 for low limitations, 2 for medium limitations and 1 for high limitations. Study type–specific considerations included the following:

- **RCTs** were primarily assessed for study methodology. Factors such as study protocol, reported adequacy of randomization, and sample selection criteria were then assessed.
- **Observational** studies were primarily assessed for study methodology. Factors such as inclusion criteria, data sources, and analytic methods used to control for confounding and bias were then assessed. Ratings were based on reviewers' judgment of the methods employed.
- **Evidence syntheses and economic analyses** were evaluated for study methodology and by the limitations of the underlying data used. Studies employing only data from RCTs or population-level datasets were considered higher quality because they are less likely to suffer from confounding or selection bias. Studies employing data from both RCTs/population datasets and observational or cross-sectional studies were considered more limited. Studies using only data from observational cohort or cross-sectional studies had the highest limitations. Other considerations included the type of analytical model use, whether deterministic sensitivity analyses (i.e., varying the model inputs in some clinically meaningful way

to test the robustness of the effect estimate) were conducted, and whether the perspective and assumptions of the model were clearly discussed.[2]

Directness was defined as how closely the evidence measures the outcomes. In other words, studies were direct if the study outcome (e.g., prostate biopsy or cancer treatment after a positive PSA test) was measured in the same population in which the low-value service occurred, and indirect if separate, independent sources were used to derive the likelihood of the exposure and outcome in a population. For example, a number of studies estimate downstream costs by identifying the prevalence of certain common downstream services and applying a previously established price or cost to those services. Directness was scored as 2 for direct and 1 for indirect. Study type–specific considerations included the following:

- **RCTs** and **observational studies** typically presented a direct analysis, though some examine costs of care using an external pricing system.
- **Evidence syntheses and economic analyses** were considered indirect if data on the low-value service and the downstream spending or service utilization were drawn from different studies or sources.

Precision was defined as the degree of statistical certainty presented with the effect estimates. Generally, studies were considered precise if effect sizes (e.g., total spending downstream of a PSA test in older men) were paired with a measure of uncertainty drawn from a statistical test (e.g., p-values, confidence intervals). In RCTs and observational studies, this requires the inclusion of a control group that did not receive the low-value service of interest. For example, studies comparing PCI with two different types of stents could not be considered precise because all study participants received PCI. Evidence syntheses and economic analyses, in contrast, may present precise estimates if probabilistic sensitivity analyses are used to quantify the uncertainty around an effect estimate.[3] Other important considerations included adequacy of sample size and presentation of power calculations when sample sizes are smaller. Studies were scored as 4 for precise, 2 for imprecise, and 0 for no evidence. Study type–specific considerations included the following:

- **RCT** precision was primarily based on sample size and the applicability of the research question (i.e., whether the study tested differences in the outcome with and without the low-value service). Especially for smaller studies where a significant finding may be difficult, discussion of statistical power was an important consideration. A study that lacked the power to detect a statistically significant relationship was considered imprecise if a finding that was regarded as clinically important was presented. Studies that did not statistically test a relationship of interest to this review were considered to lack precision even if adequate statistical testing was done on unrelated research questions.

[2] A deterministic sensitivity analysis is where model input parameters were manually changed to determine whether the outcome was affected (YHEC, 2016a).
[3] A probabilistic sensitivity analysis is a technique to quantify the level of confidence in the model output; distributions around point estimates are often tested (YHEC, 2016b).

- **Observational** study precision was also primarily based on sample size and on the applicability of the results. Because observational studies are often overpowered, less emphasis was placed on the presentation of power calculations. Precise studies presented measures of uncertainty (e.g., confidence intervals) for effect estimates of interest to this review. Studies that did not statistically test a relationship of interest to this review were considered to lack precision even if adequate statistical testing was done on unrelated research questions.
- **Evidence synthesis and economic analysis** precision was rated primarily based on the methodology used to quantify the uncertainty in the effect estimates from the syntheses. Precise studies generally employed probabilistic sensitivity analyses (i.e., analyses such as Monte Carlo simulations that use a distribution to estimate uncertainty around a model result) to generate confidence intervals around effect estimates of interest (YHEC, 2016b). Unlike observational studies and RCTs, effects examined using these methods were considered precise even without a control group of interest.

Finally, **suspected reporting bias** was assessed subjectively by reviewers. Factors such as selective reporting of study protocols and outcomes or potential conflicts of interest in study funding were considered. Studies were generally assumed to be free of reporting bias (1 point) unless evidence to the contrary was found (0 points).

The scores from each of these domains were summed and aggregated to four possible categories rating the overall study quality and applicability to our review.

High (10–8) We are very confident that the estimate of effect lies close to the true effect for this outcome.

Moderate (7–5) We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The study has some deficiencies.

Low (4–2) We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The study has major or numerous deficiencies (or both).

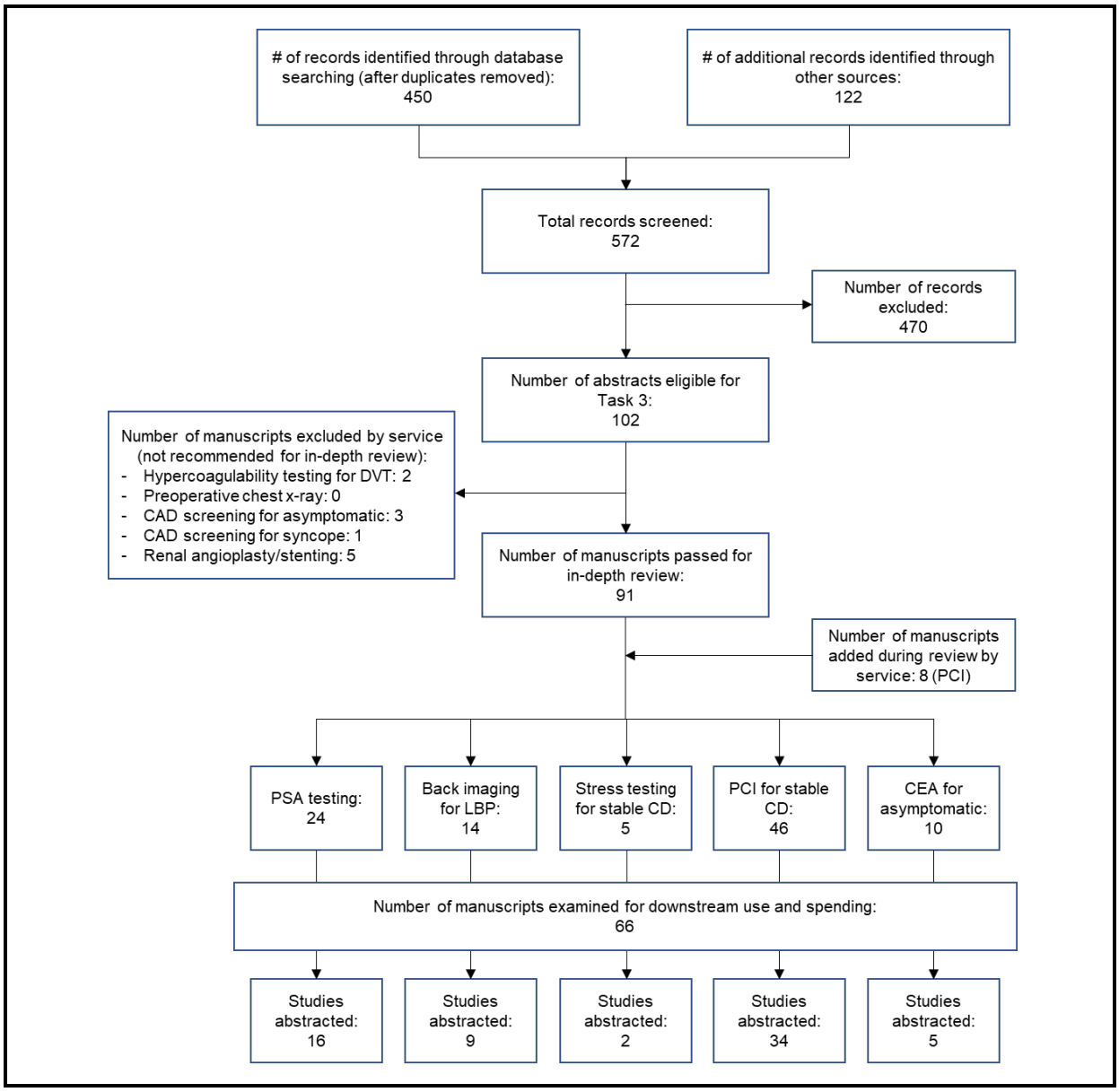
Insufficient (1–0) We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.

3. Results

3.1 Overall Results

Our preliminary abstract review identified 91 manuscripts across the five measures of low-value care. We identified 8 additional manuscripts through our review of the full text of included manuscripts (See Appendix 2). Figure 3-1 visualizes how these manuscripts were included by measure.

Figure 3-1. Search Results and Included Studies by Measure of Low-Value Care



Note: CAD = carotid artery disease, CD = coronary disease, CEA = carotid endarterectomy, DVT = deep vein thrombosis, LBP = low back pain, PCI = percutaneous coronary intervention, PSA = prostate-specific antigen

Upon full review, 66 manuscripts were ultimately examined for evidence of downstream service use and spending (Table 3-1). Thirty-three manuscripts were removed using our exclusion criteria; 11 studies (33%) were excluded for focusing on the wrong population (e.g., PCI for patients with unstable coronary disease) and 18 (55%) were excluded for not including a downstream outcome of interest. The reasons for their exclusion are described in more detail in the measure-specific results. The included studies are briefly summarized in aggregate below and described in greater detail in subsequent sections of this report. RCTs constituted 20 of the 66 studies (30%), 18 (27%) were observational studies, and the remaining 28 (42%) were evidence syntheses or economic evaluations. PCI for stable coronary disease was examined in 34 (52%) of the included studies, and 16 (24%) examined PSA testing. The remaining studies examined either stress testing for stable coronary disease (2 studies), imaging for low back pain (9 studies), or carotid endarterectomy for asymptomatic patients (5 studies). None of the included manuscripts examined multiple measures of low-value care. Included studies spanned all of the eligibility years, but the plurality (25 studies) were published between 2011 and 2015. Twenty-one of the 66 studies (32%) had high study quality and were highly applicable to our research question, 29 (44%) had moderate quality and applicability, and 16 (24%) had low quality and applicability.

The distribution of study quality and characteristics varied considerably across measures of low-value care (Table 3-1), likely because of the nature of these services. For example, studies examining costs downstream of PSA testing were more likely to be evidence syntheses (69%). The costs of PSA testing may not be incurred until several years after a PSA testing schedule is begun, and evidence syntheses allow modeling of lifetime expenditures without the significant investment of a long-term trial or observational study. In contrast, studies examining costs and service use downstream of imaging for low back pain were all either RCTs or observational studies, likely because the primary service of interest is back surgery prompted by, and occurring shortly after the imaging.

In total, 54 of the 66 studies (82%) examined downstream costs of care, and 37 studies (56%) examined downstream service use; 25 studies (38%) examined both downstream costs of care and service use. These manuscripts are described in greater detail in Table 3-2. The length of follow-up in some cases corresponded to the low-value service being examined and the typical period in which the downstream services and costs were likely to be incurred. For example, 95% of PCI manuscripts examining downstream service use had at least 1 year of follow-up after the initial procedure. Manuscripts examining PSA testing varied more, but it is important to note that these studies varied in the downstream services they examined (e.g., biopsy only for diagnosis vs. cancer treatments). Additional details for each of the measures of low-value care can be found in the next sections of this report, and the abstracts for each included study can be found in Appendices 1 and 2.

Table 3-1. Included Study Characteristics by Low-Value Service Measure

	Total		Stress		LBP		PSA		PCI		CEA	
	N	%	N	%	N	%	N	%	N	%	N	%
Total studies	66		2		9		16		34		5	
Publication year												
2000–2005	20	30%	1	50%	2	22%	4	25%	12	35%	1	20%
2006–2010	12	18%	0	0%	2	22%	1	6%	8	24%	1	20%
2011–2015	25	38%	1	50%	3	33%	7	44%	12	35%	2	40%
2016–2018	9	14%	0	0%	2	22%	4	25%	2	6%	1	20%
Study design												
RCT	20	30%	1	50%	2	22%	0	0%	17	50%	0	0%
Observational	18	27%	1	50%	7	78%	5	31%	4	12%	1	20%
Economic evaluation/ evidence synthesis	28	42%	0	0%	0	0%	11	69%	13	38%	4	80%
Country												
United States	24	36%	1	50%	6	67%	8	50%	6	18%	3	60%
Europe	19	29%	1	50%	3	33%	3	19%	10	29%	2	40%
Canada	4	6%	0	0%	0	0%	2	13%	2	6%	0	0%
Australia/New Zealand	2	3%	0	0%	0	0%	2	13%	0	0%	0	0%
Multiple	9	14%	0	0%	0	0%	1	6%	8	24%	0	0%
Other/not specified	8	12%	0	0%	0	0%	0	0%	8	24%	0	0%
Downstream outcomes												
Cost	54	82%	2	100%	6	67%	13	81%	28	82%	5	100%
Services	37	56%	2	100%	7	78%	6	38%	21	62%	1	20%
Both cost and service outcomes	25	38%	2	100%	4	44%	3	19%	15	44%	1	20%
Study quality and applicability												
High	21	32%	0	0%	6	67%	2	13%	11	32%	2	40%
Moderate	29	44%	1	50%	2	22%	9	56%	15	44%	2	40%
Low	16	24%	1	50%	1	11%	5	31%	8	24%	1	20%

Note: Stress: Stress testing for stable coronary disease; LBP: back imaging for low back pain; PSA: Prostate-specific antigen testing; PCI: percutaneous coronary intervention in stable coronary disease; CEA: carotid endarterectomy for asymptomatic patients.

Table 3-2. Study Characteristic for Downstream Service and Cost by Low-Value Service Measure

	Total		Stress		LBP		PSA		PCI		CEA	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	66		2		9		16		34		5	
Examine Downstream Service Use	37	56%	2	100%	7	78%	6	38%	21	62%	1	20%
Service Use Follow-Up Time												
< 1 month	1	3%	0	0%	1	14%	0	0%	0	0%	0	0%
1–3 months	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
4–6 months	4	11%	0	0%	1	14%	2	33%	1	5%	0	0%
7–11 months	1	3%	0	0%	1	14%	0	0%	0	0%	0	0%
1 year	16	43%	0	0%	2	29%	0	0%	14	67%	0	0%
2+ years	13	35%	2	100%	2	29%	2	33%	6	29%	1	100%
Lifetime	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Not specified	2	5%	0	0%	0	0%	2	33%	0	0%	0	0%
Examine Downstream Costs	54	82%	2	100%	6	67%	13	81%	28	82%	5	100%
Study Perspective												
Hospital	6	11%	2	100%	0	0%	0	0%	3	11%	1	20%
Payer	17	31%	0	0%	4	67%	3	23%	10	36%	0	0%
Societal	25	46%	0	0%	2	33%	10	77%	9	32%	4	80%
Not specified	1	2%	0	0%	0	0%	0	0%	1	4%	0	0%
Include Initial LVS in Costs												
Yes	49	91%	1	50%	4	67%	12	92%	27	96%	5	100%
No	5	9%	1	50%	2	33%	1	8%	1	4%	0	0%
Cost Follow-Up Time												
< 1 year	2	4%	0	0%	2	33%	0	0%	0	0%	0	0%
1–2 years	23	43%	0	0%	4	67%	2	15%	16	57%	1	20%
3–4 years	8	15%	1	50%	0	0%	1	8%	6	21%	0	0%
5+ years	3	6%	0	0%	0	0%	2	15%	0	0%	1	20%
Lifetime	15	28%	1	50%	0	0%	7	54%	4	14%	3	60%
Not specified	1	2%	0	0%	0	0%	1	8%	0	0%	0	0%

Note: Stress: Stress testing for stable coronary disease; LBP: back imaging for low back pain; PSA: Prostate-specific antigen testing; PCI: percutaneous coronary intervention in stable coronary disease; CEA: carotid endarterectomy for asymptomatic patients; LVS: low-value service

To increase comparability of downstream costs and use, studies are aggregated by study type. When feasible, estimates for the low-value population are aggregated and reported separately.

3.2 PSA Testing

PSA testing for prostate cancer has become widely recognized in recent years as a low-value health care service for older men (e.g., age 70 or older) and a service of questionable value for younger men (e.g., age 55–69). Studies have noted that the test lacks specificity (i.e., has a high false positive rate), resulting in unnecessary biopsies to confirm the diagnoses, and often identifies clinically insignificant cancers (USPSTF, 2018). The studies also note that prostate cancer treatments carry risks, are costly and painful, and may do more harm than good, especially among the elderly. Currently, USPSTF recommends against routing screening for men 70 years of age or older and suggests that men ages 55 to 69 discuss risks and benefits with their doctor (USPSTF, 2018). The "C" grade that USPSTF gave for PSA testing among men ages 55 to 69 indicates that USPSTF recommends selective use of the service because there is moderate certainty that the net benefit is small for some men. Because of important tradeoffs between the potential harms and benefits of PSA testing and new research findings, the age cutoffs for PSA testing recommendations may vary between 70 and 75 years of age, depending on when the recommendation was made (e.g., the 2008 USPSTF recommendation for PSA testing recommended against screening for men age 75 or older) (USPSTF, 2008). The low-value care measure developed by Schwartz et al. (2015) considers PSA testing for men age 75 or older to be low value. However, some professional societies recommend that patients engage in shared decision-making with their physician about undergoing the test regardless of their age (Choosing Wisely, 2013b, 2015).

Our initial searches identified 24 abstracts. After reviewing the full manuscripts, we included 16 manuscripts examining downstream costs and service use after PSA testing. The remaining studies were excluded for either not having a relevant downstream outcome (Bermudez-Tamayo et al., 2007; Heijnsdijk et al., 2012; Rao et al., 2018; Ross et al., 2000; Zhang et al., 2012) or focusing on the wrong population (e.g., biopsied patients rather than screened patients) (Babaian et al., 2006; Ellison et al., 2002; Jeng et al., 2002). Of the included studies, 5 were observational and 11 were economic evaluations/evidence syntheses. The quality of evidence for the studies ranged from high to low.

The most common downstream services observed across the included studies were prostate biopsy, radical prostatectomy, radiation therapy, hormone therapy, and active surveillance/conservative management. Estimates of their prevalence varied considerably across studies. Downstream costs also varied, largely with differences in the underlying sample of patients, the type/frequency of PSA testing examined, and the downstream services included in the cost estimates. In general, the cost of the initial PSA test and

subsequent biopsy were lower-cost services, whereas subsequent cancer treatment carried more-substantial costs. Additional detail on these studies can be found in Table 3-4 and in Appendix 4.

3.2.1 Population

The studies we examined varied considerably in the types of PSA testing and downstream services they examined. For this review, we included all forms of PSA testing (e.g., Total PSA, Percent Free PSA) because current guidance from Choosing Wisely and others do not differentiate in their assessment of low-value care. Most of the included studies either directly or implicitly in their study design acknowledge that testing a population over age 75 is of little value. Only one observational study we identified examined the total cost to the health care system of PSA testing in a population 75 years of age and older (Ma et al., 2014). The remaining studies instead focus their attention on the costs and service use of a younger population (e.g., ages 40 through 74). Although recommendations of USPSTF and other professional societies vary in how they define low-value and questionable-value age groups for PSA testing, we included these studies to contribute to the growing body of literature pertaining to the value of PSA testing in this population. In addition, although most studies reported outcomes based on a prospectively screened population, two studies reported outcomes based on the general, male Medicare population (Ma et al., 2014; Zanwar et al., 2016), and another retrospectively examined screening and downstream outcomes among a population diagnosed with prostate cancer (Shao et al., 2011).

3.2.2 Downstream Costs

Most included studies examined the downstream costs and cost-effectiveness of PSA testing by modeling the likelihood and costs of various downstream services using techniques such as decision analytic models. Downstream costs typically incorporated into the base case scenario include the initial PSA screening, procedures for diagnosis (including biopsy), and other follow-up treatment as relevant (e.g., conservative management, radiation therapy, radical prostatectomy).

For most studies, downstream costs were modeled for different screening intervals and/or populations. Because many of the studies reported lifetime costs with screening starting at different ages, downstream costs were aggregated in this report by the patient age groups to highlight the low-value population (≥ 70 years) and the questionable-value population (< 70 years) as feasible. Costs also were separately aggregated for mean cost per patient and cost to a system. For the low-value Medicare population, annual downstream costs for PSA screening ranged from $17 per beneficiary for men 85 to 99 years to $109 per beneficiary for men 75 years or older (Ma et al., 2014; Zanwar et al., 2016).[4] One economic

[4] These studies included all male Medicare beneficiaries in the sample population, regardless of PSA screening status.

evaluation reported 50-year costs (i.e., lifetime costs) to be $520 per patient for a low-value population (at least 70 years of age) with one PSA screening (Pataky et al., 2014). For men at least 75 years of age, the annual costs to Medicare ranged from $22.1 million to $155.7 million (Ma et al., 2014). For the younger population (40 to 74 years), the economic evaluations estimated that long-term costs ranged from $427 per patient (for 50-year-old men with one PSA screening) to $6,480 per patient (for men with annual screening between the ages of 50 and 74 years) (Pataky et al., 2014; Roth et al., 2016). In contrast, annual mean cost for beneficiaries 66 to 99 years and 66 to 74 years of age was estimated to be $44 and $53 per Medicare beneficiary, respectively (Ma et al., 2014). At the health care system level, annual Medicare costs were estimated to range from $369 million to $548 million for beneficiaries 66 to 74 years and 66 to 99 years of age, respectively (Ma et al., 2014). Annual costs ranged from $6.6 million to $149.3 million for population-wide screening programs in Australia and Ontario, Canada, respectively (Stone et al., 2005; Tawfik, 2015).

3.2.3 Downstream Services Used

We included six studies examining downstream service use, five of which were observational (Table 3-3). Prostate biopsy, radical prostatectomy, radiation therapy, hormone therapy, and active surveillance/conservative management were downstream services reported by more than one study. Results reported below focus on the frequencies of the downstream services that were reported in more than one study. Frequencies of the different populations of interest (e.g., Medicare population, PSA screened, and prostate cancer diagnosed) are reported separately in the table.

The most common downstream service examined by the included studies was prostate biopsy used to confirm the diagnosis of prostate cancer after a positive PSA test (5 studies). Prostate biopsy is relatively easy to examine because it typically occurs shortly after a positive PSA test. Among the observational studies, the reported frequency of prostate biopsies ranged from 1.1% after 180 days of follow-up in a general Medicare population (66 years and older, including those not screened) to 4.6% after 1 year of follow-up in a PSA-screened population (Ma et al., 2014; Richter et al., 2001; Zanwar et al., 2016). Both radical prostatectomy and radiation therapy were examined in three observational studies and one economic evaluation. Three observational studies reported the frequency of radical prostatectomy, radiation therapy, and hormone therapy (Shao et al., 2011; Walter et al., 2013; Zanwar et al., 2016). Among the general Medicare population (75 years and older, including those not screened), the frequency for radical prostatectomy was 0.1% after 2 years of follow-up, the frequency for radiation therapy ranged from 0.5% to 0.7% after 2 years of follow-up, and the frequency of hormone therapy was 0.7% after 2 years of follow-up (Zanwar et al., 2016). In contrast, in the Veterans Affairs population of PSA-screened men (65 years and older), the frequency for radical prostatectomy, radiation therapy, and

Table 3-3. Summary of Key Findings and Quality Rating: PSA Testing

Outcomes	N Studies by Study Type (included study population)	Results by Study Type (country of focus)	Source and Quality Rating
Cost			
Mean per patient, ≥ 70 years	2 observational (male Medicare population)	Annual costs for the male Medicare population ranged from $17 (men 85–99 years; USA) to $109 (men 75+ years; USA).	Ma et al. (2014),** Zanwar et al. (2016)***
	1 synthesis (PSA screened)	Cost was estimated to be $520 for 50-year follow-up (men 70 years with 1 screening; Canada).	Pataky et al. (2014)**
Annual cost to a health care system, ≥ 75 years	1 observational (male Medicare population)	Annual costs for the male Medicare population ranged from $22.1 million (men 85–99 years; USA) to $155.7 million (men 75–84 years; USA).	Ma et al. (2014)**
Mean per patient, 40–74 years	9 synthesis (PSA screened)	Costs ranged from $427 for 50-year follow-up (men 50 years with 1 screening; Canada) to $6,480 for lifetime follow-up (men 50–74 years, with 1-year screening interval; USA).	Benoit et al. (2001),* Heijnsdijk et al. (2015),** Heijnsdijk et al. (2009),** Keller et al. (2017),*** Ma et al. (2014),** Pataky et al. (2014),** Roth et al. (2016),** Sennfalt et al. (2004)*
	1 observational (male Medicare population)	Annual costs estimated to be $44 (men 66–99 years; USA) to $53 (men 66–74 years; USA).	Ma et al. (2014)**
Annual cost to a health care system, 50–74 years	2 synthesis (PSA screened)	Annual cost for a government health care system ranged from $6.6 million (national program in Australia) to $149.3 million (men 50–74 years, population-based screening in Ontario, Canada).	Stone et al. (2005),* Tawfik (2015)**
	1 observational (male Medicare population)	Annual Medicare cost for the male Medicare population was $369.0 million for men 66–74 years and $548.0 million for men 66–99 years (USA).	Ma et al. (2014)**

(continued)

Table 3-3. Summary of Key Findings and Quality Rating: PSA Testing (continued)

Outcomes	N Studies by Study Type (included study population)	Results by Study Type (country of focus)	Source
Service use			
Prostate biopsy	4 observational (2 with male Medicare population, 2 with men with PSA screening)	Among the PSA-screened men, frequency ranged from *2.1%* to *4.6%* within 1 year (65+ years, USA VA population). Among the male, Medicare population, frequency ranged from 1.1% after 180 days of follow-up (66+ years; USA) to 2.4% after 2 years of follow-up (75+years; USA).	Ma et al. (2014),** Richter et al. (2001),* Walter et al. (2013),** Zanwar et al. (2016)***
	1 synthesis (men with PSA screening)	Lifetime estimate with 4-year screening interval was 19,946 per 100,000 men ages 55–70 years and 29,954 per 100,000 men ages 55–75 years (Europe).	Heijnsdijk et al. (2009)**
Active surveillance/ conservative management	1 observational (men with prostate cancer diagnosis)	Among men diagnosed with prostate cancer (70+ years; USA), frequency ranged from 23% to 26% after 180 days of follow-up.	Shao et al. (2011)**
	1 synthesis (men with PSA screening)	Lifetime estimate with 4-year screening interval ranged from 1,310 per 100,000 men ages 55–70 years to 1,942 per 100,000 men ages 55–75 years (Europe).	Heijnsdijk et al. (2009)***
Radical prostatectomy	3 observational (1 with male Medicare population; 1 with men with PSA screening; 1 with men with prostate cancer diagnosis)	Among the male Medicare population (75+ years; USA), frequency was 0.1% after 2 years of follow-up. Among PSA-screened VA men (65+ years; USA), the frequency was *0.2%* after 5 years of follow-up. Among men diagnosed with prostate cancer (70+ years; USA), frequency ranged from 6% to 10% after 180 days of follow-up	Shao et al. (2011),** Walter et al. (2013),** Zanwar et al. (2016)***
	1 synthesis (men with PSA screening)	Lifetime estimate with 4-year screening interval was 1,559 per 100,000 men ages 55–70 years, and 2,214 per 100,000 men ages 55–75 years (Europe).	Heijnsdijk et al. (2009)**

(continued)

Table 3-3. Summary of Key Findings and Quality Rating: PSA Testing (continued)

Outcomes	N Studies by Study Type (included study population)	Results by Study Type (country of focus)	Source
Radiation therapy	3 observational (1 with male Medicare population; 1 with men with PSA screening; 1 with men with prostate cancer diagnosis)	Among the male Medicare population (75+ years; USA), frequency ranged from 0.5% to 0.7% after 2 years of follow-up. Among the PSA-screened VA population (65+ years; USA), frequency was *0.8%* after 5 years of follow-up. Among men diagnosed with prostate cancer (70+ years; USA), frequency ranged from 35% to 47% after 180 days of follow-up.	Shao et al. (2011),** Walter et al. (2013),** Zanwar et al. (2016)***
	1 synthesis (men with PSA screening)	Lifetime estimate with 4-year screening interval was 1,786 per 100,000 men ages 55–70 years and 2,608 per 100,000 men ages 55–75 years (Europe).	Heijnsdijk et al. (2009)**
Hormone therapy	3 observational (1 with male Medicare population; 1 with men with PSA screening; 1 with men with prostate cancer diagnosis)	Among the male Medicare population (75+ years; USA), frequency was 0.7% after 2 years of follow-up. Among the PSA-screened VA population (65+ years; USA), the frequency was *0.4%* after 5 years of follow-up. Among men diagnosed with prostate cancer (70+ years; USA), frequency ranged from 20% to 33% after 180 days of follow-up	Shao et al. (2011),** Walter et al. (2013),** Zanwar et al. (2016)***

Note: All costs are reported in 2018 U.S. dollars. Italicized estimates were calculated for the literature review. PSA = prostate-specific antigen, VA = US Department of Veterans Affairs

* Indicates the study received a low rating

** Indicates the study received a moderate rating

*** Indicates the study received a high rating

hormone therapy was 0.2%, 0.8%, and 0.4%, respectively, after 5 years of follow-up (Walter et al., 2013). For active surveillance/conservative management, one observational study reported that the frequency ranged from 23% to 26% after 180 days of follow-up in the population 70 years of age and older diagnosed with prostate cancer (Shao et al., 2011). Other downstream services examined included repeat PSA testing, ultrasound, imaging, palliative therapy, and outpatient visits.

3.3 Back Imaging for Low Back Pain

Imaging such as X-rays, computed tomography (CT) scans, or magnetic resonance imaging scans (MRIs) may be used to evaluate patients presenting with nonspecific low back pain (Choosing Wisely, 2012e). These scans are appropriate in specific defined patients where the pain may be caused by an emergent treatable condition, such as cancer or infection. However, such cases are rare, and back pain usually resolves on its own or with minor medical intervention (e.g., over-the-counter pain medication). Additionally, imaging is costly and requires exposing the patient to potentially unnecessary radiation in some cases. More importantly, it can result in unnecessary surgery or other treatments as well as additional visits and testing (e.g., repeat imaging tests), which carry additional costs and risks. Both Great Britain's NICE and Choosing Wisely® recommend against routinely imaging for nonspecific low back pain (Choosing Wisely, 2012a; National Institute for Health and Care Excellence, 2016). The National Committee for Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS) measure further specifies that imaging for low back pain should not be done within the first 28 days (absent certain red-flag conditions like cancer), particularly because pain improves within 2 to 3 weeks for most patients (NCQA, 2018). The less-sensitive, more-specific version of the measure used by Schwartz et al. (2014) counts imaging within 6 weeks of the diagnosis of low back pain as low value, unless there is a diagnosis on the claim that warrants imaging. Additional detail on these studies can be found in Table 3-4 and Appendix 4.

Our initial search identified 14 abstracts examining use of imaging for patients with low back pain that met our inclusion criteria. After review of the full manuscripts, 9 studies were determined to be eligible for data extraction and summary per our inclusion criteria. The remaining 5 studies were excluded for having no relevant downstream outcomes (Graves et al., 2018; Lurie et al., 2003), for not meeting the definition of a low-value service (cancer-related low back pain) (Hollingworth et al., 2003), for having a small sample with uninformative outcomes (i.e., no change in medical/surgical treatment) (Hourcade et al., 2002), or for being a duplicate study (Gilbert et al., 2004a). Of the included studies, seven were observational, and two were RCTs. The quality of evidence for the studies ranged from high to low.

Seven of the nine studies examined downstream service use, and four reported imaging in a low-value population. Key downstream services examined by these studies were surgery (or referrals), physical therapy (or referrals), additional imaging, and injections, though it is important to note that physical therapy would likely be prescribed even in the absence of the low-value service. Downstream costs for imaging for low back pain were also reported in seven included studies, and four of these reported imaging in a low-value population.

Table 3-4. Summary of Key Findings and Quality Rating: Back Imaging for Low Back Pain

Outcomes	N Studies by Study Type (included study population)	Results by Study Type (country of focus)	Source and Quality Rate
Cost			
Unadjusted mean cost per patient	2 RCTs (1 with early imaging, 1 with LBP for ≥ 6 weeks and < 6 months)	For early imaging patients (imaging performed as soon as practical), costs estimated to be $1,030 in 2 years (direct medical costs including imaging) (UK). For patients with LBP for ≥ 6 weeks and < 6 months, costs estimated to be $287 in 9 months (direct medical costs including imaging) (UK).	Gilbert et al. (2004b),*** Miller et al. (2002)***
	4 observational (1 with LBP and leg pain for 2–12 months; 3 with early imaging)	For early imaging patients, costs ranged from $22,344 to $29,313 in 2 years (direct medical costs after imaging) (USA).§ Note: one study reported estimates in a figure. For patients with pain for 2–12 months, cost estimated to be $1,399 in 9 months (direct medical costs including imaging) (Denmark).	Jensen et al. (2010),** Webster et al. (2013),*** Webster et al. (2014),*** Webster et al. (2010)**
Adjusted mean cost per patient	2 observational (1 with early imaging; 1 with timing not specified)	With timing unspecified, cost was estimated to be $1,583 in 6 months (direct medical costs including imaging) (USA). For early imaging patients, cost ranged from $23,362 to $27,542 in 2 years (direct medical costs after imaging) (USA).§	Shreibati et al. (2011),*** Webster et al. (2013)***
Service use			
Low back/spinal surgery	1 RCT (LBP with early imaging)	For early imaging patients (imaging performed as soon as practical), frequency was 6.9% after 2 years of follow-up (UK).	Gilbert et al. (2004b)***
	4 observational (2 with early imaging; 2 with timing not specified [1 with LBP and leg pain for 2–12 months])	Among early imaging patients, frequency ranged from 8.1% among patients with less-severe back pain after 3 months of follow-up to 22% after 2 years of follow-up (severity not specified). Adjusted relative risk for early imaging patients was 28 to 34 times more likely after 6-months of follow-up compared with less severe patients with no MRI (USA).§¥ Among studies with no timing specified or patients with LBP for 2–12 months, frequency ranged from 5.6% to 34.1% after 6 months of follow-up (USA).	Fried et al. (2018),* Jensen et al. (2010),** Shreibati et al. (2011),*** Webster et al. (2014),*** Webster et al. (2010)**
Physical therapy	1 RCT (LBP with early imaging)	For early imaging patients (imaging performed as soon as practical), frequency was 63.1% after 2 years of follow-up (UK).	Gilbert et al. (2004b)***
	1 observational (1 with timing not specified)	Frequency ranged from 44–48% after 1 year of follow-up (USA).	Fried et al. (2018)*

(continued)

Table 3-4. Summary of Key Findings and Quality Rating: Back Imaging for Low Back Pain (continued)

Outcomes	N Studies by Study Type (included study population)	Results by Study Type (country of focus)	Source and Quality Rating
Advance/ repeat imaging	2 observational (1 with early imaging; 1 with timing not specified)	Among patients with early imaging, frequency ranged from 7.6% among patients with less-severe back pain with early MRI after 3 months of follow-up to 17.0% among more-severe patients with early MRI after 6 months of follow-up. Adjusted relative risk for early imaging patients was 18 to 21 times more likely after 6 months of follow-up compared to less severe patients with no MRI (USA).§ ¥ When timing was not specified, frequency ranged from 4% among all LBP patients to 47% among patients referred to a spine specialist after 1 year of follow-up (USA).	Fried et al. (2018),* Webster et al. (2014)***
Injections	1 RCT (LBP with early imaging)	For early imaging patients (imaging performed as soon as practical), frequency was 17.8% after 2 years of follow-up (UK)	Gilbert et al. (2004b)***
	2 observational (1 with early imaging; 1 with timing not specified)	Among patients with early imaging, frequency ranged from 33.0% among less-severe patients after 3 months of follow-up to 46.6% among more-severe patients after 6 months of follow-up. Adjusted relative risk for early imaging patients was 27 to 33 times more likely after 6 months of follow-up compared with less-severe patients with no MRI (USA).§¥ When timing was not specified, frequency ranged from 16% to 37% among patients referred to a spine specialist after 1 year of follow-up (USA).	Webster et al. (2014),*** Fried et al. (2018)*
Outpatient/ primary care visits	1 RCT (LBP with early imaging)	For early imaging patients (imaging performed as soon as practical), frequency ranged from 70.7% to 83.5% after 2 years of follow-up (UK)	Gilbert et al. (2004b)***
	1 observational (1 with LBP and leg pain for 2–12 months)	Observed 208 patients with 3 visits (median) after 9 months of follow-up (Denmark).	Jensen et al. (2010)**

Note: All costs are reported in 2018 U.S. dollars. LBP = low back pain.

* Indicates the study received a low rating

** Indicates the study received a moderate rating

*** Indicates the study received a high rating

§ "Early imaging patients" was defined as receiving an MRI ≤ 30 days after the onset of pain.

¥ This study stratified the exposure by MRI timing (no MRI, early MRI, and timely MRI) and by case severity (less severe and more severe) to create 6 groups. For adjusted analyses, the reference population was less-severe early MRI cases (Webster et al., 2014). No MRI cases received no MRI in the 2-year study period, early MRI cases received an MRI within the first 30 days of pain onset, and timely MRI received an MRI within 42 to 180 days of pain onset. Severity based on International Classification of Diseases, Revision 9 (ICD-9) diagnosis codes. Relative risk models adjusted for age, sex, job tenure, and use of early opioids.

3.3.1 Population

Included studies contained a range of patients and types of low back pain. In addition to nonspecific low back pain, studies specified that patients with radiculopathy (Fried et al., 2018; Webster et al., 2013),[5] symptomatic lumbar spine disorders (Gilbert et al., 2004b), and leg pain were included (Jensen et al., 2010). Apart from leg pain, these populations are considered low value for imaging (however, radiculopathy is a noteworthy exception from Schwartz et al.'s definition) (2015). Most studies examined MRI use. Miller et al. (2002) examined lumbar spine x-rays. Four studies focused on the low-value population, or patients who received imaging within a month of the onset of pain (Gilbert et al., 2004b; Webster et al., 2013, 2014; Webster et al., 2010).[6]

Several studies focused on specific populations or tested changes to the care delivery process. Three studies examined the downstream impacts of MRI among workers with low back pain (Webster et al., 2013, 2014; Webster et al., 2010); another looked at emergency department patients presenting with unspecified low back pain (Aaronson et al., 2017). The remaining studies examining imaging for low back pain tested the impacts of processes such as delaying imaging (Gilbert et al., 2004b; Jensen et al., 2010; Miller et al., 2002), provider acquisition of MRI (Shreibati et al., 2011), and inclusion of epidemiological statements in radiology reports advising physicians that the imaging may be of low value (Fried et al., 2018). These studies contained useful information on the underlying rates of potentially low-value back imaging and downstream service use and expenditures.

Because the HEDIS measure specifies that imaging should not be done within 28 days of onset of pain (absent certain red flag conditions like cancer) and the measure from Schwartz et al. (2014) considers imaging within 6 weeks of the diagnosis to be low value, the writeup of the results will focus on downstream outcomes reported for early imaging.

3.3.2 Downstream Costs

Downstream costs for imaging for low back pain were reported in seven included studies; four of these reported imaging in a low-value population. Three studies (by the same first author) did not include the initial imaging in the cost calculation, but the other four included imaging costs. Unadjusted mean cost for early imaging was $1,030 per patient after 2 years of follow-up (direct medical costs, including imaging) (Gilbert et al., 2004b). Adjusted mean costs for early imaging ranged from $23,361 to $27,542 in 2 years for nonspecific low back pain patients and radiculopathy patients, respectively (both include direct medical costs

[5] Radiculopathy describes low back pain that is produced by a pinched nerve along the spine. Similar to uncomplicated low back pain, early imaging for radiculopathy is not associated with improved clinical outcomes (Modic et al., 2005).
[6] Gilbert et al. (2004b) defined early imaging as having imaging performed as soon as practical. The three Webster manuscripts defined early imaging as having imaging performed ≤ 30 days after the onset of pain.

after imaging) (Webster et al., 2013).[7] The authors reported that total costs were significantly higher in the early-MRI group than the no-MRI group for both nonspecific low back pain patients and radiculopathy patients (Webster et al., 2013).

3.3.3 Downstream Services Used

Seven of the nine studies examined downstream service use, and four of these reported imaging in a low-value population. Key downstream services examined by these studies were surgery (or referrals), physical therapy (or referrals), additional imaging, and injections. Frequency of spinal or low-back surgery after early imaging was 6.9% after 3 months of follow-up and 22.0% after 2 years of follow-up (Webster et al., 2014; Webster et al., 2010); the 6-month adjusted relative risk of receiving surgery for early imaging patients ranged from 28 to 34 times more likely than patients with less-severe low back pain who did not receive an MRI (Webster et al., 2014).[8] Although imaging timing was not specified, one study found that the adjusted probability of low back surgery after an MRI among Medicare patients of orthopedists was 34.1% (Shreibati et al., 2011). Frequency of physical therapy after early imaging was estimated to be 63% after 2 years of follow-up, whereas outpatient visits after early imaging were reported to range from 70.7% to 83.5% after 2 years of follow-up (Gilbert et al., 2004b). Follow-up imaging rates following early imaging ranged from 7.6% among patients with less-severe low back pain after 3 months of follow-up to 17.0% among patients with more-severe low back pain after 6 months of follow-up; the 6-month relative risk of follow-up imaging for early imaging patients ranged from 18 to 21 times more likely compared to patients with less-severe low back pain who did not receive an MRI (Webster et al., 2014).[8] Injection (e.g., epidural steroids) frequencies after early imaging ranged from 17.8% after 2 years of follow-up among low back pain patients to 46.4% after 6 months of follow-up among patients with more-severe low back pain (Gilbert et al., 2004b; Webster et al., 2014). Adjusted relative risk of injection for early imaging patients was 27 to 33 times more likely after 6 months of follow-up compared with patients with less-severe low back pain who did not receive an MRI (Webster et al., 2014).[8] Other downstream services reported include emergency department readmission, hospital

[7] The authors used the following variables in the multivariate model: age, sex, job tenure, jurisdiction state, morphine equivalent amount in first 15 days, time to first lumbar MRI, and average weekly medical costs before the MRI.

[8] Using low back pain claims from a workers' compensation administrative data source, Webster et al. (2014) stratified the exposure by MRI timing (no MRI, early MRI, and timely MRI) and by case severity (less severe and more severe) to create 6 groups. No MRI cases did not receive an MRI in the 2-year study period, early MRI cases received an MRI within the first 30 days of pain onset, and timely MRI received an MRI within 42 to 180 days of pain onset. Severity was based on International Classification of Diseases, Revision 9 (ICD-9) diagnosis codes; severe cases included codes for herniated disc, lumbar radiculopathy or neuropathy, spinal stenosis, sciatica, or possible instability while less-severe cases included codes for degenerative changes, nonspecific back pain, or miscellaneous changes. For adjusted analyses, the models adjusted for age, sex, job tenure, and use of early opioids; the reference population was early MRI cases with less-severe low back pain.

admission, referral to a spine specialist, synovial cyst rupture, narcotic prescription, and electromyography/nerve conduction velocity.

3.4 PCI in Stable Coronary Disease

PCI involves either balloon angioplasty or stenting to improve blood flow from blocked arteries to the heart (Choosing Wisely, 2014; Reed et al., n.d.). In patients with acute coronary conditions, this can be beneficial in reducing the risk of death and heart attack. However, several studies have found that in patients with stable coronary artery disease, these procedures do not substantively reduce the risk of negative health outcomes such as heart attack, stroke, or death (Choosing Wisely, 2014; Reed et al., n.d.). The procedures are also costly and carry risks for the patient. Choosing Wisely® recommends against PCI in patients with stable coronary disease (Choosing Wisely, 2014; Reed et al., n.d.).

Our initial search identified 38 manuscripts examining downstream costs and service use after PCI for individuals with stable coronary disease and 8 were added through our review of the full text of included manuscripts. After reviewing the full manuscripts, 34 studies were determined to be eligible for data extraction and summary per our inclusion criteria. The remaining 12 studies were excluded for not having relevant downstream outcomes (Abdelnoor et al., 2017; Amin et al., 2012; Bonaventura et al., 2012; Brophy et al., 2005; Fischell et al., 2006; Glaser et al., 2009; Jabara et al., 2008; Takura et al., 2017), for having the wrong population (Maud et al., 2010; Morgan et al., 2010; Weaver et al., 2000), or for lacking evidence (Escarcega et al., 2010). Of the included studies, 17 were RCTs, 4 were observational, and 13 were economic evaluations/evidence syntheses. The quality of evidence for the studies ranged from high to low.

Twenty-two of the included studies examined downstream service use, and 11 of these reported use in a low-value population. Key downstream services examined by these studies include coronary artery bypass surgery (CABG), repeat PCI, any revascularization (PCI or CABG), target lesion revascularization, target vessel revascularization, coronary angiograph, hospitalizations, and outpatient visits. Note that there is some overlap between these outcomes (i.e., any revascularization includes repeat PCI), and they are reported as described in their respective studies. The rates of these outcomes varied widely from study to study, ranging from less than one percent for CABG within 1 year, to 55.7% for outpatient visits within 1 year. Twenty-eight of the included studies examined downstream cost, and 15 of these reported cost in a low-value population. Among the RCTs with stable coronary disease patients, costs per patient were $5,559 at 2.5 years of follow-up and $137,051 at lifetime follow-up. Additional detail on these studies can be found in Table 3-5 and in Appendix 4.

Table 3-5. Summary of Key Findings and Quality Rating: PCI in Stable Coronary Disease

Outcomes	N Studies by Study Type (study population)	Results by Study Type (country of focus)	Sources and Quality Rating
Cost			
Mean per patient	15 RCT (6 with mix of stable and unstable CD; 9 with all stable CD)	Among patients with stable CD, costs ranged from *$5,559* in 2.5 years of follow-up (median follow-up time) (Denmark) to $137,051 for lifetime costs (USA and Canada). Among patients with stable and unstable CD, costs ranged from $11,255 (Europe and Canada) to $46,170 (USA) in 1 year of follow-up.	Zhang et al. (2011),*** Mark et al. (2009),*** Hlatky et al. (2009),*** Hambrecht et al. (2004),*** Gaster et al. (2003),** Fearon et al. (2013),*** Fearon et al. (2018),*** Favarato et al. (2003),*** Zhang et al. (2005),** Weintraub et al. (2004),** Weintraub et al. (2008),*** van Hout et al. (2005),** Serruys et al. (2001),** Cohen et al. (2012)**
	3 observational (2 with mix of stable and unstable CD; 1 with all stable CD)	Among patients with stable CD, costs ranged from $13,242 (BMS) to $15,613 (DES) in 2 years of follow-up (Taiwan). Among patients with stable and unstable CD, costs ranged from $8,540 in 6 months of follow-up (BMS; South Korea) to $20,497 in 2 years of follow-up (DES; Italy).	Hung et al. (2011),* Varani et al. (2010),* Lee et al. (2014)*
	11 syntheses (6 with mix of stable and unstable CD; 5 with all stable CD)	Among patients with stable CD, costs ranged from $7,715 in 1 year of follow-up (BMS; France) to $36,097 in 5 years of follow-up (country not specified). Among patients with stable and unstable CD, costs ranged from $2,195 in 1 year of follow-up (BMS for public institutions; Brazil) to $59,551 in 4 years of follow-up (USA).§ One study estimated the lifetime cost to be $185,543 (USA).	Wijeysundera et al. (2013),* Gada et al. (2012),** Caruba et al. (2014),*** Caruba et al. (2015),*** Beresniak et al. (2015),** Zhang et al. (2015),* Shrive et al. (2005),** Saadi et al. (2011),* Polanczyk et al. (2007),* Kuukasjärvi et al. (2007),* Brunner-La Rocca et al. (2007)**
Service use			
CABG	10 RCTs (4 with all stable CD, 6 with mix of stable and unstable CD)	Among patients with stable CD, frequency ranged from 0.7% in 1 year of follow-up (Germany) to 17% in 2.5 years of follow-up (median follow-up time) (Denmark). Among patients with stable and unstable CD, frequency ranged from 0.3% (BMS) in 1 year of follow-up (Netherlands) to 9% in 3 years of follow-up (Europe and Canada).	Gaster et al. (2003),** Hambrecht et al. (2004),*** Mark et al. (2009),*** Zeymer et al. (2003),*** Serruys et al. (2001),** van Hout et al. (2005),** SoS Investigators (2002),** Zhang et al. (2005),** Weintraub et al. (2004)**

(continued)

Table 3-5. Summary of Key Findings and Quality Rating: PCI in Stable Coronary Disease (continued)

Outcomes	N Studies by Study Type (study population)	Results by Study Type (country of focus)	Sources
	1 observational (mix of stable and unstable CD)	Frequency ranged from 2.6% to 3.9% after 1 year of follow-up (Scotland).	Denvir et al. (2007)**
	1 synthesis (mix of stable and unstable CD in 29 RCTs)	Pooled across ≤ 29 RCTs, unadjusted frequency was 2.8% after 6 to 16 months of follow-up (multiple countries).	Brophy et al. (2003)**
Repeat PCI	11 RCTs (4 with all stable CD, 7 with mix of stable and unstable CD)	Among patients with stable CD, frequency ranged from 4% in 1 year of follow-up (USA) to 61% in 2.5 years of follow-up (median follow-up time) (Denmark). Among patients with stable and unstable CD, frequency ranged from 0% (DES) to 22.9% (BMS) in 1 year of follow-up (Netherlands).	Clavijo et al. (2016),** Gaster et al. (2003),** Mark et al. (2009),*** Zeymer et al. (2003),*** Cohen et al. (2012),** Serruys et al. (2001),** van Hout et al. (2005),** SoS Investigators (2002),** Weintraub et al. (2008),*** Weintraub et al. (2004),** Zhang et al. (2005),**
	1 observational (mix of stable and unstable CD)	Frequency ranged from 9.2% to 11.7% after 1 year of follow-up (Scotland).	Denvir et al. (2007)**
	1 synthesis (mix of stable and unstable CD in 29 RCTs)	Pooled across ≤ 29 RCTs, unadjusted frequency was *16.3%* after 6 to 16 months of follow-up (multiple countries).	Brophy et al. (2003)**
Any revascularization (PCI or CABG)	5 RCTs (2 with all stable CD, 3 with mix of stable and unstable CD)	Among patients with stable CD, the lowest frequency was 10.3% in 3 years of follow-up (Europe and North America), and the highest was 12.2% in 1 year of follow-up (Brazil). Among patients with stable and unstable CD, frequency ranged from 15.5% (Europe and Canada) to 21% (Netherlands) in 1 year of follow-up.	Favarato et al. (2003),*** Fearon et al. (2018),*** Serruys et al. (2001),** SoS Investigators (2002),** Zhang et al. (2005)**
	1 observational (mix of stable and unstable CD)	Frequency ranged from 11.3% to 15.1%% after 1 year of follow-up (Scotland).	Denvir et al. (2007)**

(continued)

Table 3-5. Summary of Key Findings and Quality Rating: PCI in Stable Coronary Disease (continued)

Outcomes	N Studies by Study Type (study population)	Results by Study Type (country of focus)	Sources
Target lesion revascularization (repeat PCI or CABG)	2 RCT (1 with all stable CD; 1 with mix of stable and unstable CD)	Among patients with stable CD, frequency was *4%* (2 of 50) in 1 year of follow-up (Germany). Among patients with stable and unstable CD, frequency ranged from 0.8% (DES) to 23.6% (BMS) in 1 year of follow-up (Netherlands).	Hambrecht et al. (2004),*** van Hout et al. (2005)**
	1 observational (all stable CD)	Frequency ranged from 5% (DES) to 16% (BMS) in 1 year of follow-up and 8% (DES) to 19% (BMS) in 2 years of follow-up (Taiwan).	Hung et al. (2011)*
	2 synthesis (mix of stable and unstable CD)	Among diabetic patients, frequency ranged from 3.2% in 1 year of follow-up (DES; USA) to 13.2% in 6 months to 1 year of follow-up (BMS; 11 RCTs in multiple countries).	Babapulle et al. (2004),*** Saadi et al. (2011)*
Target vessel revascularization	3 observational (2 with mix of stable and unstable CD; 1 with all stable CD)	Among patients with stable CD, frequency ranged from 8% (DES) to 19% (BMS) in 1 year of follow-up and 12% (DES) to 22% (BMS) in 2 years of follow-up (Taiwan). Among patients with stable and unstable CD, frequency ranged from 5.1% in 1 year of follow-up (Scotland) to 15.9% in 2 years of follow-up (BMS; Italy).	Hung et al. (2011),* Varani et al. (2010),* Denvir et al. (2007)**
Coronary angiograph	2 RCT (1 with mix of stable and unstable CD; 1 with all stable CD)	Among patients with stable CD, frequency was 8.3% in 1 year of follow-up (Brazil). Among patients with stable and unstable CD, frequency ranged from 8.3% (DES) to 14.1% (BMS) in 1 year of follow-up (Netherlands).	Favarato et al. (2003),*** van Hout et al. (2005)**
Hospitalizations	5 RCT (all stable CD)	Frequency ranged from 4.0% in 1 year of follow-up (Germany) to *19.7%* (88 events among 447 patients) in 1 year of follow-up (Germany). One study reported the mean rate of cardiac hospitalizations to be 1.83 for PCI patients in 4 years (compared to 1.4 for medical therapy patients, difference $p < 0.001$) (multiple countries).	Clavijo et al. (2016),** Zeymer et al. (2003),*** Fearon et al. (2013),*** Hambrecht et al. (2004),*** Hlatky et al. (2009)***

(continued)

Table 3-5. Summary of Key Findings and Quality Rating: PCI in Stable Coronary Disease (continued)

Outcomes	N Studies by Study Type (study population)	Results by Study Type (country of focus)	Sources
Outpatient visits	2 RCT (all stable CD)	Frequency was *55.7%* (249 events among 447 patients) in 1 year of follow-up (Germany). One study reported the mean rate to be 112 for PCI patients in 4 years (compared to 109 for medical therapy patients, difference p = 0.47) (multiple countries).	Favarato et al. (2003),*** Hlatky et al. (2009)***

Note: All costs are reported in 2018 U.S. dollars. Italicized estimates were calculated for the literature review. BMS = bare metal stent PCI, CD = coronary disease, DES = drug eluting stent PCI, RCT = randomized controlled trial.

* Indicates the study received a low rating

** Indicates the study received a moderate rating

*** Indicates the study received a high rating

§ The synthesis study with a mix of stable and unstable CD patients with the next lowest mean per patient cost was $5,989 in 2 years of follow-up (country not specified) (Kuukasjärvi et al., 2007).

3.4.1 Population

Seventeen of the 34 included studies focused on PCI with stable coronary disease (the low-value population); estimates based on patients with stable coronary disease are reported separately. Most studies focused on comparing different types of procedures, including different types of PCI stents (bare metal stent [BMS], drug eluting stents [DES], no stent/balloon angioplasty, PCI guiding methods), different procedures (CABG), or therapies (11 studies compared PCI to medical therapy). For this report, results focus on estimates for the PCI group; these estimates are aggregated regardless of the stent and/or method (though results will identify the stent type when specified in the study).

3.4.2 Downstream Costs

Twenty-eight of the included studies examined downstream cost; 15 of these reported cost in a low-value population. Costs were reported as mean cost per patient, and all included the cost of the initial service and some amount of follow-up treatment. Follow-up time ranged from 6 months to lifetime. Among RCTs that only included patients with stable coronary diseases, the lowest mean cost per patient was *$5,559* in 2.5 years (median) of follow-up (total observed costs divided by number of patients), and the highest was $137,051 in lifetime costs (Gaster et al., 2003; Weintraub et al., 2008). The RCT with the highest cost included stable patients with angina pectoris (a low-value population); the RCT with the lowest cost included younger patients (≤ 70 years) with coronary disease. In one observational study that included only patients with stable coronary disease, costs ranged from $13,242 (BMS) to $15,613 (DES) after 2 years of follow-up (Hung et al., 2011). In the

evidence syntheses/economic analyses, the lowest cost for stable coronary disease patients was $7,715 (BMS) after 1 year of follow-up, and the highest was $36,097 after 5 years of follow-up (Caruba et al., 2015; Gada et al., 2012).

3.4.3 Downstream Services Used

Twenty-two of the included studies examined downstream service use; 11 of these reported use in a low-value population. Key downstream services examined by these studies include CABG, repeat PCI, any revascularization (PCI or CABG), target lesion revascularization, target vessel revascularization, coronary angiograph, hospitalizations, and outpatient visits. Because of the volume of studies, studies discussed here include RCTs that focused entirely on stable coronary disease patients for the reported downstream services (except target vessel revascularization, which is reported by observational studies). The RCTs found that among stable coronary disease patients, the lowest frequency of downstream CABG was 0.7% in 1 year of follow-up, and the highest was 17% in 2.5 years (median) follow-up (Gaster et al., 2003; Zeymer et al., 2003); in contrast, the lowest frequency of repeat PCI was 4% in 1 year of follow-up, and the highest was 61% in 2.5 years (median) follow-up (Clavijo et al., 2016; Gaster et al., 2003). For any downstream revascularization, the lowest reported frequency in stable coronary disease patients was 10.3% in 3 years of follow-up (in Europe and North America), and the highest was 12.2% in 1 year of follow-up (in Brazil) (Favarato et al., 2003; Fearon et al., 2018). Specifically, in stable patients, target lesion revascularizations were reported to have a frequency of 4% (two events among 50 patients) in 1 year of follow-up (Hambrecht et al., 2004). Stable coronary disease patients were observed to have an 8.3% frequency of coronary angiographs in 1 year of follow-up (Favarato et al., 2003), a range of 4.0% to 19.7% for hospitalizations in 1 year (Hambrecht et al., 2004; Zeymer et al., 2003), and a 55.7% frequency of outpatient visits (Favarato et al., 2003). In one observational study with stable coronary disease patients, the frequency of target vessel revascularizations ranged from 8% in 1 year of follow-up to 22% in 2 years of follow-up (Hung et al., 2011). Other services include cardiac catheterization only, coronary angiograms, and angioplasties.

3.5 Stress Testing for Stable Coronary Disease

Stress testing is used to identify patients with coronary disease and those at high risk of a future heart attack (Choosing Wisely, 2012b, 2012d). However, among stable patients who have an established diagnosis of coronary disease without any change in their clinical symptoms, the test may be of limited value. Although stress testing carries little risk to a stable patient, it is costly, particularly when accompanied by nuclear or echocardiographic imaging. More importantly, an unclear result can result in additional testing or procedures such as cardiac catheterization and interventions that will not necessarily help patients and may even carry risks and costs for the patient. Choosing Wisely® recommends against exercise stress testing for stable, asymptomatic patients (Choosing Wisely, 2012c).

Our initial search identified five abstracts examining stress testing in patients with stable coronary disease. After further review of the full manuscripts, two studies were determined to be eligible for data extraction and summary per our inclusion criteria. The other three studies (Bertoldi et al., 2017; Shaw et al., 2011; Zacharias et al., 2017) were excluded because the studies examined stress testing for the purpose of initial diagnosis of coronary disease; this is not considered a low-value service. Of the two included studies, one was observational, and one study was an RCT. Both studies were graded as having moderate quality, and the information extracted is described in Table 3-6.

Both studies reported downstream use of PCI and CABG in their respective populations. PCI rates ranged from 9% to 31%, and CABG frequency ranged from 3% to 15% in 5 years of follow-up for patients with known coronary disease. Downstream cost estimates ranged from $6,669 to $9,649 within 3 years of follow-up for patients with known or suspected coronary disease; lifetime cost estimates ranged from $145,437 to $146,858 per patient with known or suspected coronary disease. Additional detail on these studies can be found in Appendix Table 3-6 and in Appendix 4.

Table 3-6. Summary of Key Findings and Quality Rating: Stress Testing for Stable Coronary Disease

Outcomes	N Studies by Study Type (study population)	Results by Study Type (country of focus)	Source and Quality Rating
Cost			
Total observed	1 RCT (known or suspected CD)	Costs ranged from $8,103 to $9,649 per patient in 3 years of follow-up (UK).	Thom et al. (2014)*
	1 observational (known or suspected CD)	Total costs ranged from $25.3 million to $26.2 million in 3 years *(approximately $6,669 to $6,783 per patient)* (USA).§ Note that these costs also included societal economic costs.	Marwick et al. (2003)**
Lifetime	1 observational (known or suspected CD)	Lifetime costs ranged from $557.5 million to $561.4 million *(approximately $145,437 to $146,858 per patient)* (USA).§ Note that these costs also included societal economic costs.	Marwick et al. (2003)**

(continued)

Table 3-6 Summary of Key Findings and Quality Rating: Stress Testing for Stable Coronary Disease (continued)

Outcomes	N Studies by Study Type (study population)	Results by Study Type (country of focus)	Source and Quality Rating
Service use			
PCI	1 RCT (known or suspected CD)	Frequency ranged from *21%* to *27%* after 3 years of follow-up for known or suspected CD patients (UK).	Thom et al. (2014)*
	1 observational (known CD)	Risk-adjusted rate ranged from 9% to 31% after 5 years of follow-up for known CD patients (USA).¥	Marwick et al. (2003)**
CABG	1 RCT (known or suspected CD)	Frequency ranged from *12%* to *15%* after 3 years of follow-up for known or suspected CD patients (UK).	Thom et al. (2014)*
	1 observational (known CD)	Risk-adjusted rate ranged from 3% to 12% after 5 years of follow-up for known CD patients (USA).¥	Marwick et al. (2003)**

Note: All costs are reported in 2018 U.S. dollars. Italicized estimates were calculated for the literature review. CD = coronary disease

* Indicates the study received a low rating

** Indicates the study received a moderate rating

*** Indicates the study received a high rating

§ The total observed cost and the estimated lifetime costs were calculated for 3,860 exercise echocardiography patients and 3,796 exercise electrocardiography patients. Costs also included the societal economic cost for cardiac death (Marwick et al., 2003).

¥ The risk-adjusted model included cardiac risk factors, symptoms, prior myocardial infarction, and a propensity score (Marwick et al., 2003).

3.5.1 Stress Tests Examined

One observational study (Marwick et al., 2003) examined the downstream use and costs of exercise echocardiography (stress test with imaging) and of exercise electrocardiography (stress test without imaging). The second study, an RCT, (Thom et al., 2014) examined the downstream use and costs of single photon emission CT (stress test with imaging; SPECT), cardiac MRI (stress test with imaging), stress echocardiography (stress test with imaging), and coronary angiography (not a stress test). Coronary angiography results were not included because coronary angiography is not a stress test.

3.5.2 Population

Both included studies compared downstream cost and use after specific stress tests (with and without imaging) among patients with known or suspected coronary disease. The observational study separately reported downstream service use for known coronary

disease. However, neither study allows for exact estimation of downstream costs for patients with known stable coronary disease because both studies include costs for patients with suspected coronary disease. Estimates based on patients with known coronary disease are reported when possible.

3.5.3 Downstream Costs

Both studies reported total observed downstream spending after stress tests, and the observational study included societal economic costs and calculated the lifetime cost. Total observed costs calculated in the RCT ranged from $8,103 to $9,649 per patient with known or suspected coronary disease after 3 years of follow-up when the initial service and follow-up costs were included (Thom et al., 2014). The observational study estimated total observed costs to be $25.3 million to $26.1 million (calculated to be approximately $6,669 to $6,783 per patient) for patients with known or suspected coronary disease after 3 years of follow-up; this study included the societal economic cost for cardiac death in the cost calculation (Marwick et al., 2003). This study also estimated the lifetime cost of stress testing in patients with known or suspected coronary disease to be $557.5 million to $561.4 million (approximately $145,437 to $146,858 per patient; this estimate includes the societal economic cost of cardiac death) (Marwick et al., 2003).

3.5.4 Downstream Services Used

Both studies reported downstream use of PCI and CABG after stress tests in their respective populations. For PCI, the observational study reported that the risk-adjusted rate of PCI among known coronary disease patients ranged from 9% to 31% in up to 5 years of follow-up (Marwick et al., 2003).[9] The RCT reported the frequency of PCI among known or suspected coronary disease patients as ranging from 21% to 27% in 3 years of follow-up (Thom et al., 2014). For CABG, the observational study reported the risk-adjusted rate of CABG as ranging from 3% to 12% in up to 5 years for known coronary disease patients (Marwick et al., 2003),[9] and the RCT reported frequency ranged from 12% to 15% in 3 years among patients with known or suspected coronary disease (Thom et al., 2014). Other downstream services reported include catheterization, revascularization, other hospital admission, imaging (angiography, SPECT, cardiac MRI, echocardiography, PET scan), and other types of visits (follow-up, outpatient).

3.6 Carotid Endarterectomy in Asymptomatic Patients

Carotid endarterectomy is a surgical procedure designed to clear a blockage of the carotid artery (Choosing Wisely, 2013a). It is considered most useful in patients with a blockage who have had symptoms such as a stroke or transient ischemic attack, or in patients with a severe blockage (> 70%) and no symptoms between 40 and 75 years of age who receive

[9] The risk-adjusted model included cardiac risk factors, symptoms, prior myocardial infarction, and a propensity score (Marwick et al., 2003).

care at a center that achieves a low risk of surgical complications (< 3% surgical mortality). However, in other asymptomatic patients, including those over the age of 75 or those with less significant narrowing (< 70%), it may be of lower value (Choosing Wisely, 2013a, 2013c).[10] Carotid endarterectomy is an expensive, invasive procedure that carries risks including stroke (which it is intended to prevent) (Choosing Wisely, 2013a). Choosing Wisely® recommends against carotid endarterectomy in asymptomatic patients unless they present with a severe blockage and are at low risk for complications (Choosing Wisely, 2013c).

Our initial search identified 10 abstracts. After further review of the full manuscripts, 5 studies were determined to be eligible for data extraction and summary per our inclusion criteria. The remaining 5 studies were excluded for insufficient sample size (Kim et al., 2014), no relevant downstream outcomes (Dakour-Aridi et al., 2018; Illig et al., 2003; Luebke et al., 2016), and wrong population (i.e., recurrent carotid endarterectomy is not a low-value service) (Jain et al., 2007). Of the included studies, one was observational and four were evidence syntheses. The quality of evidence for the studies ranged from moderate to high.

One observational study (Wallaert et al., 2016) reported that among asymptomatic patients, the cost of carotid endarterectomy and its follow-up procedures ranged from $10,313 to $20,875 after 2 years of follow-up. The remaining studies, which were all evidence syntheses or economic evaluations, reported lifetime costs broken down by age, gender, or percent stenosis. Only one study, Wallaert et al. (2016), examined downstream services, specifically readmission and reintervention at 2 years. Additional detail on these studies can be found in Table 3-7 and in Appendix 4.

3.6.1 Population

Four studies included asymptomatic patients only (Henriksson et al., 2008; Pandya et al., 2015; Thapar et al., 2013; Wallaert et al., 2016), and one study included a mix of symptomatic and asymptomatic patients (Kilaru et al., 2003). The low-value population is asymptomatic patients with less-severe blockages (< 70% stenosis). One study (Pandya et al., 2015) reported costs for the low-value population separately (patients with 50% to 69% stenosis); no studies separately reported services for this population. Three studies included a mix of patients with more- and less-severe blockages (Henriksson et al., 2008; Thapar et al., 2013), and two studies included only patients with more-severe blockages (>70% stenosis) (Kilaru et al., 2003; Pandya et al., 2015).

[10] Studies that use administrative claims data cannot determine the level of stenosis or blockage in patients. Instead, these studies use a history of stroke or transient ischemic attack as a proxy for high levels of stenosis (Schwartz et al., 2015).

Table 3-7. Summary of Key Findings and Quality Rating: Carotid Endarterectomy in Asymptomatic Patients

Outcomes	N Studies by Study Type (included study population)	Results by Study Type (country of focus)	Source and Quality Rating
Cost			
Mean per patient	1 observational (all asymptomatic)	For asymptomatic patients with no % stenosis specified, costs ranged from $10,313 to $20,875 in 2 years (USA).	Wallaert et al. (2016)**
Mean per patient, 60-69 years old	3 synthesis (all asymptomatic)	For asymptomatic patients with no % stenosis specified, costs ranged from $10,183 for lifetime follow-up (UK) to $28,778 for 5-year follow-up (Sweden). For asymptomatic patients with 50–69% stenosis, cost was $27,703 for lifetime follow-up (USA).	Thapar et al. (2013),*** Pandya et al. (2015),*** Henriksson et al. (2008)**
Mean per patient, 70-79 years old	3 synthesis (2 all asymptomatic, 1 mix of symptomatic/ asymptomatic)	For asymptomatic patients, costs ranged from $21,813 for 5-year follow-up (no % stenosis specified; Sweden) to $24,548 for lifetime follow-up (50–69% stenosis) (USA). For symptomatic and asymptomatic patients with no % stenosis specified, cost estimated to be $46,288 for lifetime follow-up (USA).	Pandya et al. (2015),*** Henriksson et al. (2008), Kilaru et al. (2003)*
Mean per patient, 80 years old	1 synthesis (all asymptomatic)	For asymptomatic patients with 50–69% stenosis, cost was $21,785 for lifetime follow-up (USA).	Pandya et al. (2015)***
Service use			
Readmission§	1 observational (all asymptomatic)	For asymptomatic patients with no % stenosis specified, frequency ranged from 10.2% to 14.4% after 2 years of follow-up (USA).	Wallaert et al. (2016)**
Reintervention	1 observational (all asymptomatic)	For asymptomatic patients with no % stenosis specified, frequency ranged from 5.8% to 7.7% after 2 years of follow-up (USA).	Wallaert et al. (2016)**

Note: All costs are reported in 2018 U.S. dollars. Italicized estimates were calculated for the literature review.

* Indicates the study received a low rating

** Indicates the study received a moderate rating

*** Indicates the study received a high rating

§ Readmission was deemed to be related to the initial procedure if the admission occurred within 30 days of discharge for the initial procedure, and reintervention was defined as a "revisional procedure (either CEA or carotid artery stent) or progression of contralateral carotid stenosis requiring revascularization (CEA or CAS [carotid angioplasty and stenting])" (Wallaert et al., 2016).

3.6.2 Downstream Costs

One observational study reported that among asymptomatic patients (with percent stenosis not specified), the mean cost of carotid endarterectomy and its follow-up procedures ranged from $10,313 to $20,875 after 2 years of follow-up (Wallaert et al., 2016). The remaining studies (which are evidence syntheses or economic evaluations) reported costs broken down by age, gender, or percent stenosis. The lowest cost reported for asymptomatic individuals between 60 and 69 years (with percent stenosis not specified) was $10,183 per patient after lifetime follow-up (Thapar et al., 2013), and the highest was $28,778 per patient after 5 years of follow-up (Henriksson et al., 2008). Cost was estimated to be $27,703 per patient for lifetime follow-up for asymptomatic patients who were at least 60 years of age with 50% to 69% stenosis (Pandya et al., 2015). For asymptomatic individuals from 70 to 79 years, costs could be as low as $21,813 after 5 years of follow-up (with percent stenosis not specified) to as high as $24,548 after lifetime follow-up (with 50% to 69% stenosis) (Henriksson et al., 2008; Pandya et al., 2015). In asymptomatic patients who were at least 80 years of age with 50% to 69% stenosis, estimated cost was $21,785 per patient for lifetime follow-up (Pandya et al., 2015).

3.6.3 Downstream Services Used

Wallaert et al. (2016) examined downstream services, specifically frequency of readmission and reintervention associated with the initial CEA at 2 years among asymptomatic patients (with percent stenosis not specified).[11] The authors reported that the frequency of readmission among asymptomatic patients ranged from 10.2% to 14.4%, depending on patients' risk-of-death level at 2 years. Similarly, the frequency of reintervention ranged from 5.8% to 7.7% at 2 years.

[11] Wallaert et al. (2016) defined readmission to be related to the initial procedure if the admission occurred within 30 days of discharge for the initial procedure. The authors defined reintervention as a "revisional procedure (either CEA or carotid artery stent) or progression of contralateral carotid stenosis requiring revascularization (CEA or CAS [carotid angioplasty and stenting])."

4. Discussion

Low-value health care continues to be an important issue for health care policymakers, and downstream spending and service use is an important component of the overall impact these services have on the U.S. health care system. In this literature review, we examined the health care service use and spending that occurs downstream of five measures of low-value care: PSA testing, back imaging for nonspecific low back pain, PCI for patients with stable coronary disease, stress testing for stable coronary disease, and carotid endarterectomy for asymptomatic patients. Each of these services has been defined in the literature as being of potentially low value in their respective populations, either because the potential risks outweigh the potential benefits or because there is little or no clinical benefit. An important aspect of low-value care is subsequent testing and service use, which often carry additional costs and risks. To date, however, evidence specifically examining these downstream activities has not been consistently examined. Furthermore, much of the literature examining downstream spending consists of evidence syntheses and economic analyses, which typically combine the results of trials and observational studies examining the likelihood of certain outcomes to estimate total downstream spending. Literature directly examining downstream spending (i.e., where cost data are drawn from the same population/study as outcome data) is far more limited, and a great deal remains unexplored. As such, the total spending and service utilization reported across studies in this review varied widely. In general, however, downstream spending was higher for cardiac procedures and imaging; this spending aligns with MedPAC's previously published spending estimates from the initial low-value services (MedPAC, 2017).

Although some downstream services were common to nearly all studies of a particular low-value service (e.g., biopsy after a positive PSA test), others were less consistent. For example, although six of the seven studies examining services downstream of low back pain imaging examined subsequent surgical intervention, only one or two of the studies looked at repeat imaging or outpatient visits. Differences in the downstream services included in a study may be caused by different definitions of what services are considered downstream (e.g., is physical therapy directly related to receiving imaging for low back pain?) or challenges in attributing the downstream service to the initial low-value service (e.g., repeat PCI as previously described)

Similarly, studies that examined downstream spending typically quantified that spending by attributing cost values to downstream service use, and the types of services they chose to include varied considerably from study to study. Some studies chose to look at all health care spending for a specified period of time. Others, such as economic evaluations that synthesized data from multiple sources, would select a series of common downstream services or health outcomes and generate cost estimates based on the costs or prices of those events and their likelihood of occurring. Some studies include social economic costs in

addition to direct health care costs. The choice of which services to include can therefore have an important effect on the estimates of downstream spending, and the differences between cost estimates across included studies should be interpreted in that context.

4.1 Caveats to the Search Strategy and Comparisons

Each of the included manuscripts examines some form of downstream service use or health care spending following the use of the low-value service. However, not all of these studies regard the initial service itself as low value. Notably, a significant number of the studies examining the effectiveness or cost-effectiveness of PCI in stable coronary disease compared the use of different types of stents. These studies do not regard PCI for the stable coronary disease patient as low value and simply ask which stent is better. However, these studies contribute important information about the amount of health care spending and service use that occur after the initial PCI procedure, and were therefore included.

For this review, we only included studies that examined downstream health care service use or spending. As a result, numerous studies examining only the specified low-value services and health outcomes were not included. Our initial review process favored including studies if it was unclear whether downstream costs or service use were examined. However, we acknowledge that by emphasizing downstream in our search criteria, some studies examining downstream service use or spending may have been overlooked. For this reason, we also reviewed reference lists for all papers to identify any possible studies that were not found with our initial search strategies.

Additionally, although we designed our search criteria to be as inclusive as possible and manually reviewed references for systematic reviews, our search may have missed abstracts that used different terminology than we specified in our search criteria.

Costs of care were converted to 2018 U.S. dollars and service counts were converted to frequencies in an attempt to make a more-useful comparison among studies. It is important to note, however, that there are significant underlying differences in costs of care between countries and health systems not accounted for in these conversions. Prostate cancer treatment, for example, may cost far more in the United States than in Europe, and treatment strategies also improve over time. Likewise, downstream service use may vary because of country-specific regulations, the availability of certain treatments, and other factors that may not be observable in our review. Care should be taken when interpreting differences in service use and costs of care across studies.

4.2 Limitations

This review is subject to several limitations, and the results should be interpreted as such. First, the studies included in this review were conducted across several different countries and published as early as 2000 (with data collected several additional years prior). There

are potentially important differences in the medical technology, practice standards, and costs of care available to patients across the world, and they can also change considerably over time. Although we converted and inflated costs to 2018 U.S. dollars, this process does not account for how the underlying factors that drive the costs of care can change in ways that affect costs independent of general inflation.

Second, many of the studies we included do not explicitly examine the underlying population of patients for whom the services of interest are considered to be of lower value. For example, PCI is considered a low-value service when applied to patients with stable coronary disease. A number of included studies examine patient populations that include both stable and unstable coronary disease, and they do not always differentiate their results by disease severity. We elected to include these studies because they contain important information about downstream service use and spending, but the results from these studies should be interpreted with caution.

Third, many of the included studies do not have the primary purpose of examining downstream spending. For example, as previously described, many included studies were conducted to compare the total costs of care for or the cost effectiveness of different types of stents used in PCI (e.g., BMS vs. DES). Thus, significance tests and measures of uncertainty in these studies were only used to examine the cost or cost-effectiveness differences between those two groups, rather than in comparison to optimal medical therapy (i.e., no PCI). However, despite the lack of control group, these studies still present useful information about the total costs of care for patients with stable coronary disease receiving PCI and were therefore included.

Fourth, study populations often varied by study type. RCTs tended to have a much more specific population, which often did not strictly align with the population of interest in the measures of low-value care. In contrast, observational studies tended to include much broader populations, but these studies also carry limitations inherent in conducting observational data analysis (e.g., unmeasured confounding). In several cases, however, we found estimates of cost and use downstream of the low-value service that were relatively consistent across the different study types. Furthermore, we were able to separately report spending and use estimates for a low-value population for most measures.

Fifth, our reporting of downstream services was dependent on what services were reported and how they were reported in the studies. Therefore, although we can identify which downstream services were frequently reported, we are limited in our ability to state which services rarely or commonly occur downstream of a low-value service because not all studies report on the same set of downstream services. For example, a positive PSA test is usually followed by a biopsy to confirm the diagnosis of prostate cancer. In contrast, adverse outcomes following PCI may result in a number of different cardiac interventions that are not consistently reported across studies. Furthermore, some of the downstream

services examined may have been provided even in the absence of the low-value service (e.g., physical therapy after imaging for nonspecific low back pain). In cost estimates, it was often not possible to separately report costs excluding these services. More importantly, however, our aim was to report all services occurring downstream of the low-value service, to present a complete picture of patient trajectories. The "effect" of the downstream service should be interpreted in this context.

Finally, several of the low-value services included in this review yielded few studies explicitly examining service use and costs of care downstream of the low-value service. Although it is possible that studies were overlooked in our review, we suspect that for some measures, there is simply a lack of recent literature examining downstream outcomes. This may be due in part to the measures already being well-established as low value (e.g., PSA testing over age 75), or perhaps to an inherent difficulty in accurately identifying and examining the low-value service or population. For example, stress testing in patients with stable coronary disease can be difficult to capture absent an RCT given that stress testing is often done to diagnose stable coronary disease (which would not meet the criteria for low-value care), and it can be difficult to distinguish this in secondary data sources. This gap in the literature represents an important area of potential future research.

4.3 Conclusions

This review identified and examined 66 manuscripts on health care use and spending downstream of five measures of low-value health care services. These manuscripts included randomized trials, observational studies, and evidence syntheses, and generally had high or moderate quality. The studies examined a range of different downstream services and costs of care, and estimates of their likelihood and magnitude varied across studies. Downstream service use and spending are core components of what makes these health care services potentially low-value. Understanding the nature of these outcomes is essential to adequately assess and maximize the value of the health care delivered to patients. Literature examining downstream spending and service use remains limited for most measures of low-value care, making this an important area for future research to maximize the value of the health care that is delivered to patients.

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Appendix 1:
Preliminary Literature Review of 10 Low-Value Services

August 2018

Preliminary Literature Review of 10 Low-Value Services

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1. Introduction

1.1 Overview and Objective

The Medicare Payment Advisory Commission (MedPAC) seeks to better understand the use of and spending for health care services that occur downstream of a set of previously established low-value services. To that end, MedPAC is seeking a systematic review of available literature examining the evidence of these low-value services' effects on downstream service use and spending.

This memo describes our initial review of the peer-reviewed, government, and grey literature surrounding 10 measures of low-value care identified by MedPAC. The purpose of the initial review was to develop a general understanding of the scope of the literature available for each of these measures and to identify and recommend a subset of the measures for the more-thorough assessment under Task 3. Specifically, we identified available literature examining health care service use and spending occurring downstream of at least one of the low-value health care services of interest to determine which measures have sufficient published evidence to benefit from an in-depth review.

The remainder of the introduction describes the challenges associated with defining low-value services, the measures of interest in this review, and how we have conceptualized downstream service use and health care spending in this analysis. The methods section describes our search strategy, study selection, and data abstraction. The results section presents findings organized by low-value service. Finally, the discussion section summarizes the results and the low-value services that we recommend for more-thorough review and synthesis.

1.2 Low-Value Services and the Importance of Understanding Downstream Spending and Utilization

Low-value services are defined as the provision of medical services that have little or no clinical benefit or when the risk of harm outweighs the potential benefit. Experts have estimated that $200 billion is attributed to provision of low-value health care annually (Berwick & Hackbarth, 2012). Propelled by the 2010 Institute of Medicine report "The Healthcare Imperative" and initiatives like Choosing Wisely® to reduce waste and inefficiencies in care, numerous researchers and organizations have documented the identification and measurement of low-value services use among different populations, including children, elderly adults, and adults with commercial insurance (Barnett, Linder, Clark, & Sommers, 2017; Carter et al., 2017; Choosing Wisely, 2018; Chua et al., 2016; Colla et al., 2018; Mafi, Wee, Davis, & Landon, 2016; Schwartz, Landon, Elshaug, Chernew, & McWilliams, 2014; Segal et al., 2015; Yong, Saunders, & Olsen, 2010).

Using 31 measures of low-value service use identified by (Schwartz et al., 2015; Schwartz et al., 2014) MedPAC estimated the total cost of low-value health care services to Medicare in 2014 to be between $2.4 and $6.5 billion; 23 to 37 percent of beneficiaries received at least one of these low-value services (MedPAC, 2017). Among these measures, high spending in low-value service use was driven by cardiovascular tests/procedures, other surgical procedures, and imaging, while high volume was driven by imaging, cancer screening, and diagnostic and preventive testing. However, as MedPAC and others have noted, in addition to being restricted to low-value service use that can be measured using claims data, these estimates likely understate the spending on and impact of low-value service use because they do not include spending on downstream services that might result from undergoing a low-value test or procedure. Many low-value services have low or very low upfront costs to administer and cause little direct harm to patients (Mafi et al., 2017). However, these tests may result in unnecessary anxiety and a cascade of follow-up tests and procedures that harm the patient and increase health care spending. For example, cost-effectiveness research suggests that the prostate-specific antigen (PSA) screening test for prostate cancer (which costs $144 on average) accounts for a mere 2% of lifetime PSA costs (Mafi et al., 2017; Shteynshlyuger & Andriole, 2011). Understanding the health care costs and patient outcomes of subsequent services that arise from the initial low-value service is essential to quantifying the magnitude of potential savings that can be achieved by reducing these services. This evidence suggests that developing policy recommendations around low-value care services will require careful consideration of the impact on volume and spending along with the ability to accurately identify low-value service use to optimally prioritize efforts to reduce use of such services. Averting these unnecessary costs and potential adverse sequalae on patients would be an important development for Medicare, the U.S. health care system, and patients.

1.3 Downstream Health Care Service Utilization and Spending in Concept

Downstream service use and spending is an integral part of the definition of low-value care because unnecessary spending or treatments resulting from the low-value service can play a key role in what makes it low-value. In this preliminary review, we conceptualized downstream as a health care service or health care spending that occurs as a direct result of one of the low-value health care services of interest. For example, downstream service use and spending from a positive PSA test would include a biopsy used to confirm the diagnosis. A confirmed diagnosis may also result in additional cancer treatments.

In this review, we used two questions to identify studies examining downstream health care service utilization and spending. First, was the service or spending examined considered to be a result of or in any way affected by the low-value health care service of interest? For example, a study examining biopsy and cancer treatment costs after PSA testing would be considered downstream. Second, is the downstream service also a low-value service? A key

example of this is studies that examine the likelihood of repeat stenting after percutaneous coronary intervention (PCI) in patients with stable coronary disease. If the patient continues to be stable, a second stenting procedure would be of equally low value and would not be any more useful than the initial procedure. We would not consider this to be a downstream service on its own, but studies examining total costs of care after PCI would still be eligible for inclusion. Additional detail on study selection criteria can be found in the methods section.

1.4 Low-Value Services Included in This Review

Among the 31 low-value services identified by (Schwartz et al., 2015; Schwartz et al., 2014), MedPAC selected the following 10 services for preliminary review of downstream spending or utilization in peer-reviewed, government, and grey literature (Table 1-1). These measures are described in more detail in the results, including characteristics that make them low-value according to the literature.

Table 1-1. Low-Value Services Identified by MedPAC

Service	Population
PSA testing	Male patients ≥ 75 years
Hypercoagulability testing for patients with deep vein thrombosis (DVT)	Patients with DVT
Preoperative chest radiography	Patients undergoing non-cardiothoracic surgeries
Back imaging for patients with non-specific low back pain	All patients
Screening for carotid artery disease in asymptomatic adults	All patients
Screening for carotid artery disease for syncope	Syncope patients
Stress testing for stable coronary disease	Patients with ischemic heart disease
PCI with balloon angioplasty or stent placement for stable coronary disease	Patients with ischemic heart disease
Renal artery angioplasty or stenting	Patients with hypertension
Carotid endarterectomy for asymptomatic adults	All patients

2. Methods

2.1 Search Strategies

We searched PubMed®, CINAHL, the Cochrane Library, and the New York Academy of Medicine Grey Literature Database for English-language articles published between January 1, 2000, and August 3, 2018. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, measures, and outcomes. **Appendix A** describes the search strategy and terms, including exact search terms used for each database. We also conducted targeted searches for published and unpublished literature by searching the websites of Choosing Wisely®, the United States Preventive Services Task Force (USPSTF), the Centers for Medicare & Medicaid Services, the American Academy of Family Physicians, Great Britain's National Institute for Health and Care Excellence (NICE), the Patient-Centered Outcomes Research Institute, and Massachusetts Blue Cross Blue Shield. Finally, to supplement our electronic searches, we manually reviewed the reference lists of pertinent systematic review articles and added all previously unidentified relevant articles to our database.

2.2 Study Selection

We selected studies for inclusion in the preliminary review using the criteria presented in Table 2-1. Included studies must have been published in the year 2000 or later, must examine at least one of the 10 low-value health care services of interest, does not exclude the examination of either service use or spending that occurs downstream of the low-value service, must examine adults (age 18 or older, excluding studies of children only), must have a sample size of greater than 20, and must have been published in English. Systematic literature reviews were excluded, but their reference lists were manually reviewed for studies not picked up in our searches, as noted above.

We imported all references identified into EndNote X8 (Thomson Reuters, New York, NY) for abstract review. Two team members independently reviewed titles and abstracts for exclusion criteria. Studies that did not explicitly meet exclusion criteria after abstract review were retained for subsequent in-depth review. A consensus process was used to resolve disagreements, and a third team member resolved any remaining disagreements.

Table 2-1. Inclusion Criteria

	Inclusion Criteria	Rationale
Measure	Examines one of the 10 low-value services of interest	General conceptual studies are not of interest in this review. Only studies that contain one of the 10 low-value services of interest will be included.
Outcome	Does not exclude examination of downstream service use or spending	Studies that do not examine health care spending or service use downstream of the low-value service of interest are not of interest in this review. However, studies that examined spending or use but did not explicitly exclude downstream outcomes were included initially.
Study population	Study population includes adults (exclude studies of children only)	The Medicare population is primarily composed of elderly individuals. Many of the low-value services pertain to adult or elderly populations.
Study population	Sample size of 20 or more	Case studies and studies of smaller samples lack the statistical power necessary for generalizable results.
Study design	Randomized controlled trial (RCT), observational, or synthesis	Systematic literature reviews do not generate independent estimates of downstream service use or costs.
Language	Published in English	

Each included abstract was examined for the following factors: study design (randomized controlled trial [RCT], observational, or synthesis), sample size (excluding syntheses), the country where the study was conducted, measure(s) examined, whether the abstract explicitly described examining downstream service use or health care spending, and whether the study itself conceptualizes the health care service of interest as low-value care. Abstracts were identified as an RCT if specified in the abstract or if investigators applied a treatment or experiment on the study population, observational if investigators observed the study population and measured the outcome without assigning treatments, or synthesis if a decision or simulation model (e.g., meta-analysis, Markov, microsimulation, cost-effectiveness) was used to estimate downstream service use or costs (Kuntz et al., 2013). It is important to note that abstracts can at times be unclear, and content was inferred where possible with the understanding that it may be clarified upon in-depth review.

2.3 Measure Recommendations

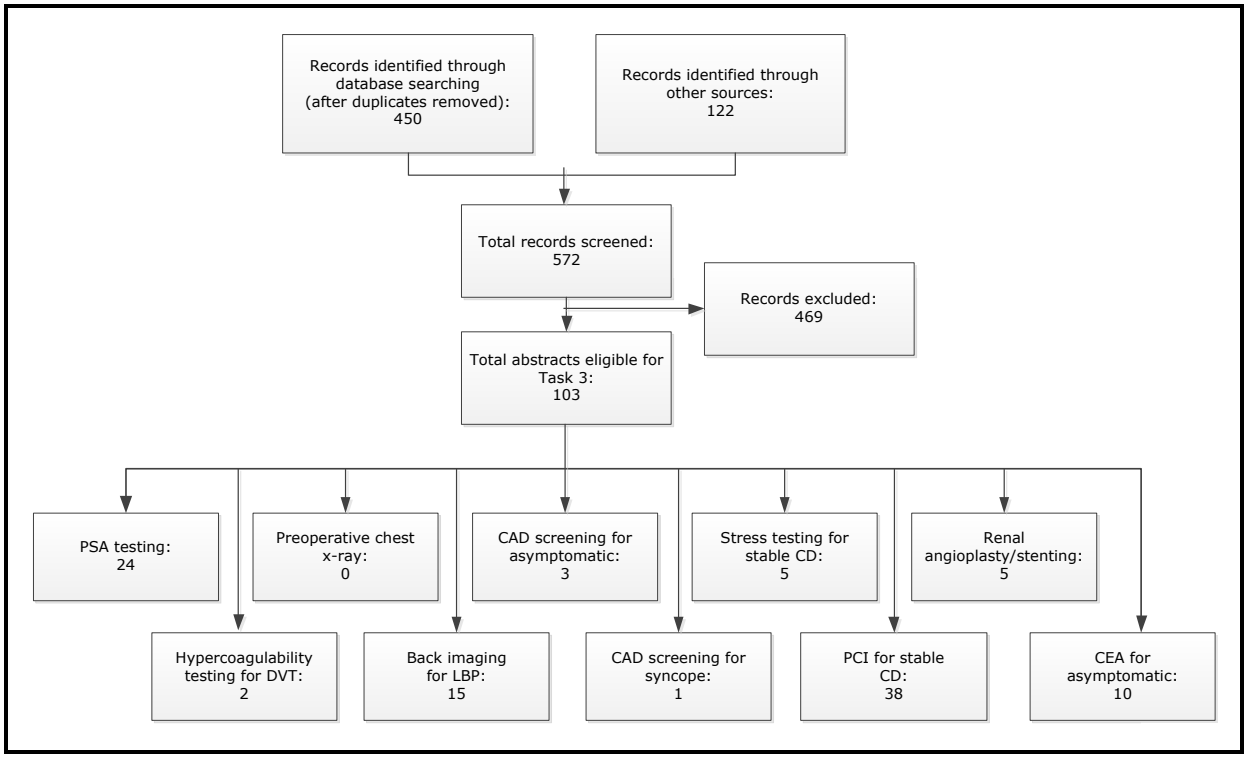
The primary selection criterion to make recommendations on which measures of low-value service use to examine in the in-depth review was the total number of studies. Ties were broken examining the type of studies; RCTs and observational studies were favored over synthesis studies because synthesis studies generally aggregate information from multiple sources, which may include the identified RCTs and observational studies.

3. Results

3.1 Overview of the Preliminary Review

Our searches yielded 572 unique abstracts. Of these, 103 were selected for inclusion based on our criteria. Figure 3-1 visualizes how these manuscripts were included by measure.

Figure 3-1. Search Results and Included Studies by Measure of Low-Value Care



Note: CAD = carotid artery disease, CD = coronary disease, CEA = carotid endarterectomy, DVT = deep vein thrombosis, LBP = low back pain, PCI = percutaneous coronary intervention, PSA = prostate-specific antigen.

Table 3-1 presents the distribution of the included studies by measure of low-value care and study design. Included studies mostly examined three measures of low-value care: PCI for stable coronary disease (38 studies), PSA testing (24 studies), and back imaging for low back pain (15 studies). The next most prevalent measures in our search were coronary endarterectomy for asymptomatic adults (10 studies), stress testing for stable coronary disease (5 studies), and renal artery angioplasty or stenting (5 studies). Less than five abstracts each were found for the remaining four measures (screening for carotid artery disease in asymptomatic adults [3 studies], hypercoagulability testing in deep vein thrombosis (DVT) patients [2 studies], screening for carotid artery disease in patients with syncope [1 study], and preoperative chest X-ray [0 studies]). Among the 103 abstracts, 26 were studies based on RCTs, 34 were observational studies, and 43 were evidence

syntheses. Below we describe how each service is considered low-value, the number of included studies by measure, and the abstracted characteristics of those studies.Appendix B presents the included manuscripts by measure, Appendix C presents the abstracted study characteristics, and Appendix D includes the complete abstracts by recommended measure.

Table 3-1. Manuscript Count by Study Design

Measure	Total	RCT	Observational	Synthesis
PSA testing	24	0	8	16
Hypercoagulability testing for DVT	2	0	0	2
Preoperative chest X-ray	0	0	0	0
Back imaging for low back pain	15	4	10	1
CAD screening for asymptomatic	3	0	1	2
CAD screening for syncope	1	0	1	0
Stress testing for stable CD	5	3	1	1
PCI for stable CD	38	17	7	14
Renal angioplasty/stenting	5	1	1	3
Carotid endarterectomy (CEA) for asymptomatic	10	1	5	4
Total	103	26	34	43

3.2 PCI in Stable Coronary Disease

PCI involves either balloon angioplasty or stenting to improve blood flow from blocked arteries to the heart (Choosing Wisely, 2014; Reed & Pearson). In patients with acute coronary conditions, this can be beneficial in reducing the risk of death and heart attack. However, several studies have found that in patients with stable coronary artery disease, these procedures do not substantively reduce the risk of negative health outcomes such as heart attack, stroke, or death (Choosing Wisely, 2014; Reed & Pearson). The procedures are also costly and carry risks for the patient. Choosing Wisely® recommends against PCI in patients with stable coronary disease (Choosing Wisely, 2014; Reed & Pearson).

Our searches identified 38 manuscripts examining downstream costs and service use after PCI for individuals with stable coronary disease. Of these, 17 were RCTs, 7 were observational studies, and the remaining 14 were evidence syntheses. Study setting varied, but 12 of the included studies were conducted in the United States. Most abstracts described examining downstream healthcare spending in some fashion, most within 1 year of the procedure. Only eight studies examined downstream service use. Also of note is that very few of these studies characterized PCI as being a low-value service for individuals with stable coronary disease.

3.3 PSA Testing

PSA testing for prostate cancer has become widely recognized in recent years as a low-value health care service, especially among individuals above age 75 (Choosing Wisely, 2013c). Studies have noted that the test lacks specificity (i.e., has a high false positive rate), resulting in unnecessary biopsies to confirm the diagnoses (Choosing Wisely, 2013c), and often "overdiagnosis" in identifying clinically insignificant cancers. The studies also note that prostate cancer treatments carry risks, are costly and painful, and may do more harm than good, especially among the elderly. Currently, Choosing Wisely® recommends against PSA testing below age 50 or above age 74 unless one is at high risk for prostate cancer and suggests that men ages 50 to 74 discuss the benefits and risks with their doctor (Choosing Wisely, 2013c). Similarly, USPSTF recommends against routing screening for men 70 years of age or older and suggests that men ages 55 to 69 discuss risks and benefits with their doctor (U.S. Preventive Services). Moreover, USPSTF only recently changed their recommendations and previously had classified all PSA testing as not recommended.

Our searches identified 24 manuscripts examining downstream costs and service use after PSA testing.[1] Of these, 8 studies were observational, and the remaining 16 were evidence syntheses. Among the observational studies, 6 were conducted in the United States(one was conducted in Taiwan and one was unclear), and nearly all examined either downstream health spending or biopsy, which is used to confirm the prostate cancer diagnosis. In contrast, the syntheses largely examined longer-term costs and quality of life. More than half of the studies explicitly identified PSA testing as a low-value health care service.

3.4 Back Imaging for Low Back Pain

Imaging such as X-rays, computed tomography (CT) scans, or magnetic resonance imaging scans (MRIs) may be used to evaluate patients presenting with non-specific low back pain (Choosing Wisely, 2012f). These scans are most important in identifying whether the pain is being caused by an emergent treatable condition such as cancer or infection. However, such outcomes are rare, and back pain usually resolves on its own or with minor medical intervention (e.g., over-the-counter pain medication). Additionally, imaging is costly and requires exposing the patient to potentially unnecessary radiation. It also can result in unnecessary surgery, which carries additional costs and risks. Both Great Britain's NICE and Choosing Wisely® recommend against routinely imaging for non-specific low back pain (Choosing Wisely, 2012c; National Institute for Health and Care Excellence, 2016a).

Our searches identified 15 manuscripts examining use of imaging for patients with low back pain that met our inclusion criteria. Of these, four were RCTs, one was a synthesis, and the remaining studies were observational. All were conducted either in the United States or Europe, and all except the synthesis describe examining either downstream service

[1] Our search strategy looked for PSA testing in general and did not limit the measure by patient age. See Appendix A for specific search terms.

utilization or health care spending after the low-value service. Seven of the studies explicitly described examining downstream spending, and twelve described examining some form of downstream service utilization. The synthesis examined costs per case and per quality-adjusted life year but did not explicitly describe whether these expenditures occurred downstream of the low-value service. Nine of the studies characterized imaging for low back pain as a low-value service.

3.5 Carotid Endarterectomy (CEA) in Asymptomatic Patients

Carotid endarterectomy is a surgical procedure designed to clear a blockage of the carotid artery (Choosing Wisely, 2013a). It is considered most useful in patients with a severe blockage or those who have had symptoms such as a stroke or transient ischemic attack, or in patients with a severe blockage and no symptoms between 40 and 75 years of age who are at low risk of complications. However, in other asymptomatic patients, it may be of lower value. CEA is an expensive, invasive procedure that carries risks including stroke and heart attack (which it is intended to prevent) (Choosing Wisely, 2013a). Choosing Wisely® recommends against CEA in asymptomatic patients unless they present with a severe blockage and are at low risk for complications (Choosing Wisely, 2013d).

Our searches identified 10 studies meeting our inclusion criteria. These included one RCT, five observational studies, and four evidence syntheses. Seven of these studies explicitly examined downstream health care spending, and none explicitly examined downstream health care service use. Four studies were explicitly identified as being conducted in the United States, but several others were unclear. Only one explicitly described the service as low value for asymptomatic patients.

3.6 Stress Testing for Patients with Stable Coronary Disease

Stress testing is used to evaluate risk of heart disease and heart attack (Choosing Wisely, 2012d, 2012e). However, among stable patients who have an established diagnosis of coronary disease, the test may be of limited value. Although stress testing carries little risk to a stable patient, it is costly, particularly when accompanied by nuclear or echocardiographic imaging. An unclear result can result in additional testing or procedures that carry risks and costs for the patient. Moreover, a "positive" test can result in cardiac catheterization and interventions that will not necessarily be helpful to patients. Choosing Wisely® recommends against exercise stress testing for stable, asymptomatic patients (Choosing Wisely, 2012g).

Our searches identified five manuscripts examining stress testing in patients with stable coronary disease that met our inclusion criteria. Of these, three were RCTs, one was an observational study, and one was an evidence synthesis. Two of these studies explicitly examined downstream spending, and two examined downstream service use. None of the

studies were clearly conducted in the United States or explicitly described the service as low-value care.

3.7 Renal Artery Angioplasty or Stenting

Renal angioplasty and stenting are sometimes used to treat difficult-to-control hypertension in patients with atherosclerotic renal artery stenosis. However, two large RCTs have shown these procedures to be of limited clinical benefit when compared with medical therapy alone (Cooper et al., 2014; Astral Investigators et al., 2009). The treatment remains of questionable value in the medical community, and organizations like Choosing Wisely® and NICE have not released official guidance on its use.

Our searches identified five manuscripts examining renal artery angioplasty or stenting that met our inclusion criteria. One study was an RCT, one was observational, and three were evidence syntheses. None of the studies were conducted in the United States. Two of these studies explicitly examined downstream spending, and two examined downstream service use. Two manuscripts explicitly described the service as low-value care.

3.8 Screening for Carotid Artery Disease in Asymptomatic Patients

Screening for carotid artery disease typically involves ultrasound imaging of the carotid artery to check for blockages that can lead to stroke. However, as noted by Choosing Wisely® and others, carotid artery blockages are rare and are unlikely to cause stroke absent other symptoms or risk factors (Choosing Wisely, 2013a, 2015). They also note that there is a high false positive rate, resulting in unnecessary follow-up testing and procedures that carry costs and risks for the patient. Choosing Wisely® recommends against screening for carotid artery disease without a history or sudden symptoms of a stroke or mini-stroke (Choosing Wisely, 2013a).

Our searches identified three manuscripts examining downstream costs and service use after screening for CAD in asymptomatic patients. Of these, one was an observational study and two were evidence syntheses. Only one of the studies (an evidence synthesis) explicitly examined downstream spending, and none explicitly examined downstream service use. Only one of the five studies was conducted in the United States. None explicitly described the service as low-value care.

3.9 Hypercoagulability Testing for Patients with DVT

Hypercoagulability (thrombophilia) testing is sometimes done as part of the evaluation of patients with DVT (Choosing Wisely, 2013e). However, this set of testing is costly and rarely affects subsequent treatment, particularly for those who present after a provoked DVT (e.g., in the setting of prolonged travel or surgery). Experts recommended reserving such workups for those at higher risk for a hypercoagulable disorder (e.g., family history, recurrent venous thromboembolism [VTE], multiple sites, etc.). Additionally, Choosing

Wisely® (Choosing Wisely, 2013e) and others have noted that the test would not change the management of VTE occurring in the setting of major transient VTE risk factors, and they therefore recommend against routine thrombophilia testing in this context.

Our searches identified two manuscripts examining downstream costs and service use after hypercoagulability testing for DVT patients. Both studies were evidence syntheses that explicitly examined downstream spending. One study was conducted in the United States. Neither explicitly described the service as low-value care.

3.10 Screening for Carotid Artery Disease for Syncope

Carotid ultrasound is sometimes used to evaluate patients presenting with syncope (Choosing Wisely, 2013b; Scott et al., 2014). However, as has been noted by Choosing Wisely® and others, simple syncope is likely unrelated to carotid artery disease, and the test therefore has limited potential benefit absent signs or symptoms of a stroke.

Our searches identified one manuscript examining screening for CAD in patients with syncope that met our inclusion criteria. This study was an observational study conducted in the United States. It explicitly described the service as low-value care.

3.11 Preoperative Chest Radiography (X-ray)

A chest X-ray is sometimes used to screen patients for medical conditions such as congestive heart failure and/or to establish a baseline before surgery (Choosing Wisely, 2012b). However, absent symptoms of heart or lung disease, this procedure may be of limited benefit before non-cardiothoracic surgery. Choosing Wisely® notes that a chest X-ray is unlikely to find anything of concern in low-risk, asymptomatic patients. It also exposes the patient to radiation. Additionally, the scan can appear misleading, indicating an abnormality where none exists. This could lead to unnecessary follow-up testing (e.g., additional, more-costly imaging), which may carry risks and costs to the patient. Choosing Wisely® recommends preoperative chest X-ray only for patients who have symptoms of a heart or lung condition or a diagnosis of heart or lung disease, whereas NICE recommends against routine chest X-ray before elective survey (Choosing Wisely, 2012a; National Institute for Health and Care Excellence, 2016b).

Our searches did not identify any manuscripts examining downstream costs and service use after preoperative chest X-ray.

4. Discussion and Recommendation

Across the 10 measures of interest, we identified 103 manuscripts that met our inclusion criteria. Most manuscripts examined downstream spending, service use, or both in 3 of the 10 specified measures. We found between 5 and 10 manuscripts for 3 other measures, and less than 5 manuscripts were found for the remaining 4 measures.

4.1 Recommendation

On the basis of our searches, we recommend selecting the following measures for in-depth review (Table 4-1). Each of these measures had five or more manuscripts identified in our searches that we believe will yield useful insights about downstream costs of care or health care service use after in-depth review. Note that the recommendation for PSA testing has been expanded to older male patients and does not specify an age cutoff.

Table 4-1. Low-Value Services Recommended for In-Depth Review

Service	Population
PCI with balloon angioplasty or stent placement for stable coronary disease	Patients with ischemic heart disease
PSA testing	Older male patients
Back imaging for patients with non-specific low back pain	All patients
Carotid endarterectomy for asymptomatic adults	All patients
Stress testing for stable coronary disease	Patients with ischemic heart disease

We recommend the first four measures for in-depth review because we identified the highest number of manuscripts for these measures. Although stress testing for stable coronary disease and renal artery angioplasty or stenting both yielded five abstracts each, we recommend in-depth review for stress testing for stable coronary disease over renal artery angioplasty or stenting because four of the five manuscripts identified for stress testing for stable coronary disease were RCTs or observations studies, as opposed to two of the five manuscripts for renal artery angioplasty or stenting. Notably, both measures had two studies conducted in Europe, two studies that were unclear in study location, and one study that was conducted in a middle-income country.

4.2 Caveats to the Search Strategy

Each of the included manuscripts examines some form of downstream service utilization or health care spending following the use of the low-value service. However, not all of these studies regard the initial service itself as low-value. Notably, a significant number of the studies examining the effectiveness or cost-effectiveness of PCI in stable coronary disease

compared the use of different types of stents. These studies do not regard PCI for the stable coronary disease patient as low value and simply ask which stent is better. However, these studies contribute important information the amount of health care spending and service utilization that occur after the initial PCI procedure, and were therefore included.

For this review, we only included studies that examined downstream health care service utilization or spending. As a result, a number of studies examining only the specified low-value services were not included. Our process favored inclusion in cases where it was unclear whether downstream costs or service utilization were examined. However, we acknowledge that by emphasizing downstream in our search criteria, it is possible that some studies examining downstream service use or spending were overlooked. For this reason, we also reviewed reference lists for all papers to identify any possible studies that were not found with our initial search strategies.

An additional important point involves our interpretation of what constitutes downstream spending and service utilization. In particular, several studies of PCI examine the likelihood of having a subsequent revascularization. In this review, however, we did not consider repeating PCI in a still-stable patient to be downstream, but rather a reoccurrence of the same low-value service. We could have done this differently, as once someone has been stented, acute stent thrombosis or in-stent reocclusions can result. Similarly, many studies examined patient health outcomes following the low-value service. However, given that we were specifically interested in downstream service use and spending, we did not include these studies unless they also examined the costs or service utilization associated with those health outcomes.

Finally, although we designed our search criteria to be as inclusive as possible and manually reviewed references for systematic reviews, our search may have missed abstracts that used different terminology than we specified in our search criteria. However, given the distribution of the studies across the measures, we do not believe that these additional studies would alter our recommendations for which measures to include for further review. For some measures, we suspect that researchers simply have not yet studied downstream costs and service use because of the inherent difficulty in defining these concepts. For example, service use downstream of preoperative chest X-ray could be conceptualized as downstream to either the X-ray or the subsequent operation.

4.3 Conclusion

We searched peer-reviewed, government, and grey literature for studies of health care service use and spending downstream of 10 previously identified measures of low-value health care services. After reviewing titles and abstracts, five measures were recommended with a sufficient number of studies identified to further examine in in-depth review. These measures (PCI for stable coronary disease, PSA testing for older men, back imaging for non-

specific low back pain, carotid endarterectomy for asymptomatic adults, and stress testing for stable coronary disease) all had at least five manuscripts that met our pre-specified inclusion criteria. Each of the manuscripts will be obtained and reviewed in-depth to extract relevant information about health care service utilization and spending downstream of the low-value services of interest.

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Appendix A.
Search Strategy and Terms

A.1 Search Overview

Last Search Run: August 3, 2018

Population: Adults ≥18 (exclude children and adolescents). Population varies by the measure in question.

Time: 2000 or later

Language: English

Sample Size: Studies with sample sizes ≥20

Study Type: Exclude dissertations and conference proceedings

Interventions: One of 10 low-value services.

Outcomes: Spending and utilization for downstream health care services/delivery of care.

Geography: Not restricting to just US studies

Databases: PubMed, CINAHL, Cochrane, New York Academy of Medicine Grey Literature Database, Google Scholar

A.2 Search Specifications

Criteria: Must meet Search set 1 AND Search set 2 AND specific intervention

Utilization Terms:

Search set 1: downstream OR "down stream" OR "cost-effective*" OR "lifelong cost*" OR "quality-adjusted life year*" OR QALY OR "disability-adjusted life year*" OR DALY OR "value based care" OR "value-based care" OR "cost benefit*" OR "low value care" OR "low-value care" OR "low value service*" OR "low-value service*" OR overuse* OR "inappropriate care" OR "unnecessary" OR "overtreatment" OR "low value" OR "low-value"

Search set 2: service use OR utilization OR utilisation OR cost OR costs OR spend* OR expenditure* OR payment* OR "quality of life" (downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR

overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh])

Population/Intervention Terms:

1. *Prostate-specific antigen (PSA) testing (Male patients ≥75, (though age can vary, measure refers to elderly)*

(PSA test*[ti] OR PSA screen*[ti] OR Prostate-specific antigen test*[ti] OR Prostate-specific antigen screen*[ti] OR ((PSA[ti] OR Prostate-specific antigen[ti] OR ERSPC[ti]) AND (test*[ti] OR screen*[ti] OR detect*[ti])) OR ("Prostate-Specific Antigen"[Majr] AND "Prostatic Neoplasms/diagnosis"[Majr]))

2. *Hypercoagulability testing for patients with deep vein thrombosis (Patients with deep vein thrombosis)*

("Thrombophilia/diagnosis"[Mesh:NoExp] OR thrombophilia test*[tw] OR hypercoagulability test*[tw] OR thrombophilia screen*[tw] OR hypercoagulability screen*[tw] OR ((thrombophilia[ti] OR hypercoagulability[ti]) AND (test*[ti] OR screen*[ti]))) AND (deep vein thrombosis[tw] OR venous thrombosis[tw] OR "Venous Thrombosis"[Mesh])

3. *Preoperative chest radiography (Patient undergoing non-cardiothoracic surgeries)*

("Preoperative Care"[Mesh] OR "Preoperative Period"[Mesh] OR preoperative[tw] OR pre-operative[tw] OR pre-op[tw] OR preop[tw]) AND ("Radiography, Thoracic"[Mesh] OR chest radiography[tw] OR chest X-ray*[tw] OR ((chest[ti] OR thoracic[ti]) AND (radiography[ti] OR X-ray*[ti])))

4. *Back imaging for patients with non-specific low back pain (just say "back pain") (all patients)*

(downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw] OR treatment confidence[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health

Expenditures"[Mesh] OR "Decision Making"[Mesh]) AND ("Back Pain"[Majr] OR back pain[ti]) AND ("Tomography"[Majr] OR "Diagnostic Imaging"[Majr] OR imaging[ti] OR X-ray*[ti] OR tomography[ti] OR radiography[ti])

5. Screening for carotid artery disease in asymptomatic adults (all patients)

(downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw] OR "clinical equivalency"[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh]) AND ("Carotid Artery Diseases"[Majr] OR carotid artery disease*[ti] OR carotid stenosis[ti] OR carotid atherosclerosis[ti] OR carotid artery thrombosis[ti] OR carotid thrombosis[ti] OR coronary artery calcium scanning[ti]) AND ("Mass Screening"[Mesh] OR "Diagnostic Imaging"[Mesh] OR screen*[ti] OR imaging[ti] OR test*[ti] OR randomized trial[ti]) AND asymptomatic[tw]

6. Screening for carotid artery disease for syncope (Syncope patients)

("Carotid Artery Diseases"[Mesh] OR carotid artery disease*[tw] OR carotid stenosis[tw] OR carotid atherosclerosis[tw] OR carotid artery thrombosis[tw] OR carotid thrombosis[tw]) AND ("Mass Screening"[Mesh] OR "Diagnostic Imaging"[Mesh] OR screen*[tw] OR imaging[tw] OR test*[tw] OR tests[tw] OR testing[tw]) AND ("Syncope"[Mesh] OR faint*[tw] OR syncope[tw])

7. Stress testing for stable coronary disease (Patients with ischemic heart disease)

("Exercise Test"[Majr] OR exercise test*[ti] OR stress test*[ti]) AND ("Myocardial Ischemia"[Majr] OR "Coronary Disease"[Majr] OR myocardial ischemia[ti] OR coronary disease*[ti] OR ischemic heart disease*[ti] OR coronary artery disease*[ti]) AND (stable[tw] OR low risk[tw] OR asymptomatic[tw])

8. Percutaneous coronary intervention with balloon angioplasty or stent placement for stable coronary disease (Patients with ischemic heart disease)

("Percutaneous Coronary Intervention"[Majr] OR "Angioplasty, Balloon"[Majr] OR "Stents"[Majr] OR stent*[ti] OR angioplasty[ti] OR percutaneous coronary intervention*[ti]) AND ("Myocardial Ischemia"[Majr] OR "Coronary Disease"[Majr] OR myocardial ischemia[ti]

OR coronary disease*[ti] OR ischemic heart disease*[ti] OR coronary artery disease*[ti]) AND (stable[tw] OR low risk[tw] OR asymptomatic[tw])

9. Renal artery angioplasty or stenting (Patients with hypertension)

(renal artery angioplasty[tw] OR renal artery stent*[tw] OR renal arterial stent*[tw] OR renal arterial angioplasty[tw] OR ("percutaneous transluminal angioplasty"[tw] AND "renal artery"[tw]) OR (("Angioplasty, Balloon"[Mesh] OR "Stents"[Mesh]) AND "Renal Artery Obstruction") OR ((renal artery stenosis[tw] OR renal arterial stenosis[tw]) AND (angioplasty[tw] OR stent*[tw]))) AND ("Hypertension"[Mesh] OR hypertension[tw] OR hypertensive[tw] OR high blood pressure[tw])

10. Carotid endarterectomy for asymptomatic adults (all patients)

("Endarterectomy, Carotid"[Majr] OR "Endarterectomy, Carotid/adverse effects"[Mesh] OR carotid endarterectomy[ti] OR carotid endarterectomies[ti]) AND asymptomatic[tw]

A.3 Database Specific Searches

PubMed

8/3/18 PubMed Search

Search	Query	Items Found
#1	Add Search (downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh]) AND (PSA test*[ti] OR PSA screen*[ti] OR Prostate-specific antigen test*[ti] OR Prostate-specific antigen screen*[ti] OR ((PSA[ti] OR Prostate-specific antigen[ti] OR ERSPC[ti]) AND (test*[ti] OR screen*[ti] OR detect*[ti])) OR ("Prostate-Specific Antigen"[Majr] AND "Prostatic Neoplasms/diagnosis"[Majr])) Filters: Publication date from 2000/01/01; English	83
#2	Add Search (downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh]) AND ("Thrombophilia/diagnosis"[Mesh:NoExp] OR thrombophilia test*[tw] OR hypercoagulability test*[tw] OR thrombophilia screen*[tw] OR hypercoagulability screen*[tw] OR ((thrombophilia[ti] OR hypercoagulability[ti]) AND (test*[ti] OR screen*[ti]))) AND (deep vein thrombosis[tw] OR venous thrombosis[tw] OR "Venous Thrombosis"[Mesh]) Filters: Publication date from 2000/01/01; English	19

Search	Query	Items Found
#3	Add Search (downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh]) AND ("Preoperative Care"[Mesh] OR "Preoperative Period"[Mesh] OR preoperative[tw] OR pre-operative[tw] OR pre-op[tw] OR preop[tw]) AND ("Radiography, Thoracic"[Mesh] OR chest radiography[tw] OR chest X-ray*[tw] OR ((chest[ti] OR thoracic[ti]) AND (radiography[ti] OR X-ray*[ti]))) Filters: Publication date from 2000/01/01; English	24
#4	Add Search (downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw] OR treatment confidence[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh] OR "Decision Making"[Mesh]) AND ("Back Pain"[Majr] OR back pain[ti]) AND ("Tomography"[Majr] OR "Diagnostic Imaging"[Majr] OR imaging[ti] OR X-ray*[ti] OR tomography[ti] OR radiography[ti]) Filters: Publication date from 2000/01/01; English	38

Search	Query	Items Found
#5	Add Search (downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw] OR "clinical equivalency"[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh]) AND ("Carotid Artery Diseases"[Majr] OR carotid artery disease*[ti] OR carotid stenosis[ti] OR carotid atherosclerosis[ti] OR carotid artery thrombosis[ti] OR carotid thrombosis[ti] OR coronary artery calcium scanning[ti]) AND ("Mass Screening"[Mesh] OR "Diagnostic Imaging"[Mesh] OR screen*[ti] OR imaging[ti] OR test*[ti] OR randomized trial[ti]) AND asymptomatic[tw] Filters: Publication date from 2000/01/01; English	43
#6	Add Search (downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh]) AND ("Carotid Artery Diseases"[Mesh] OR carotid artery disease*[tw] OR carotid stenosis[tw] OR carotid atherosclerosis[tw] OR carotid artery thrombosis[tw] OR carotid thrombosis[tw]) AND ("Mass Screening"[Mesh] OR "Diagnostic Imaging"[Mesh] OR screen*[tw] OR imaging[tw] OR test*[tw] OR tests[tw] OR testing[tw]) AND ("Syncope"[Mesh] OR faint*[tw] OR syncope[tw])) Filters: Publication date from 2000/01/01; English	3

Search	Query	Items Found
#7	Add Search (downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh]) AND ("Exercise Test"[Majr] OR exercise test*[ti] OR stress test*[ti]) AND ("Myocardial Ischemia"[Majr] OR "Coronary Disease"[Majr] OR myocardial ischemia[ti] OR coronary disease*[ti] OR ischemic heart disease*[ti] OR coronary artery disease*[ti]) AND (stable[tw] OR low risk[tw] OR asymptomatic[tw]) Filters: Publication date from 2000/01/01; English	22
#8	Add Search (downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh]) AND ("Percutaneous Coronary Intervention"[Majr] OR "Angioplasty, Balloon"[Majr] OR "Stents"[Majr] OR stent*[ti] OR angioplasty[ti] OR percutaneous coronary intervention*[ti]) AND ("Myocardial Ischemia"[Majr] OR "Coronary Disease"[Majr] OR myocardial ischemia[ti] OR coronary disease*[ti] OR ischemic heart disease*[ti] OR coronary artery disease*[ti]) AND (stable[tw] OR low risk[tw] OR asymptomatic[tw]) Filters: Publication date from 2000/01/01; English	79

Search	Query	Items Found
#9	Add Search (downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh]) AND (renal artery angioplasty[tw] OR renal artery stent*[tw] OR renal arterial stent*[tw] OR renal arterial angioplasty[tw] OR ("percutaneous transluminal angioplasty"[tw] AND "renal artery"[tw]) OR (("Angioplasty, Balloon"[Mesh] OR "Stents"[Mesh]) AND "Renal Artery Obstruction") OR ((renal artery stenosis[tw] OR renal arterial stenosis[tw]) AND (angioplasty[tw] OR stent*[tw]))) AND ("Hypertension"[Mesh] OR hypertension[tw] OR hypertensive[tw] OR high blood pressure[tw]) Filters: Publication date from 2000/01/01; English	9
#10	Add Search (downstream[tw] OR cost-effective*[tw] OR lifelong cost*[tw] OR quality-adjusted life year*[tw] OR QALY[tw] OR disability-adjusted life year*[tw] OR DALY[tw] OR "value based care"[tw] OR "value-based care"[tw] OR cost benefit*[tw] OR "low value care"[tw] OR "low-value care"[tw] OR low value service*[tw] OR low-value service*[tw] OR overuse*[tw] OR "inappropriate care"[tw] OR "unnecessary"[tw] OR "overtreatment"[tw] OR "low value"[tw] OR "low-value"[tw] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Medical Overuse"[Mesh] OR overutilization[tw] OR overutilisation[tw] OR "Unnecessary Procedures"[Mesh] OR unnecessary procedure*[tw]) AND (service use[tw] OR utilization[tw] OR utilisation[tw] OR cost[tw] OR costs[tw] OR spending[tw] OR expenditure*[tw] OR payment*[tw] OR "quality of life"[tw] OR "Quality of Life"[Mesh] OR "Utilization Review"[Mesh] OR "utilization"[Subheading] OR "Health Resources/utilization"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Health Expenditures"[Mesh]) AND ("Endarterectomy, Carotid"[Majr] OR "Endarterectomy, Carotid/adverse effects"[Mesh] OR carotid endarterectomy[ti] OR carotid endarterectomies[ti]) AND asymptomatic[tw] Filters: Publication date from 2000/01/01; English	37
#11	Add Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) Filters: Publication date from 2000/01/01; English	387
#12	Add Search (#11 NOT ("Academic Dissertations"[Publication Type] OR "Meeting Abstracts"[Publication Type] OR "Comment"[Publication Type] OR "Letter"[Publication Type] OR "Editorial"[Publication Type])) Filters: Publication date from 2000/01/01; English	365

Search	Query	Items Found
#13	Add Search (#12 NOT (("Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh])) Filters: Publication date from 2000/01/01; English	361 (57)

CINAHL

8/3/18 CINAHL Search

Search	Query	Items Found
S1	(downstream OR "cost-effective*" OR "lifelong cost*" OR "quality-adjusted life year*" OR "QALY" OR "disability-adjusted life year*" OR "DALY" OR "value based care" OR "value-based care" OR "cost benefit*" OR "low value care" OR "low-value care" OR "low value service*" OR "low-value service*" OR overuse* OR "inappropriate care" OR "unnecessary" OR "overtreatment" OR "low value" OR "low-value" OR MH "Disability-Adjusted Life Years" OR MH "Quality-Adjusted Life Years" OR MH "Cost Benefit Analysis" OR overutilization OR overutilisation OR MH "Unnecessary Procedures" OR "unnecessary procedure*") AND ("service use" OR utilization OR utilisation OR cost OR costs OR spending OR expenditure* OR payment* OR "quality of life" OR MH "Quality of Life+" OR MH "Costs and Cost Analysis+" OR MH "Utilization Review" OR MH "Health Resource Utilization") Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	12,262
S2	((ZG "adolescent: 13-18 years" OR ZG "child, preschool: 2-5 years" OR ZG "child: 6-12 years" OR ZG "infant, newborn: birth-1 month" OR ZG "infant: 1-23 months") NOT (ZG "adult: 19-44 years" OR ZG "aged, 80 & over" OR ZG "aged: 65+ years" OR ZG "middle aged: 45-64 years")) OR TI (child* OR adolescen* OR teen* OR youth* OR infant*) OR ((ZT "commentary" OR ZT "doctoral dissertation" OR ZT "editorial" OR ZT "letter" OR ZT "letter to the editor" OR ZT "masters thesis" OR ZT "proceeding" OR ZT "proceedings" OR ZT "conference paper" OR ZT "conference proceeding")) Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	424,241
S3	S1 NOT S2 Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE	10,217
S4	S3 AND ((TI "PSA test*" OR TI "PSA screen*" OR TI "Prostate-specific antigen test*" OR TI "Prostate-specific antigen screen*" OR ((TI "PSA" OR TI "Prostate-specific antigen" OR TI "ERSPC") AND (TI test* OR TI screen* OR TI detect*)) OR (MH "Prostate-Specific Antigen" AND MH "Prostatic Neoplasms+/DI"))) Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	15
S5	S3 AND (("thrombophilia test*" OR "hypercoagulability test*" OR "thrombophilia screen*" OR "hypercoagulability screen*" OR ((TI thrombophilia OR TI hypercoagulability) AND (TI test* OR TI screen*))) AND ("deep vein thrombosis" OR "venous thrombosis" OR MH "Venous Thrombosis+")) Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	1

Search	Query	Items Found
S6	S3 AND ((MH "Preoperative Care+" OR MH "Preoperative Period+" OR preoperative OR "pre-operative" OR "pre-op" OR "preop") AND (MH "Radiography, Thoracic+" OR "chest radiography" OR "chest X-ray*" OR ((TI chest OR TI thoracic) AND (TI radiography OR TI "X-ray*")))) Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	5
S7	S3 AND ((MH "Back Pain+" OR TI "back pain") AND (MH "Tomography+" OR MH "Diagnostic Imaging+" OR TI imaging OR TI "X-ray*" OR TI tomography OR TI radiography)) Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	20
S8	S3 AND ((MH "Carotid Artery Diseases+" OR "carotid artery disease*" OR "carotid stenosis" OR "carotid atherosclerosis" OR "carotid artery thrombosis" OR "carotid thrombosis" OR "coronary artery calcium scanning") AND (MH "Health Screening" OR MH "Diagnostic Imaging+" OR screen* OR imaging OR test* OR "randomized trial") AND asymptomatic) Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	0
S9	S3 AND ((MH "Carotid Artery Diseases+" OR "carotid artery disease*" OR "carotid stenosis" OR "carotid atherosclerosis" OR "carotid artery thrombosis" OR "carotid thrombosis" OR "coronary artery calcium scanning") AND (MH "Health Screening" OR MH "Diagnostic Imaging+" OR screen* OR imaging OR test*) AND (MH "Syncope+" OR faint* OR syncope)) Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	0
S10	S3 AND ((MH "Exercise Test+" OR "exercise test*" OR "stress test*") AND (MH "Myocardial Ischemia+" OR MH "Coronary Disease+" OR "myocardial ischemia" OR "coronary disease*" OR "ischemic heart disease*" OR "coronary artery disease*") AND (stable OR "low risk" OR asymptomatic)) Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	2
S11	S3 AND ((MH "Angioplasty, Transluminal, Percutaneous Coronary" OR MH "Angioplasty, Balloon+" OR MH "Stents+" OR stent* OR angioplasty OR "percutaneous coronary intervention*") AND (MH "Myocardial Ischemia+" OR MH "Coronary Disease+" OR "myocardial ischemia" OR "coronary disease*" OR "ischemic heart disease*" OR "coronary artery disease*") AND (stable OR "low risk OR asymptomatic") Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	1
S12	S3 AND (("renal artery angioplasty" OR "renal artery stent*" OR "renal arterial stent*" OR "renal arterial angioplasty" OR ((MH "Angioplasty, Balloon+" OR MH "Stents+") AND "Renal Artery Obstruction") OR (("renal artery stenosis" OR "renal arterial stenosis") AND (angioplasty OR stent*)) OR ("percutaneous transluminal angioplasty" AND "renal artery")) AND (MH "Hypertension+" OR hypertension OR hypertensive OR "high blood pressure")) Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	0
S13	S3 AND ((MH "Endarterectomy, Carotid" OR "carotid endarterectomy" OR "carotid endarterectomies") AND asymptomatic) Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	2

Search	Query	Items Found
S14	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 Limiters - Published Date: 20000101-20181231; English Language; Exclude MEDLINE records	46

Cochrane

8/3/18 Cochrane Search

Search	Query	Items found
1	(downstream or cost next effective* or lifelong next cost* or "quality-adjusted life" next year* or "QALY" or "disability-adjusted life" next year* or "DALY" or "value based care" or "value-based care" or cost next benefit* or "low value care" or "low-value care" or "low value" next service* or "low-value" next service* or overuse* or "inappropriate care" or overutilization or overutilisation or unnecessary next procedure* or unnecessary or overtreatment or "low value" or "low-value") and ("service use" or utilization or utilisation or cost or costs or spending or expenditure* or payment* or "quality of life"):ti,ab,kw Publication Year from 2000 to 2018	32217
2	(child* or adolescen* or teen* or youth*) not (adult* or elderly):ti or (child* or adolescen* or teen* or youth*) not (adult* or elderly):kw Publication Year from 2000 to 2018	72761
3	#1 not #2	29725
4	PSA next test* or PSA next screen* or "Prostate-specific antigen" next test* or "Prostate-specific antigen" next screen* or ((PSA or "Prostate-specific antigen" or ERSPC) and (test* or screen* or detect*)):ti or "Prostate-Specific Antigen" and "Prostatic Neoplasms":kw Publication Year from 2000 to 2018	1175
5	#3 and #4	44
6	(Thrombophilia next diagnosis or thrombophilia next test* or hypercoagulability next test* or thrombophilia next screen* or hypercoagulability next screen* or ((thrombophilia or hypercoagulability) near/2 (test* or screen*))) and ("deep vein thrombosis" or "venous thrombosis"):ti,ab,kw Publication Year from 2000 to 2018	18
7	#3 and #6	5
8	("Preoperative Care" or "Preoperative Period" or preoperative or "pre-operative" or "pre-op" or "preop") and ("Radiography Thoracic" or "Thoracic Radiography" or "chest radiography" or "chest X-ray" or "chest X-rays" or ((chest or thoracic) near/2 (radiography or "X-ray" or "X-rays"))):ti,ab,kw Publication Year from 2000 to 2018	62
9	#3 and #8	4
10	back pain and (tomography or "diagnostic imaging" or imaging or "X-ray" or "X-rays" or radiography):ti or "back pain" and (tomography or "diagnostic imaging" or imaging or "X-ray" or "X-rays" or radiography):kw Publication Year from 2000 to 2018	441
11	#3 and #10	31

Search	Query	Items found
12	("carotid artery" next disease* or "carotid stenosis" or "carotid atherosclerosis" or "carotid artery thrombosis" or "carotid thrombosis" or "coronary artery calcium scanning") and ("mass screening" or "diagnostic imaging" or screen* or imaging or test*) and asymptomatic:ti,ab,kw Publication Year from 2000 to 2018	100
13	#3 and #12	4
14	("carotid artery" next disease* or "carotid stenosis" or "carotid atherosclerosis" or "carotid artery thrombosis" or "carotid thrombosis") and ("mass screening" or "diagnostic imaging" or screen* or imaging or test*) and (faint* or syncope):ti,ab,kw Publication Year from 2000 to 2018	3
15	#3 and #14	0
16	(exercise next test* or stress next test*) and (myocardial next ischemia or coronary next disease* or "ischemic heart" next disease* or "coronary artery" next disease*) and (stable or "low risk" or asymptomatic):ti,ab,kw Publication Year from 2000 to 2018	346
17	#3 and #16	22
18	("Angioplasty Balloon" or stent* or angioplasty or "percutaneous coronary" next intervention*) and ("myocardial ischemia" or coronary next disease* or "ischemic heart" next disease* or "coronary artery" next disease*) and (stable or "low risk" or asymptomatic):ti or ("Angioplasty Balloon" or stent* or angioplasty or "percutaneous coronary" next intervention*) and ("myocardial ischemia" or coronary next disease* or "ischemic heart" next disease* or "coronary artery" next disease*) and (stable or "low risk" or asymptomatic):kw Publication Year from 2000 to 2018	205
19	#3 and #18	10
20	("renal artery angioplasty" or "renal artery" next stent* or "renal arterial" next stent* or "renal arterial angioplasty" or (("Angioplasty Balloon" or "Stents") and "Renal Artery Obstruction") or (("renal artery stenosis" or "renal arterial stenosis") and (angioplasty or stent*)) or ("percutaneous transluminal angioplasty" and "renal artery")) and (hypertension or hypertensive or "high blood pressure"):ti,ab,kw Publication Year from 2000 to 2018	68
21	#3 and #20	2
22	("Endarterectomy Carotid" or "carotid endarterectomy" or "carotid endarterectomies") and asymptomatic:ti,ab,kw Publication Year from 2000 to 2018	208
23	#3 and #22	14

New York Academy of Medicine Grey Literature Database & Google Scholar

8/3/18 New York Academy of Medicine Grey Literature Database & Google Scholar Search

Query
(downstream OR "cost-effective*" OR "lifelong cost*" OR "quality-adjusted life year*" OR QALY OR "disability-adjusted life year*" OR DALY OR "value based care" OR "value-based care" OR "cost benefit*" OR "low value care" OR "low-value care" OR "low value service*" OR "low-value service"* OR overuse* OR "inappropriate care" OR overutilization OR overutilisation OR "unnecessary procedure*" OR "unnecessary" OR "overtreatment" OR "low value" OR "low-value") AND ("service use" OR utilization OR utilisation OR cost OR costs OR spending OR expenditure* OR payment* OR "quality of life")
("PSA test*" OR "PSA screen*" OR "Prostate-specific antigen test*" OR "Prostate-specific antigen screen*" OR ((PSA OR "Prostate-specific antigen" OR ERSPC) AND (test* OR screen* OR detect*))
("thrombophilia test*" OR "hypercoagulability test*" OR "thrombophilia screen*" OR "hypercoagulability screen*" OR ((thrombophilia OR hypercoagulability) AND (test* OR screen*))) AND ("deep vein thrombosis" OR "venous thrombosis")
(preoperative OR "pre-operative" OR "pre-op" OR preop) AND ("chest radiography" OR "chest X-ray*" OR ((chest OR thoracic) AND (radiography OR X-ray*)))
"back pain" AND (imaging OR "X-ray*" OR tomography OR radiography)
("carotid artery disease*" OR "carotid stenosis" OR "carotid atherosclerosis" OR "carotid artery thrombosis" OR "carotid thrombosis" OR "coronary artery calcium scanning") AND (screen* OR imaging OR test* OR "randomized trial") AND asymptomatic
("carotid artery disease*" OR "carotid stenosis" OR "carotid atherosclerosis" OR "carotid artery thrombosis" OR "carotid thrombosis") AND (screen* OR imaging OR test* OR tests OR testing) AND (faint* OR syncope)
("exercise test*" OR "stress test*") AND ("myocardial ischemia" OR "coronary disease*" OR "ischemic heart disease*" OR "coronary artery disease*") AND (stable OR "low risk" OR asymptomatic)
(sent* OR angioplasty OR "percutaneous coronary intervention*") AND ("myocardial ischemia" OR "coronary disease*" OR "ischemic heart disease*" OR "coronary artery disease*") AND (stable OR "low risk" OR asymptomatic)
("renal artery angioplasty" OR "renal artery stent*" OR "renal arterial stent*" OR "renal arterial angioplasty" OR (("renal artery stenosis" OR "renal arterial stenosis") AND (angioplasty OR stent*)) OR ("percutaneous transluminal angioplasty" AND "renal artery")) AND (hypertension OR hypertensive OR "high blood pressure")
("carotid endarterectomy" OR "carotid endarterectomies") AND asymptomatic

Appendix B.
Citations by Measure

Prostate-specific antigen (PSA) testing for men over age 75

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5. Heijnsdijk, E. A., de Carvalho, T. M., Auvinen, A., Zappa, M., Nelen, V., Kwiatkowski, M., . . . de Koning, H. J. (2015). Cost-effectiveness of prostate cancer screening: a simulation study based on ERSPC data. J Natl Cancer Inst, 107(1), 366. doi:10.1093/jnci/dju366

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9. Jeng, H. S., Huang, S. P., Chou, Y. H., & Huang, C. H. (2002). Detection of prostate cancer--experience of seven years in KMUH and review of literature. Kaohsiung J Med Sci, 18(6), 281-288.

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11. Ma, X., Wang, R., Long, J. B., Ross, J. S., Soulos, P. R., Yu, J. B., . . . Gross, C. P. (2014). The cost implications of prostate cancer screening in the Medicare population. Cancer, 120(1), 96-102. doi:10.1002/cncr.28373

12. Martin, A. J., Lord, S. J., Verry, H. E., Stockler, M. R., & Emery, J. D. (2013). Risk assessment to guide prostate cancer screening decisions: a cost-effectiveness analysis. Med J Aust, 198(10), 546-550.

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101. Pandya, A., Gupta, A., Kamel, H., Navi, B. B., Sanelli, P. C., & Schackman, B. R. (2015). Carotid artery stenosis: cost-effectiveness of assessment of cerebrovascular reserve to guide treatment of asymptomatic patients. Radiology, 274(2), 455-463. doi:10.1148/radiol.14140501

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103. Wallaert, J. B., Newhall, K. A., Suckow, B. D., Brooke, B. S., Zhang, M., Farber, A. E., . . . Vascular Quality, I. (2016). Relationships between 2-Year Survival, Costs, and Outcomes following Carotid Endarterectomy in Asymptomatic Patients in the Vascular Quality Initiative. Ann Vasc Surg, 35, 174-182. doi:10.1016/j.avsg.2016.01.024

Appendix C.
Included Study Characteristics

First Author/ Publication Year*	Measure	Study Design	US Based	Examined Downstream		Describes Measure as LVC
				Services	Cost	
Babaian 2006[1]	PSA testing	Observational	Unclear	Yes	Yes	No
Benoit 2001[2]	PSA testing	Synthesis	Yes	No	Yes	No
Bermudez-Tamayo 2007[3]	PSA testing	Synthesis	No	No	Yes	No
Ellison 2002[4]	PSA testing	Synthesis	Yes	No	No	No
Heijnsdijk 2015[5]	PSA testing	Synthesis	No	No	Yes	Yes
Heijnsdijk 2016[6]	PSA testing	Synthesis	No	Yes	Yes	Yes
Heijnsdijk 2009[7]	PSA testing	Synthesis	No	Yes	Yes	Yes
Heijnsdijk 2012[8]	PSA testing	Synthesis	No	Yes	No	Yes
Jeng 2002[9]	PSA testing	Observational	No	No	No	No
Keller 2017[10]	PSA testing	Synthesis	No	No	Yes	No
Ma 2014[11]	PSA testing	Observational	Yes	No	Yes	No
Martin 2013[12]	PSA testing	Synthesis	No	No	No	No
Pataky 2014[13]	PSA testing	Synthesis	No	No	Yes	No
Rao 2018[14]	PSA testing	Observational	Yes	No	Yes	Yes
Richter 2001[15]	PSA testing	Observational	Yes	No	No	Yes
Ross 2000[16]	PSA testing	Synthesis	Yes	Yes	No	Yes
Roth 2016[17]	PSA testing	Synthesis	Yes	Yes	No	Yes
Sennfalt 2004[18]	PSA testing	Synthesis	No	No	No	Yes
Shao 2011[19]	PSA testing	Observational	Yes	Yes	No	Yes
Stone 2005[20]	PSA testing	Synthesis	No	No	Yes	Yes
Tawfik 2015[21]	PSA testing	Synthesis	No	No	Yes	No
Walter 2013[22]	PSA testing	Observational	Yes	Yes	No	Yes
Zanwar 2016[23]	PSA testing	Observational	Yes	Yes	Yes	Yes
Zhang 2012[24]	PSA testing	Synthesis	Yes	No	No	No
Auerbach 2004[25]	Hypercoagulability testing for DVT	Synthesis	Yes	No	Yes	No
Simpson 2009[26]	Hypercoagulability testing for DVT	Synthesis	No	No	Yes	No
Aaronson 2017[27]	Back imaging for LBP	Observational	Unclear	Yes	No	Yes
Fried 2018[28]	Back imaging for LBP	Observational	Yes	Yes	No	Yes
Gilbert 2004[29]	Back imaging for LBP	RCT	No	Yes	No	No

First Author/ Publication Year*	Measure	Study Design	US Based	Examined Downstream		Describes Measure as LVC
				Services	Cost	
Gilbert 2004[30]	Back imaging for LBP	RCT	No	Yes	No	No
Gilbert 2004[31]	Back imaging for LBP	RCT	No	Yes	Yes	No
Graves 2018[32]	Back imaging for LBP	Observational	Yes	Yes	Yes	Yes
Hollingworth 2003[33]	Back imaging for LBP	Synthesis	Yes	No	No	No
Hourcade 2002[34]	Back imaging for LBP	Observational	No	Yes	No	No
Jensen 2010[35]	Back imaging for LBP	Observational	No	Yes	Yes	No
Lurie 2003[36]	Back imaging for LBP	Observational	Yes	Yes	No	Yes
Miller 2002[37]	Back imaging for LBP	RCT	No	No	Yes	Yes
Shreibati 2011[38]	Back imaging for LBP	Observational	Yes	Yes	No	Yes
Webster 2013[39]	Back imaging for LBP	Observational	Yes	Yes	Yes	Yes
Webster 2014[40]	Back imaging for LBP	Observational	Yes	No	Yes	Yes
Webster 2010[41]	Back imaging for LBP	Observational	Yes	Yes	Yes	Yes
Baber 2015[42]	CAD screening for asymptomatic	Observational	Yes	No	No	No
Hogberg 2018[43]	CAD screening for asymptomatic	Synthesis	No	No	Yes	No
Wardlaw 2006[44]	CAD screening for asymptomatic	Synthesis	Unclear	No	No	No
Scott 2014[45]	CAD screening for syncope	Observational	Yes	No	No	Yes
Bertoldi 2017[46]	Stress testing for stable CD	Synthesis	No	Yes	Yes	No
Marwick 2003[47]	Stress testing for stable CD	Observational	Unclear	No	Yes	No
Shaw 2011[48]	Stress testing for stable CD	RCT	Unclear	Yes	No	No
Thom 2014[49]	Stress testing for stable CD	RCT	No	No	No	No
Zacharias 2017[50]	Stress testing for stable CD	RCT	No	No	No	No
Abdelnoor 2017[51]	PCI for stable CD	Synthesis	No	Yes	Yes	No
Amin 2012[52]	PCI for stable CD	Synthesis	Yes	No	No	No

First Author/ Publication Year*	Measure	Study Design	US Based	Examined Downstream		Describes Measure as LVC
				Services	Cost	
Beresniak 2015[53]	PCI for stable CD	Synthesis	No	No	Yes	No
Bonaventura 2012[54]	PCI for stable CD	Synthesis	No	No	Yes	No
Brophy 2003[55]	PCI for stable CD	Synthesis	No	No	No	No
Brophy 2005[56]	PCI for stable CD	Synthesis	Unclear	Yes	No	No
Brunner-La Rocca 2007[57]	PCI for stable CD	RCT	No	No	Yes	No
Caruba 2014[58]	PCI for stable CD	Synthesis	Unclear	No	Yes	No
Clavijo 2016[59]	PCI for stable CD	RCT	Yes	No	No	No
Cohen 2012[60]	PCI for stable CD	RCT	Yes	No	Yes	No
Escarcega 2010[61]	PCI for stable CD	Observational	Unclear	Yes	No	No
Favarato 2003[62]	PCI for stable CD	RCT	No	No	Yes	No
Fearon 2018[63]	PCI for stable CD	RCT	Yes	No	Yes	No
Fearon 2013[64]	PCI for stable CD	RCT	Yes	No	Yes	No
Gada 2012[65]	PCI for stable CD	Synthesis	Yes	No	Yes	No
Gaster 2003[66]	PCI for stable CD	RCT	Unclear	No	Yes	No
Hambrecht 2004[67]	PCI for stable CD	RCT	Unclear	Yes	Yes	No
Hlatky 2009[68]	PCI for stable CD	RCT	Unclear	Yes	Yes	No
Hung 2011[69]	PCI for stable CD	Observational	No	No	No	No
Kuukasjärvi 2007[70]	PCI for stable CD	Synthesis	No	No	No	No
Lee 2014[71]	PCI for stable CD	Observational	No	No	Yes	No
Mark 2009[72]	PCI for stable CD	Observational	Yes	No	Yes	No
Maud 2010[73]	PCI for stable CD	Synthesis	Yes	No	Yes	No
Morgan 2010[74]	PCI for stable CD	Observational	No	No	Yes	No
Polanczyk 2007[75]	PCI for stable CD	Synthesis	No	No	Yes	No
Saadi 2011[76]	PCI for stable CD	Synthesis	Unclear	No	Yes	No
Serruys 2001[77]	PCI for stable CD	RCT	Unclear	No	No	No
Shrive 2005[78]	PCI for stable CD	Synthesis	No	Yes	Yes	No
Takura 2017[79]	PCI for stable CD	Observational	No	No	No	No
van Hout 2005[80]	PCI for stable CD	RCT	No	No	Yes	No
Weaver 2000[81]	PCI for stable CD	RCT	Yes	Yes	Yes	No
Weintraub 2008[82]	PCI for stable CD	RCT	Yes	No	Yes	No
Weintraub 2004[83]	PCI for stable CD	RCT	No	No	Yes	No

First Author/ Publication Year*	Measure	Study Design	US Based	Examined Downstream		Describes Measure as LVC
				Services	Cost	
Wijeysundera 2013[84]	PCI for stable CD	Synthesis	No	No	Yes	Yes
Zeymer 2003[85]	PCI for stable CD	RCT	No	Yes	No	No
Zhang 2011[86]	PCI for stable CD	RCT	Yes	No	Yes	No
Zhang 2015[87]	PCI for stable CD	Observational	Yes	No	Yes	No
Zhang 2005[88]	PCI for stable CD	RCT	No	No	Yes	No
Axelrod 2003[89]	Renal angioplasty/stenting	Synthesis	Unclear	No	Yes	No
Cooper 2014[90]	Renal angioplasty/stenting	RCT	Unclear	Yes	No	Yes
Duda 2000[91]	Renal angioplasty/stenting	Synthesis	No	No	No	No
van Helvoort-Postulart 2007[92]	Renal angioplasty/stenting	Synthesis	No	No	Yes	No
Sathyamurthy 2014[93]	Renal angioplasty/stenting	Observational	No	Yes	No	Yes
Dakour-Aridi 2018[94]	CEA for asymptomatic	Observational	Yes	No	No	No
Henriksson 2008[95]	CEA for asymptomatic	RCT	No	No	Yes	No
Illig 2003[96]	CEA for asymptomatic	Observational	Yes	No	Yes	No
Jain 2007[97]	CEA for asymptomatic	Observational	Unclear	No	No	No
Kilaru 2003[98]	CEA for asymptomatic	Synthesis	Yes	No	Yes	No
Kim 2014[99]	CEA for asymptomatic	Observational	No	No	No	No
Luebke 2016[100]	CEA for asymptomatic	Synthesis	No	No	Yes	No
Pandya 2015[101]	CEA for asymptomatic	Synthesis	Unclear	No	Yes	No
Thapar 2013[102]	CEA for asymptomatic	Synthesis	No	No	Yes	No
Wallaert 2016[103]	CEA for asymptomatic	Observational	Yes	No	Yes	Yes

* Full citations can be found by reference number in Appendix B. Full abstract summaries for recommended measures can be found by reference number in Appendix D.
Note: CAD = carotid artery disease, CD = coronary disease, CEA = carotid endarterectomy, DVT = deep vein thrombosis, LBP = low back pain, LVC = low-value care, PCI = percutaneous coronary intervention, PSA = prostate-specific antigen, RCT = randomized controlled trial, US = United States.

Appendix D.
Included Abstracts by Recommended Measure

Prostate-specific antigen (PSA) testing for men over age 75

1. **Babaian, R. J., Naya, Y., Cheli, C., & Fritsche, H. A. (2006). The detection and potential economic value of complexed prostate specific antigen as a first line test. J Urol, 175(3 Pt 1), 897-901; discussion 901. doi:10.1016/S0022-5347(05)00343-5**

   PURPOSE: Prostate cancer detection is subject to a number of variables that can lead to unnecessary biopsies and associated costs. Measuring cPSA has been proposed as an alternative to tPSA for the early detection of prostate cancer. MATERIALS AND METHODS: Between November 1998 and April 2000, 1,362 men underwent transrectal ultrasound guided biopsies at 7 institutions. Of 1,243 evaluable men 467 with tPSA between 2.5 and 6.0 ng/ml, and normal digital rectal examination were analyzed. Statistical analysis used to compare cancer detection rates between PSA assays was performed using the Mann-Whitney U test. A separate group of 2,807 men who participated in a free cancer detection program was used to determine the current tPSA distribution and assess the economic impact of cPSA. RESULTS: Cancer was detected in 31.5% of the men (147 of 467) with tPSA between 2.5 and 6.0 ng/ml. Using a 2.2 ng/ml cPSA cutoff point detected 93.9% of cancers and would have avoided 20.3% of unnecessary biopsies in men with tPSA between 2.5 and 4.0 ng/ml. A 2.2 ng/ml cPSA cutoff point achieved an 11.9% overall decrease in the number of unnecessary biopsies in the tPSA range of 2.5 to 6.0 ng/ml with accompanying 98% sensitivity. The decrease in unnecessary biopsies is potentially associated with substantial health care cost savings. CONCLUSIONS: In the clinically relevant sensitivity ranges a 2.2 ng/ml cPSA cutoff point decreases the number of unnecessary biopsies and maintains higher specificity than a tPSA threshold of 2.5 ng/ml, illustrating the potential value of cPSA as a first line diagnostic test.

2. **Benoit, R. M., Gronberg, H., & Naslund, M. J. (2001). A quantitative analysis of the costs and benefits of prostate cancer screening. Prostate Cancer Prostatic Dis, 4(3), 138-145. doi:10.1038/sj.pcan.4500510**

   The present study attempts to quantitate in an economically and clinically meaningful manner the cost and cost-effectiveness of prostate cancer screening and subsequent treatment, including complications from that treatment. Outcome data from large prostate cancer screening trials using prostate specific antigen (PSA) and digital rectal examination (DRE) and PSA alone were used to construct the screening model. The benefit of screening is expressed in years of life saved by screening, which is calculated by comparing the survival rate of men with prostate cancer to the survival rate of men in the general population. The cost of screening, treatment, and complications were estimated using the Medicare data base and published reports on the cost, morbidity and mortality for radical prostatectomy. The cost per year of life saved by prostate cancer screening with PSA and DRE was $2339-3005 for men aged 50-59, $3905-5070 for men aged 60-69, and $3574-4627 overall for men aged 50-69. The cost per year of life saved by prostate cancer screening with PSA alone for men aged 50-70 was $3822-4956. A sensitivity analysis demonstrates that the cost per year of life saved by prostate cancer screening will not change substantially even if the assumptions in this model have been underestimated or overestimated by 100%. This study quantifies only those parameters which can be reliably compared in concrete terms such as dollars, treatment impact on survival, published complication rates and published treatment costs. Using this type of analysis, prostate cancer screening appears to be a cost-effective intervention. However, the issue of whether prostate cancer screening is cost-effective will be decided definitively only when randomized, controlled trials are available to quantify the costs and benefits of prostate cancer screening.Prostate Cancer and Prostatic Diseases (2001) 4, 138-145.

3. Bermudez-Tamayo, C., Martin Martin, J. J., Gonzalez Mdel, P., & Perez Romero, C. (2007). Cost-effectiveness of percent free PSA for prostate cancer detection in men with a total PSA of 4-10 ng/ml. Urol Int, 79(4), 336-344. doi:10.1159/000109720

OBJECTIVE: To assess the cost-effectiveness of two diagnostic strategies for prostate cancer in men with prostate-specific antigen (PSA) levels of 4-10 ng/ml and normal digital rectal examination (DRE). DESIGN: Cost-effectiveness analysis was performed using a decision tree model. Data collection and a systematic review of patients at the Urology Department (Carlos Haya Hospital) were made. 101 patients over the age of 40 with PSA levels of 4-10 ng/ml and normal DRE were selected. Transrectal ultrasound-guided prostate biopsy (TRUS-Bx) and percent free PSA testing prior to TRUS-Bx were performed. The outcome measures used were the incremental cost-effectiveness ratio, and costs were calculated through activity-based costing. The effectiveness was measured by means of the number of detected cases, test utility and actual cases (detected cases minus lost cases). RESULTS: Using base-case analysis, the strategy of percent free PSA + TRUS-Bx was found to be the most cost-effective. The incremental cost-effectiveness ratio for free PSA + TRUS-Bx compared with TRUS-Bx was EUR 2,277.40. Strategy 2 (TRUS-Bx) would be more cost-effective if the cost of percent free PSA increased to EUR 21.64 or if prostate cancer prevalence increased to 26%. CONCLUSIONS: The use of percent free PSA prior to TRUS-Bx is the most cost-effective diagnostic strategy. However, this result is very sensitive and strategy 2 (TRUS-Bx) would be more cost-effective if the cost of the percent free PSA increased to EUR 21.64 or if the prevalence of prostate cancer increased to above 26%.

4. Ellison, L., Cheli, C. D., Bright, S., Veltri, R. W., & Partin, A. W. (2002). Cost-benefit analysis of total, free/total, and complexed prostate-specific antigen for prostate cancer screening. Urology, 60(4 Suppl 1), 42-46.

Refinements in prostate-specific antigen (PSA) through the use of its derivatives have augmented early detection rates of prostate cancer. However, these improvements are coupled with relatively large increases in unit cost per detected cancer. We used decision-analytic modeling to determine the most appropriate PSA derivative for population-based screening. We constructed a decision-analytic model to determine the PSA derivative with the highest cost-benefit ratio for prostate cancer screening. We defined 5 screening strategies: total PSA (tPSA) 4.0 ng/mL; free PSA/tPSA (f/tPSA) in conjunction with tPSA; and complexed PSA (cPSA) 3.8, 3.4, and 3.0 ng/mL. Prostate cancer prevalence, false-positive rates, and false-negative rates for each test strategy were calculated from a database of 2138 men. The direct costs were obtained from literature review and our department of clinical chemistry. The derivative cPSA with a positive threshold of 3.8 ng/mL was the dominant strategy. The average cost of screening was 138.93 dollars. The strategy of tPSA became dominant when the cost of cPSA was >35.00 dollars or the cost of a prostate biopsy was <67.30 dollars. To match the false-negative rate of tPSA 4.0 ng/mL, a cPSA threshold of 3.0 ng/mL is necessary (sensitivity 92.5%). At this level, the marginal cost increase over tPSA is 9.40 dollars. The dominant strategy for population-based prostate cancer screening is use of cPSA with a positive threshold of 3.8 ng/mL. The use of cPSA with a threshold of 3.0 ng/mL identifies a similar number of cancers with fewer biopsies than tPSA at 4.0 ng/mL.

5. Heijnsdijk, E. A., de Carvalho, T. M., Auvinen, A., Zappa, M., Nelen, V., Kwiatkowski, M., . . . de Koning, H. J. (2015). Cost-effectiveness of prostate cancer screening: a simulation study based on ERSPC data. J Natl Cancer Inst, 107(1), 366. doi:10.1093/jnci/dju366

BACKGROUND: The results of the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial showed a statistically significant 29% prostate cancer mortality reduction for the men screened in the intervention arm and a 23% negative impact on the life-years gained because of quality of life. However, alternative prostate-specific antigen (PSA) screening strategies for the population may exist, optimizing the effects on mortality reduction, quality of life, overdiagnosis, and costs. METHODS: Based on data of the ERSPC trial, we predicted the numbers of prostate cancers diagnosed, prostate cancer deaths averted, life-years and quality-adjusted life-years (QALY) gained, and cost-effectiveness of 68 screening strategies starting at age 55 years, with a PSA threshold of 3, using microsimulation modeling. The screening strategies varied by age to stop screening and screening interval (one to 14 years or once in a lifetime screens), and therefore number of tests. RESULTS: Screening at short intervals of three years or less was more cost-effective than using longer intervals. Screening at ages 55 to 59

years with two-year intervals had an incremental cost-effectiveness ratio of $73000 per QALY gained and was considered optimal. With this strategy, lifetime prostate cancer mortality reduction was predicted as 13%, and 33% of the screen-detected cancers were overdiagnosed. When better quality of life for the post-treatment period could be achieved, an older age of 65 to 72 years for ending screening was obtained. CONCLUSION: Prostate cancer screening can be cost-effective when it is limited to two or three screens between ages 55 to 59 years. Screening above age 63 years is less cost-effective because of loss of QALYs because of overdiagnosis.

6. Heijnsdijk, E. A., Denham, D., & de Koning, H. J. (2016). The Cost-Effectiveness of Prostate Cancer Detection with the Use of Prostate Health Index. Value Health, 19(2), 153-157. doi:10.1016/j.jval.2015.12.002

BACKGROUND: Clinical trial results suggested that prostate-specific antigen (PSA) screening can reduce prostate cancer mortality. Nevertheless, because the specificity of the PSA test for cancer detection is low, it leads to many negative biopsies. The Beckman Coulter Prostate Health Index (PHI) testing demonstrates improved specificity compared with the PSA-only screening and therefore may improve the cost-effectiveness of prostate cancer detection. OBJECTIVE: To examine the cost-effectiveness of adding PHI testing to improve cancer detection for men with elevated serum PSA. METHODS: A microsimulation model, based on the results of the European Randomized Study of Screening for Prostate Cancer trial, was used to evaluate the effects of PSA screening and PHI reflex testing. We predicted the numbers of prostate cancers, negative biopsies, deaths, quality-adjusted life-years gained, and cost-effectiveness of both PSA (cutoff 3 ng/mL) and PHI (cutoff 25) testing methods for a European population, screened from age 50 to 75 years at 4-year intervals. RESULTS: When the PHI test was added to the PSA screening, for men with a PSA between 3 and 10 ng/mL, the model predicted a 23% reduction in negative biopsies. This would lead to a 17% reduction in costs for diagnostics and 1% reduction in total costs for prostate cancer. The cost-effectiveness (3.5% discounted) was 11% better. Limitations found were the modeling assumptions on the sensitivity and specificity of PHI by tumor stage and cutoff values. CONCLUSIONS: Compared with PSA-only screening, the use of a PHI test can substantially reduce the number of negative biopsies and improve the cost-effectiveness of prostate cancer detection.

7. Heijnsdijk, E. A., der Kinderen, A., Wever, E. M., Draisma, G., Roobol, M. J., & de Koning, H. J. (2009). Overdetection, overtreatment and costs in prostate-specific antigen screening for prostate cancer. Br J Cancer, 101(11), 1833-1838. doi:10.1038/sj.bjc.6605422

BACKGROUND: Prostate cancer screening with prostate-specific antigen (PSA) has shown to reduce prostate cancer mortality in the European Randomised study of Screening for Prostate Cancer (ERSPC) trial. Overdetection and overtreatment are substantial unfavourable side effects with consequent healthcare costs. In this study the effects of introducing widespread PSA screening is evaluated. METHODS: The MISCAN model was used to simulate prostate cancer growth and detection in a simulated cohort of 100,000 men (European standard population) over 25 years. PSA screening from age 55 to 70 or 75, with 1, 2 and 4-year-intervals is simulated. Number of diagnoses, PSA tests, biopsies, treatments, deaths and corresponding costs for 100,000 men and for United Kingdom and United States are compared. RESULTS: Without screening 2378 men per 100,000 were predicted to be diagnosed with prostate cancer compared with 4956 men after screening at 4-year intervals. By introducing screening, the costs would increase with 100% to 60,695,000 euro. Overdetection is related to 39% of total costs (23,669,000 euro). Screening until age 75 is relatively most expensive because of the costs of overtreatment. CONCLUSION: Introduction of PSA screening will increase total healthcare costs for prostate cancer substantially, of which the actual screening costs will be a small part.

8. Heijnsdijk, E. A., Wever, E. M., Auvinen, A., Hugosson, J., Ciatto, S., Nelen, V., . . . de Koning, H. J. (2012). Quality-of-life effects of prostate-specific antigen screening. N Engl J Med, 367(7), 595-605. doi:10.1056/NEJMoa1201637

BACKGROUND: After 11 years of follow-up, the European Randomized Study of Screening for Prostate Cancer (ERSPC) reported a 29% reduction in prostate-cancer mortality among men who underwent screening for prostate-specific antigen (PSA) levels. However, the extent to which harms to quality of life resulting from overdiagnosis and treatment counterbalance this benefit is

uncertain. METHODS: On the basis of ERSPC follow-up data, we used Microsimulation Screening Analysis (MISCAN) to predict the number of prostate cancers, treatments, deaths, and quality-adjusted life-years (QALYs) gained after the introduction of PSA screening. Various screening strategies, efficacies, and quality-of-life assumptions were modeled. RESULTS: Per 1000 men of all ages who were followed for their entire life span, we predicted that annual screening of men between the ages of 55 and 69 years would result in nine fewer deaths from prostate cancer (28% reduction), 14 fewer men receiving palliative therapy (35% reduction), and a total of 73 life-years gained (average, 8.4 years per prostate-cancer death avoided). The number of QALYs that were gained was 56 (range, -21 to 97), a reduction of 23% from unadjusted life-years gained. To prevent one prostate-cancer death, 98 men would need to be screened and 5 cancers would need to be detected. Screening of all men between the ages of 55 and 74 would result in more life-years gained (82) but the same number of QALYs (56). CONCLUSIONS: The benefit of PSA screening was diminished by loss of QALYs owing to postdiagnosis long-term effects. Longer follow-up data from both the ERSPC and quality-of-life analyses are essential before universal recommendations regarding screening can be made. (Funded by the Netherlands Organization for Health Research and Development and others.).

9. **Jeng, H. S., Huang, S. P., Chou, Y. H., & Huang, C. H. (2002). Detection of prostate cancer--experience of seven years in KMUH and review of literature. Kaohsiung J Med Sci, 18(6), 281-288.**

   Prostate cancer has become the 7th most common malignancy in Taiwan in 2000. To our knowledge, many diagnostic tests have been developed, including digital rectal examination (DRE), transrectal ultrasound (TRUS), prostate specific antigen (PSA), PSA density (PSAD), PSA velocity, age-specific PSA, and free-to-total PSA, but none of them has been proven to be definitely effective in deciding which person is to receive prostate biopsy. Viewpoints vary with clinician and area. A total of 300 patients over 7-year time period received DRE, TRUS, PSA, and PSAD tests and then had prostate biopsy in Kaohsiung Medical University Hospital. We collect our results and review the literature to find the cost-effectiveness of the tests to prevent unnecessary biopsy and delay in diagnosis. Fifty-two patients (19%) with PSA > 4 ng/ml had prostate cancer. Only 10.5% of patients with prostate cancer had abnormal TRUS lesions, and 20% with prostate cancer showed abnormal DRE results. Because of DRE is non-invasive and inexpensive, we commend the annual use of DRE combined with PSA check in males of 50 years and above to screen for prostate cancer, despite the poor sensitivity of DRE. Therefore, in cases where there is either PSA > 4 ng/ml or abnormal DRE results, it is suggested that patients receive prostate biopsy. There is still no definite conclusion in other diagnostic tests including TRUS.

10. **Keller, A., Gericke, C., Whitty, J. A., Yaxley, J., Kua, B., Coughlin, G., & Gianduzzo, T. (2017). A Cost-Utility Analysis of Prostate Cancer Screening in Australia. Appl Health Econ Health Policy, 15(1), 95-111. doi:10.1007/s40258-016-0278-6**

    BACKGROUND AND OBJECTIVES: The Goteborg randomised population-based prostate cancer screening trial demonstrated that prostate-specific antigen (PSA)-based screening reduces prostate cancer deaths compared with an age-matched control group. Utilising the prostate cancer detection rates from this study, we investigated the clinical and cost effectiveness of a similar PSA-based screening strategy for an Australian population of men aged 50-69 years. METHODS: A decision model that incorporated Markov processes was developed from a health system perspective. The base-case scenario compared a population-based screening programme with current opportunistic screening practices. Costs, utility values, treatment patterns and background mortality rates were derived from Australian data. All costs were adjusted to reflect July 2015 Australian dollars (A$). An alternative scenario compared systematic with opportunistic screening but with optimisation of active surveillance (AS) uptake in both groups. A discount rate of 5 % for costs and benefits was utilised. Univariate and probabilistic sensitivity analyses were performed to assess the effect of variable uncertainty on model outcomes. RESULTS: Our model very closely replicated the number of deaths from both prostate cancer and background mortality in the Goteborg study. The incremental cost per quality-adjusted life-year (QALY) for PSA screening was A$147,528. However, for years of life gained (LYGs), PSA-based screening (A$45,890/LYG) appeared more favourable. Our alternative scenario with optimised AS improved cost utility to A$45,881/QALY, with screening becoming cost effective at a 92 % AS uptake rate. Both modelled scenarios were most sensitive to the utility of patients before and after intervention, and the discount rate used. CONCLUSION: PSA-based screening is not cost effective

compared with Australia's assumed willingness-to-pay threshold of A$50,000/QALY. It appears more cost effective if LYGs are used as the relevant outcome, and is more cost effective than the established Australian breast cancer screening programme on this basis. Optimised utilisation of AS increases the cost effectiveness of prostate cancer screening dramatically.

11. Ma, X., Wang, R., Long, J. B., Ross, J. S., Soulos, P. R., Yu, J. B., . . . Gross, C. P. (2014). The cost implications of prostate cancer screening in the Medicare population. Cancer, 120(1), 96-102. doi:10.1002/cncr.28373

BACKGROUND: Recent debate about prostate-specific antigen (PSA)-based testing for prostate cancer screening among older men has rarely considered the cost of screening. METHODS: A population-based cohort of male Medicare beneficiaries aged 66 to 99 years, who had never been diagnosed with prostate cancer at the end of 2006 (n = 94,652), was assembled, and they were followed for 3 years to assess the cost of PSA screening and downstream procedures (biopsy, pathologic analysis, and hospitalization due to biopsy complications) at both the national and the hospital referral region (HRR) level. RESULTS: Approximately 51.2% of men received PSA screening tests during the 3-year period, with 2.9% undergoing biopsy. The annual expenditures on prostate cancer screening by the national fee-for-service Medicare program were $447 million in 2009 US dollars. The mean annual screening cost at the HRR level ranged from $17 to $62 per beneficiary. Downstream biopsy-related procedures accounted for 72% of the overall screening costs and varied significantly across regions. Compared with men residing in HRRs that were in the lowest quartile for screening expenditures, men living in the highest HRR quartile were significantly more likely to be diagnosed with prostate cancer of any stage (incidence rate ratio [IRR] = 1.20, 95% confidence interval [CI] = 1.07-1.35) and localized cancer (IRR = 1.30, 95% CI = 1.15-1.47). The IRR for regional/metastasized cancer was also elevated, although not statistically significant (IRR = 1.31, 95% CI = 0.81-2.11). CONCLUSIONS: Medicare prostate cancer screening-related expenditures are substantial, vary considerably across regions, and are positively associated with rates of cancer diagnosis.

12. Martin, A. J., Lord, S. J., Verry, H. E., Stockler, M. R., & Emery, J. D. (2013). Risk assessment to guide prostate cancer screening decisions: a cost-effectiveness analysis. Med J Aust, 198(10), 546-550.

OBJECTIVES: To apply the most recent evidence from randomised trials of prostate-specific antigen (PSA) screening and explore the potential value of risk assessments to guide the use of PSA screening in practice. DESIGN: A decision model that incorporated a Markov process was developed in 2012 to estimate the net benefit and cost of PSA screening versus no screening as a function of baseline risk. MAIN OUTCOME MEASURES: Quality-adjusted life-2013s (QALYs) and costs. RESULTS: The harms of screening outweighed the benefits under a number of plausible scenarios. Conclusions were sensitive to the estimated quality-of-life impacts of prostate cancer treatment as well as the incidence of cancers not detected by screening tests (poorer prognosis) and those that were detected by screening tests (better prognosis). The base-case incremental cost-effectiveness ratio of PSA screening was $168,611 per QALY for men with average risk, $73,452 per QALY for men with two times the average risk, and $22,938 [corrected] per QALY for men with five times the average risk. CONCLUSIONS: PSA screening was not found to be cost-effective for men at an average-to-high risk of prostate cancer, but may be cost-effective for men at very high risk. Inexpensive approaches for identifying men at very high risk are needed, as is further research on the size of clinical benefit of early detection in this population. The potential for the costs of risk assessment to be offset by reduced costs of PSA screening also warrants investigation.

13. Pataky, R., Gulati, R., Etzioni, R., Black, P., Chi, K. N., Coldman, A. J., . . . Peacock, S. (2014). Is prostate cancer screening cost-effective? A microsimulation model of prostate-specific antigen-based screening for British Columbia, Canada. Int J Cancer, 135(4), 939-947. doi:10.1002/ijc.28732

Prostate-specific antigen (PSA) screening for prostate cancer may reduce mortality, but it incurs considerable risk of over diagnosis and potential harm to quality of life. Our objective was to evaluate the cost-effectiveness of PSA screening, with and without adjustment for quality of life, for the British Columbia (BC) population. We adapted an existing natural history model using BC incidence, treatment, cost and mortality patterns. The modeled mortality benefit of screening

derives from a stage-shift mechanism, assuming mortality reduction consistent with the European Study of Randomized Screening for Prostate Cancer. The model projected outcomes for 40-year-old men under 14 combinations of screening ages and frequencies. Cost and utility estimates were explored with deterministic sensitivity analysis. The incremental cost-effectiveness of regular screening ranged from $36,300/LYG, for screening every four years from ages 55 to 69 years, to $588,300/LYG, for screening every two years from ages 40 to 74 years. The marginal benefits of increasing screening frequency to 2 years or starting screening at age 40 years were small and came at significant cost. After utility adjustment, all screening strategies resulted in a loss of quality-adjusted life years (QALYs); however, this result was very sensitive to utility estimates. Plausible outcomes under a range of screening strategies inform discussion of prostate cancer screening policy in BC and similar jurisdictions. Screening may be cost-effective, but the sensitivity of results to utility values suggests individual preferences for quality versus quantity of life should be a key consideration.

14. Rao, K., Liang, S., Cardamone, M., Joshu, C. E., Marmen, K., Bhavsar, N., . . . Pollack, C. E. (2018). Cost implications of PSA screening differ by age. BMC Urol, 18(1), 38. doi:10.1186/s12894-018-0344-5

BACKGROUND: Multiple guidelines seek to alter rates of prostate-specific antigen (PSA)-based prostate cancer screening. The costs borne by payers associated with PSA-based screening for men of different age groups-including the costs of screening and subsequent diagnosis, treatment, and adverse events-remain uncertain. We sought to develop a model of PSA costs that could be used by payers and health care systems to inform cost considerations under a range of different scenarios. METHODS: We determined the prevalence of PSA screening among men aged 50 and higher using 2013-2014 data from a large, multispecialty group, obtained reimbursed costs associated with screening, diagnosis, and treatment from a commercial health plan, and identified transition probabilities for biopsy, diagnosis, treatment, and complications from the literature to generate a cost model. We estimated annual total costs for groups of men ages 50-54, 55-69, and 70+ years, and varied annual prostate cancer screening prevalence in each group from 5 to 50% and tested hypothetical examples of different test characteristics (e.g., true/false positive rate). RESULTS: Under the baseline screening patterns, costs of the PSA screening represented 10.1% of the total costs; costs of biopsies and associated complications were 23.3% of total costs; and, although only 0.3% of all screen eligible patients were treated, they accounted for 66.7% of total costs. For each 5-percentage point decrease in PSA screening among men aged 70 and older for a single calendar year, total costs associated with prostate cancer screening decreased by 13.8%. For each 5-percentage point decrease in PSA screening among men 50-54 and 55-69 years old, costs were 2.3% and 7.3% lower respectively. CONCLUSIONS: With constrained financial resources and with national pressure to decrease use of clinically unnecessary PSA-based prostate cancer screening, there is an opportunity for cost savings, especially by focusing on the downstream costs disproportionately associated with screening men 70 and older.

15. Richter, F., Dudley, A. W., Jr., Irwin, R. J., Jr., & Sadeghi-Nejad, H. (2001). Are we ordering too many PSA tests? Prostate cancer diagnosis and PSA screening patterns for a single Veterans Affairs Medical Center. J Cancer Educ, 16(1), 38-41. doi:10.1080/08858190109528722

BACKGROUND: Limits on the frequency of PSA testing and an endpoint for the age of the screened population have not been established. The numbers of performed serum PSA tests, cost evolution, and utilization patterns by various subspecialties in one medical center were analyzed to gain insight into trends in screening for early detection of prostate cancer and gather information about the appropriate use of PSA testing. METHOD: Computerized records were reviewed for numbers of PSA tests obtained, prostate biopsies performed, and prostate cancer cases diagnosed in the VA NJ-Health Care System from 1996 to 1998. In addition, PSA tests performed during two representative weeks in 1996 and 1997 were analyzed to evaluate a smaller cohort of patients with regard to age, consequences of the test results in their management, and subspecialties ordering the tests. RESULTS: PSA testing increased steadily between 1992 and 1998, with the most significant change (152% increase) between 1997 (9,410 tests) and 1998 (23,684). Prostate cancer diagnoses by biopsy were 164/434 (37.8%) in 1997 and 195/507 (38.5%) in 1998. For the 14,274 additional PSA tests obtained in 1998, 31 more prostate cancers were diagnosed. Prostate cancer diagnoses per PSA tests were 164/9,410

(1.8%) in 1997 and 195/23,684 (0.8%) in 1998. Primary care providers ordered 61% of the PSA tests. CONCLUSIONS: Most PSA tests at this institution were ordered by general practitioners, and the number of PSA tests ordered for men over 75 was high. The dramatic increase between 1997 and 1998 was not accompanied by a similar rise in the diagnosis of prostate cancer, raising the possibility of indiscriminate PSA testing or unnecessary repetition of testing. Guidelines for prostate cancer screening and continued PSA testing in the geriatric population may need further clarification.

16. Ross, K. S., Carter, H. B., Pearson, J. D., & Guess, H. A. (2000). Comparative efficiency of prostate-specific antigen screening strategies for prostate cancer detection. Jama, 284(11), 1399-1405.

CONTEXT: Despite widespread use of serum prostate-specific antigen (PSA) testing to detect prostate cancer, the relative effectiveness of different PSA screening strategies is unknown. OBJECTIVE: To compare prostate cancer mortality, PSA testing rates, and biopsy rates using various PSA screening strategies, including the standard strategy of annually testing men aged 50 through 75 years. DESIGN AND SETTING: A Monte-Carlo simulation based on a Markov model was used to simulate the natural history of prostate cancer using different starting ages, testing intervals, and PSA thresholds for prostate biopsy. Age-specific PSA levels and prostate biopsy detection probabilities were determined from population data and surgical series. MAIN OUTCOME MEASURES: Numbers of prevented prostate cancer deaths, PSA tests, and prostate biopsies per 1000 men aged 40 through 80 years, compared among 7 different strategies vs no screening. RESULTS: Compared with annual PSA testing beginning at age 50 years, the strategy of PSA testing at ages 40 and 45 years followed by biennial testing beginning at age 50 years was estimated to simultaneously reduce prostate cancer mortality and number of PSA tests and biopsies performed per 1000 men. Specifically, compared with no screening, the standard strategy prevents 3.2 deaths, with an additional 10,500 PSA tests and 600 prostate biopsies, while the earlier but less frequent strategy prevents 3.3 deaths, with an additional 7500 PSA tests and 450 prostate biopsies. Strategies that lowered the PSA threshold for prostate biopsy to below 4.0 ng/mL or strategies that used age-specific PSA levels were not more efficient than use of a PSA threshold of 4.0 ng/mL. These 2 findings remained true under all sensitivity analyses performed to test assumptions of the model. CONCLUSION: Recognizing that the efficacy of PSA screening is unproved, the standard strategy of annual PSA screening beginning at age 50 years appears to be less effective and more resource intensive compared with a strategy that begins earlier but screens biennially instead of annually. JAMA. 2000;284:1399-1405.

17. Roth, J. A., Gulati, R., Gore, J. L., Cooperberg, M. R., & Etzioni, R. (2016). Economic Analysis of Prostate-Specific Antigen Screening and Selective Treatment Strategies. JAMA Oncol, 2(7), 890-898. doi:10.1001/jamaoncol.2015.6275

IMPORTANCE: Prostate-specific antigen (PSA) screening for prostate cancer is controversial. Experts have suggested more personalized or more conservative strategies to improve benefit-risk tradeoffs, but the value of these strategies-particularly when combined with increased conservative management for low-risk cases-is uncertain. OBJECTIVES: To evaluate the potential cost-effectiveness of plausible PSA screening strategies and to assess the value added by increased use of conservative management among low-risk, screen-detected cases. DESIGN, SETTING, AND PARTICIPANTS: A microsimulation model of prostate cancer incidence and mortality was created. A simulated contemporary cohort of US men beginning at 40 years of age underwent 18 strategies for PSA screening. Treatment strategies included (1) contemporary treatment practices based on age and cancer stage and grade observed in the Surveillance, Epidemiology, and End Results program in 2010 or (2) selective treatment practices whereby cases with a Gleason score lower than 7 and clinical T2a stage cancer or lower are treated only after clinical progression, and all other cases undergo contemporary treatment practices. National and trial data on PSA growth, screening and biopsy patterns, incidence of prostate cancer, treatment distributions, treatment efficacy, mortality, health-related quality of life, and direct medical expenditure were analyzed. Data were collected from March 18, 2009, to August 15, 2014, and analyzed from November 20, 2012, to December 11, 2015. INTERVENTIONS: Eighteen screening strategies that vary by start and stop age, screening interval, and criteria for biopsy referral and contemporary or selective treatment practices. MAIN OUTCOMES AND MEASURES: Life-years (LYs), quality-adjusted life-years (QALYs), direct medical expenditure, and cost per LY and QALY gained. RESULTS: All 18 screening strategies were associated with increased LYs

(range, 0.03-0.06) and costs ($263-$1371) compared with no screening, with the cost ranging from $7335 to $21649 per LY. With contemporary treatment, only strategies with biopsy referral for PSA levels higher than 10.0 ng/mL or age-dependent thresholds were associated with increased QALYs (0.002-0.004), and only quadrennial screening of patients aged 55 to 69 years was potentially cost-effective in terms of cost per QALY (incremental cost-effectiveness ratio, $92446). With selective treatment, all strategies were associated with increased QALYs (0.002-0.004), and several strategies were potentially cost-effective in terms of cost per QALY (incremental cost-effectiveness ratio, $70831-$136332). CONCLUSIONS AND RELEVANCE: For PSA screening to be cost-effective, it needs to be used conservatively and ideally in combination with a conservative management approach for low-risk disease.

18. **Sennfalt, K., Sandblom, G., Carlsson, P., & Varenhorst, E. (2004). Costs and effects of prostate cancer screening in Sweden--a 15-year follow-up of a randomized trial. Scand J Urol Nephrol, 38(4), 291-298.**

    OBJECTIVE: To estimate the lifetime cost per detected potentially curable cancer and the economic impact on healthcare of repeated screening for prostate cancer in Sweden in a cohort of men aged 50-69 years. MATERIAL AND METHODS: All 9171 men in a geographically defined population were included: 1492 were randomized to screening in four rounds every third year and 7679 constituted a control group. Digital rectal examination and prostate-specific antigen screening in different combinations were used as diagnostic measures. Costs associated with administration of the screening programme, loss of patient time, diagnostic measures and management strategies were included. A decision model was developed to calculate the total cost of the programme. RESULTS: The incremental cost per extra detected localized cancer was 168,000 SEK and per potentially curable cancer 356,000 SEK. Introducing this screening programme for prostate cancer in Sweden would incur 244 million SEK annually in additional costs for screening and treatment compared to a non-screening strategy. CONCLUSION: There is still no scientific evidence that patients will benefit from screening programmes. Prostate cancer screening would probably be perceived as cost-effective if potentially curable patients gained on average at least 1 year of survival.

19. **Shao, Y. H., Albertsen, P. C., Shih, W., Roberts, C. B., & Lu-Yao, G. L. (2011). The impact of PSA testing frequency on prostate cancer incidence and treatment in older men. Prostate Cancer Prostatic Dis, 14(4), 332-339. doi:10.1038/pcan.2011.29**

    To quantify the downstream impact of PSA testing on cancer characteristics and utilization of cancer therapies among men aged 70 or older, we utilized patients diagnosed with prostate cancer in 2004-2005 in the Surveillance, Epidemiology and End Results (SEER)-Medicare and their Medicare claims before their cancer diagnosis during 2000-2005. Among men in the highest testing group (4-6 PSA tests), 75% were diagnosed with low- or intermediate-risk of disease, but 77% received treatments within 180 days of cancer diagnosis. More than 45% of newly diagnosed patients in 2004-2005 had 4-6 PSA tests before their cancer diagnosis during 2000-2005. Men in the high testing group were 3.57 times more likely to receive cancer treatments (either surgery, radiation or hormonal therapy) when compared with men who had no previous PSA testing during the same time period. Among men aged 75+ diagnosed with low-risk cancer, men in the high testing group were 78% more likely to receive treatment than those who had no previous PSA testing. In conclusion, given the lack of evidence of effective treatment for elderly patients diagnosed with low- and intermediate-risk prostate cancer and our inability to distinguish indolent from aggressive cancer, more frequent PSA testing among elderly population may exacerbate the risk of overdiagnosis and overtreatment.

20. **Stone, C. A., May, F. W., Pinnock, C. B., Elwood, M., & Rowett, D. S. (2005). Prostate cancer, the PSA test and academic detailing in Australian general practice: an economic evaluation. Aust N Z J Public Health, 29(4), 349-357.**

    OBJECTIVES: To evaluate whether introduction of a national education program for GPs to improve decision making relating to the use of prostate specific antigen (PSA) testing for screening represents 'value-for-money' from the perspective of the Australian Government. METHODS: The annual equivalent costs and consequences of a proposed national program in steady state operation are estimated for Australia using 1996 as the reference year. Because of the controversy about the efficacy of screening using PSA testing, two scenarios are modelled.

Uncertainty in the model is examined using Monte Carlo simulation methods. RESULTS: In scenario one, our model predicts that the national program would cost dollars 12.5 million (gross) or dollars 6.6 million (net), would reduce the burden of disease by 4.7% of total DALYs due to prostate cancer in those aged 70 and over, with no loss of life and an incremental cost effectiveness ratio (ICER) of dollars 16,000/DALY (gross) and dollars 8,500/DALY (net). In scenario two, the proposed program would cost dollars 12.5 million (gross) or dollars 7.1 million (net), would reduce the burden of disease by 3.1% of total, increase by 44 the prostate cancer deaths at an ICER of dollars 24,000/DALY (gross) and dollars 14,000/DALY (net). CONCLUSIONS: These findings, with an overall health benefit at moderate cost and acceptable ICER, support the case for consideration of a national education program on the assumption that prostate cancer screening over age 70 does not reduce mortality. A larger Australian study currently being conducted should provide stronger evidence on the value of implementing a full national program.

21. Tawfik, A. (2015). Prostate-Specific Antigen (PSA)-Based Population Screening for Prostate Cancer: An Economic Analysis. Ont Health Technol Assess Ser, 15(11), 1-37.

BACKGROUND: The prostate-specific antigen (PSA) blood test has become widely used in Canada to test for prostate cancer (PC), the most common cancer among Canadian men. Data suggest that population-based PSA screening may not improve overall survival. OBJECTIVES: This analysis aimed to review existing economic evaluations of population-based PSA screening, determine current spending on opportunistic PSA screening in Ontario, and estimate the cost of introducing a population-based PSA screening program in the province. METHODS: A systematic literature search was performed to identify economic evaluations of population-based PSA screening strategies published from 1998 to 2013. Studies were assessed for their methodological quality and applicability to the Ontario setting. An original cost analysis was also performed, using data from Ontario administrative sources and from the published literature. One-year costs were estimated for 4 strategies: no screening, current (opportunistic) screening of men aged 40 years and older, current (opportunistic) screening of men aged 50 to 74 years, and population-based screening of men aged 50 to 74 years. The analysis was conducted from the payer perspective. RESULTS: The literature review demonstrated that, overall, population-based PSA screening is costly and cost-ineffective but may be cost-effective in specific populations. Only 1 Canadian study, published 15 years ago, was identified. Approximately $119.2 million is being spent annually on PSA screening of men aged 40 years and older in Ontario, including close to $22 million to screen men younger than 50 and older than 74 years of age (i.e., outside the target age range for a population-based program). A population-based screening program in Ontario would cost approximately $149.4 million in the first year. LIMITATIONS: Estimates were based on the synthesis of data from a variety of sources, requiring several assumptions and causing uncertainty in the results. For example, where Ontario-specific data were unavailable, data from the United States were used. CONCLUSIONS: PSA screening is associated with significant costs to the health care system when the cost of the PSA test itself is considered in addition to the costs of diagnosis, staging, and treatment of screen-detected PCs.

22. Walter, L. C., Fung, K. Z., Kirby, K. A., Shi, Y., Espaldon, R., O'Brien, S., . . . Hoffman, R. M. (2013). Five-year downstream outcomes following prostate-specific antigen screening in older men. JAMA Intern Med, 173(10), 866-873. doi:10.1001/jamainternmed.2013.323

IMPORTANCE: Despite ongoing controversies surrounding prostate-specific antigen (PSA) screening, many men 65 years or older undergo screening. However, few data exist that quantify the chain of events following screening in clinical practice to better inform decisions. OBJECTIVE: To quantify 5-year downstream outcomes following a PSA screening result exceeding 4.0 ng/mL in older men. DESIGN AND SETTING: Longitudinal cohort study in the national Veterans Affairs health care system. PARTICIPANTS: In total, 295,645 men 65 years or older who underwent PSA screening in the Veterans Affairs health care system in 2003 and were followed up for 5 years using national Veterans Affairs and Medicare data. MAIN OUTCOME MEASURES: Among men whose index screening PSA level exceeded 4.0 ng/mL, we determined the number who underwent prostate biopsy, were diagnosed as having prostate cancer, were treated for prostate cancer, and were treated for prostate cancer and were alive at 5 years according to baseline characteristics. Biopsy and treatment complications were also assessed. RESULTS: In total, 25,208 men (8.5%) had an index PSA level exceeding 4.0 ng/mL. During the 5-year follow-up

period, 8313 men (33.0%) underwent at least 1 prostate biopsy, and 5220 men (62.8%) who underwent prostate biopsy were diagnosed as having prostate cancer, of whom 4284 (82.1%) were treated for prostate cancer. Performance of prostate biopsy decreased with advancing age and worsening comorbidity (P < .001), whereas the percentage treated for biopsy-detected cancer exceeded 75% even among men 85 years or older, those with a Charlson-Deyo Comorbidity Index of 3 or higher, and those having low-risk cancer. Among men with biopsy-detected cancer, the risk of death from non-prostate cancer causes increased with advancing age and worsening comorbidity (P < .001). In total, 468 men (5.6%) had complications within 7 days after prostate biopsy. Complications of prostate cancer treatment included new urinary incontinence in 584 men (13.6%) and new erectile dysfunction 588 men (13.7%). CONCLUSIONS AND RELEVANCE: Performance of prostate biopsy is uncommon in older men with abnormal screening PSA levels and decreases with advancing age and worsening comorbidity. However, once cancer is detected on biopsy, most men undergo immediate treatment regardless of advancing age, worsening comorbidity, or low-risk cancer. Understanding downstream outcomes in clinical practice should better inform individualized decisions among older men considering PSA screening.

23. **Zanwar, P., Lin, Y. L., Kuo, Y. F., & Goodwin, J. S. (2016). Downstream tests, treatments, and annual direct payments in older men cared for by primary care providers with high or low prostate-specific antigen screening rates using 100 percent Texas U.S. Medicare public insurance claims data: a retrospective cohort study. BMC Health Serv Res, 16, 17. doi:10.1186/s12913-016-1265-1**

BACKGROUND: All authorities recommend against prostate specific antigen (PSA) screening in men 75 years and older. However, some primary care physicians (PCPs) continue to have high rates of PSA, with large variation in testing. We assessed the tests, treatments, and payments for prostate cancer care in men aged 75 or older who have PCPs with high or low PSA testing rates. METHODS: We performed a retrospective cohort study using the 2010 Medicare beneficiaries aged 75 or older in Texas, United States who had no prostate cancer in 2007-2009 and had an identifiable PCP. We first identified high vs. low PSA testing PCPs, and then grouped older men in the two PCP groups. We determined health care visits to any provider and to urologists in office and outpatient settings. We estimated the direct medical payments for prostate cancer care for diagnostics, treatments and visits to providers in 2010-2011 using the generalized gamma model with log link function. RESULTS: In multilevel, multivariable analyses, 25.4% (n = 550) of PCPs had PSA testing rates in men aged 75 or older that were significantly higher than the mean rate of all 2,169 Texas PCPs; 29.4% (n = 638) had rates that were significantly lower. In all, 22,853 vs. 23,929 older men were cared for by PCPs with high vs. low testing rates. Older men cared for by high PSA rate PCPs were more likely to receive a PSA test (OR 3.64, 95% CI 3.48-3.80), a biopsy (OR 1.16, 95% CI 1.02-1.31), an ultrasound (OR 1.19, 95% CI 1.07-1.32) or any radiation treatment (OR 1.31, 95% CI 1.03-1.66) than men cared for by low PSA rate PCPs. Men with high PSA rate PCPs were 1.21 (95% CI 1.05-1.39) times more likely to have such outpatient visits. The average annual adjusted Medicare payments for prostate cancer care was $25.60 higher for patients cared for by PCPs with high PSA test rates. CONCLUSIONS: Older men seeing PCPs with high rates of PSA testing undergo more testing and treatments for prostate cancer, with higher Medicare insurance payments. Future studies are needed to delineate whether men seeing PCPs with low testing rates likely received PSA tests from other providers.

24. **Zhang, J., Denton, B. T., Balasubramanian, H., Shah, N. D., & Inman, B. A. (2012). Optimization of PSA screening policies: a comparison of the patient and societal perspectives. Med Decis Making, 32(2), 337-349. doi:10.1177/0272989X11416513**

OBJECTIVE: To estimate the benefit of PSA-based screening for prostate cancer from the patient and societal perspectives. METHOD: A partially observable Markov decision process model was used to optimize PSA screening decisions. Age-specific prostate cancer incidence rates and the mortality rates from prostate cancer and competing causes were considered. The model trades off the potential benefit of early detection with the cost of screening and loss of patient quality of life due to screening and treatment. PSA testing and biopsy decisions are made based on the patient's probability of having prostate cancer. Probabilities are inferred based on the patient's complete PSA history using Bayesian updating. DATA SOURCES: The results of all PSA tests and biopsies done in Olmsted County, Minnesota, from 1993 to 2005 (11,872 men and 50,589 PSA test results). OUTCOME MEASURES: Patients' perspective: to maximize expected quality-adjusted

life years (QALYs); societal perspective: to maximize the expected monetary value based on societal willingness to pay for QALYs and the cost of PSA testing, prostate biopsies, and treatment. RESULTS: From the patient perspective, the optimal policy recommends stopping PSA testing and biopsy at age 76. From the societal perspective, the stopping age is 71. The expected incremental benefit of optimal screening over the traditional guideline of annual PSA screening with threshold 4.0 ng/mL for biopsy is estimated to be 0.165 QALYs per person from the patient perspective and 0.161 QALYs per person from the societal perspective. PSA screening based on traditional guidelines is found to be worse than no screening at all. CONCLUSIONS: PSA testing done with traditional guidelines underperforms and therefore underestimates the potential benefit of screening. Optimal screening guidelines differ significantly depending on the perspective of the decision maker.

Back imaging for patients with non-specific low back pain

27. Aaronson, E. L., Yun, B. J., Mort, E., Brown, D., Raja, A. S., Kaafarani, H. M. A., . . . Lee, J. (2017). Association of magnetic resonance imaging for back pain on seven-day return visit to the Emergency Department. Emerg Med J, 34(10), 677-679. doi:10.1136/emermed-2016-206250

BACKGROUND: The prevalence of back pain is rising, as is the use of high-cost imaging in the ED. The objective of our study was to determine if an MRI in the ED for patients with back pain resulted in a lower incidence of ED return visit and to determine if these patients had longer ED length of stay (LOS) and use of ED observation. METHODS: A retrospective cohort study of consecutive patients seen with back pain was conducted at an urban, university-affiliated ED between 1 January 2012 and 11 July 2014. The association of MRI on return within 7 days was assessed using a chi(2) test and a multivariable logistic regression model and the difference in median ED LOS was compared using a Wilcoxon rank-sum test. RESULTS: During the study period, 6094 patients were evaluated in the ED with back pain as the primary diagnosis. Of these, 797 (13%) received an MRI. Among all patients with back pain, 277 (4.5%) returned within 7 days. Univariate analysis found that patients who received an MRI were no less likely to return within 7 days than patients who did not (4.3% vs 4.6%; p=0.68). Patients who had an MRI were more likely to be admitted to observation (74.2% vs 10.8%; p<0.0001) and had a longer ED LOS (median 4.8 hours vs 2.7; p<0.0001). Multivariable regression confirmed that MRI did not decrease the rate of a 7-day return visit (OR=0.98; 95% CI 0.68 to 1.42). CONCLUSIONS: In patients with uncomplicated back pain, performing an MRI will not mitigate their likelihood of return; however, it leads to a longer ED LOS and more ED observation admissions.

28. Fried, J. G., Andrew, A. S., Ring, N. Y., & Pastel, D. A. (2018). Changes in Primary Care Health Care Utilization after Inclusion of Epidemiologic Data in Lumbar Spine MR Imaging Reports for Uncomplicated Low Back Pain. Radiology, 287(2), 563-569. doi:10.1148/radiol.2017170722

Purpose To determine whether inclusion of an epidemiologic statement in radiology reports of lumbar magnetic resonance (MR) imaging influences downstream health care utilization in the primary care population. Materials and Methods Beginning July 1, 2013, a validated epidemiologic statement regarding prevalence of common findings in asymptomatic patients was included in all lumbar MR imaging reports at a tertiary academic medical center. Data were collected from July 1, 2012, through June 30, 2014, and retrospective analysis was completed in September 2016. The electronic medical record was reviewed to capture health care utilization rates in patients for 1 year after index MR imaging. Of 4527 eligible adult patients with low back pain referred for lumbar spine MR imaging during the study period, 375 patients had their studies ordered by in-network primary care providers, did not have findings other than degenerative disease, and had at least one follow-up encounter within the system within 1 year of index MR imaging. In the before-and-after study design, a pre-statement-implementation cohort was compared with a post-statement-implementation cohort by using univariate and multivariate statistical models to evaluate treatment utilization rates in these groups. Results Patients in the statement group were 12% less likely to be referred to a spine specialist (137 of 187 [73%] vs 159 of 188 [85%]; P = .007) and were 7% less likely to undergo repeat imaging (seven of 187 [4%] vs 20 of 188 [11%]; P = .01) compared with patients in the nonstatement group. The intervention was not

associated with any change in narcotic prescription (53 of 188 [28%] vs 54 of 187 [29%]; P = .88) or with the rate of low back surgery (24 of 188 [13%] vs 16 of 187 [9%]; P = .19). Conclusion In this study, inclusion of a simple epidemiologic statement in lumbar MR imaging reports was associated with decreased utilization in high-cost domains of low back pain management. ((c)) RSNA, 2018.

29. Gilbert, F. J., Grant, A. M., Gillan, M. G. C., Vale, L., Scott, N. W., Campbell, M. K., . . . Porter, R. W. (2004). Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial. Health Technology Assessment, 8(17), 1-+.

Objectives: To establish whether the early use of sophisticated imaging techniques influences the clinical management and outcome of patients with low back pain (LBP) and whether it is cost-effective. Design: A pragmatic multicentre randomised controlled trial using a standard two parallel group approach incorporating an economic evaluation. For a subgroup of trial participants, a controlled 'before and after' approach was used to assess the impact of 'early imaging' on clinicians' diagnostic and therapeutic confidence. Setting and participants: A total of 782 participants who had been referred by their general practitioner to a consultant orthopaedic specialist or neurosurgeon because of symptomatic lumbar spine disorders. The study included 14 hospitals in Scotland and one in England over a 24-month period. Results: Participants in both groups reported an improvement in health status at 8 and 24 months with the 'early imaging' group having statistically significantly better outcome. Other than the proportion of participants receiving imaging (90% versus 30%), there were few differences between the groups in the management received throughout the 24-month follow-up. The total number of outpatient consultations in the two groups was similar although more people in the 'early imaging' group had return outpatient appointments during the 8-month follow-up. Clinicians' diagnostic confidence, between trial entry and follow-up, increased significantly for both groups with a greater increase in the 'early imaging' group. The cost of imaging was the main determinant of the difference in total costs between the groups and it was estimated that 'early imaging' could provide an additional 0.07 quality-adjusted life-years (QALYs), at an additional average cost of pound61 over the 24-month follow-up. Using non-imputed costs and QALYs but adjusted for baseline differences in EQ-5D score, the mean incremental cost per QALY of 'early imaging' was pound870. The results were sensitive to the costs of imaging and the confidence intervals surrounding estimates of average costs and QALYs. Conclusions: The early use of sophisticated imaging does not appear to affect management overall but does result in a slight improvement in clinical outcome at an estimated cost of pound870 per QALY. Imaging was associated with an increase in clinicians' diagnostic confidence, particularly for non-specialists. Further research is required to determine if more rapid referral to sophisticated imaging and secondary care is important in the acute episode and whether the use of imaging would be more beneficial for particular categories of LBP.

30. Gilbert, F. J., Grant, A. M., Gillan, M. G., Vale, L. D., Campbell, M. K., Scott, N. W., . . . Scottish Back Trial, G. (2004). Low back pain: influence of early MR imaging or CT on treatment and outcome--multicenter randomized trial. Radiology, 231(2), 343-351. doi:10.1148/radiol.2312030886

PURPOSE: To establish whether early use of magnetic resonance (MR) imaging or computed tomography (CT) influences treatment and outcome of patients with low back pain (LBP) and whether it is cost-effective. MATERIALS AND METHODS: In a multicenter randomized study, two imaging policies for LBP were compared in 782 participants with symptomatic lumbar spine disorders who were referred to orthopedists or neurosurgeons. Participants were randomly allocated to early (393 participants; mean age, 43.9 years; range, 16-82 years) or delayed selective (389 participants; mean age, 42.8 years; range, 14-82 years) imaging groups. Delayed selective imaging referred to imaging restricted to patients in whom a clear clinical need subsequently developed. Main outcome measures were Aberdeen Low Back Pain (ALBP) score, Short Form 36 (SF-36) score (for multidimensional health status), EuroQol (EQ-5D) score (for quality-adjusted life-year [QALY] estimates), and healthcare resource use at 8 and 24 months after randomization. Data were evaluated with analysis of covariance, ordinal logistic regression analysis, and chi(2) and Mann-Whitney tests. RESULTS: Both groups showed improvement in ALBP score, but this was greater in the early group (adjusted mean difference between groups, -3.05 points [95% CI: -5.16, -0.95; P =.005] and -3.62 points [95% CI: -5.92, -1.32; P =.002]

at 8 and 24 months, respectively). Scores for SF-36 (bodily pain domain) and EQ-5D were also significantly better at 24 months. Clinical treatment was similar in both groups. Differences in total costs reflected cost of imaging. Imaging provided an adjusted mean additional QALY of 0.041 during 24 months at a mean incremental cost per QALY of $2,124. CONCLUSION: Early use of imaging does not appear to affect treatment overall. Decisions about the use of imaging depend on judgments concerning whether the small observed improvement in outcome justifies additional cost.

31. Gilbert, F. J., Grant, A. M., Gillan, M. G., Vale, L., Scott, N. W., Campbell, M. K., . . . Porter, R. W. (2004). Does early imaging influence management and improve outcome in patients with low back pain? A pragmatic randomised controlled trial. Health Technol Assess, 8(17), iii, 1-131.

OBJECTIVES: To establish whether the early use of sophisticated imaging techniques influences the clinical management and outcome of patients with low back pain (LBP) and whether it is cost-effective. DESIGN: A pragmatic multicentre randomised controlled trial using a standard two parallel group approach incorporating an economic evaluation. For a subgroup of trial participants, a controlled 'before and after' approach was used to assess the impact of 'early imaging' on clinicians' diagnostic and therapeutic confidence. SETTING AND PARTICIPANTS: A total of 782 participants who had been referred by their general practitioner to a consultant orthopaedic specialist or neurosurgeon because of symptomatic lumbar spine disorders. The study included 14 hospitals in Scotland and one in England over a 24-month period. RESULTS: Participants in both groups reported an improvement in health status at 8 and 24 months with the 'early imaging' group having statistically significantly better outcome. Other than the proportion of participants receiving imaging (90% versus 30%), there were few differences between the groups in the management received throughout the 24-month follow-up. The total number of outpatient consultations in the two groups was similar although more people in the 'early imaging' group had return outpatient appointments during the 8-month follow-up. Clinicians' diagnostic confidence, between trial entry and follow-up, increased significantly for both groups with a greater increase in the 'early imaging' group. The cost of imaging was the main determinant of the difference in total costs between the groups and it was estimated that 'early imaging' could provide an additional 0.07 quality-adjusted life-years (QALYs), at an additional average cost of 61 British pounds over the 24-month follow-up. Using non-imputed costs and QALYs but adjusted for baseline differences in EQ-5D score, the mean incremental cost per QALY of 'early imaging' was 870 British pounds. The results were sensitive to the costs of imaging and the confidence intervals surrounding estimates of average costs and QALYs. CONCLUSIONS: The early use of sophisticated imaging does not appear to affect management overall but does result in a slight improvement in clinical outcome at an estimated cost of 870 British pounds per QALY. Imaging was associated with an increase in clinicians' diagnostic confidence, particularly for non-specialists. Further research is required to determine if more rapid referral to sophisticated imaging and secondary care is important in the acute episode and whether the use of imaging would be more beneficial for particular categories of LBP.

32. Graves, J. M., Fulton-Kehoe, D., Jarvik, J. G., & Franklin, G. M. (2018). Impact of an Advanced Imaging Utilization Review Program on Downstream Health Care Utilization and Costs for Low Back Pain. Med Care, 56(6), 520-528. doi:10.1097/MLR.0000000000000917

BACKGROUND: Early magnetic resonance imaging (MRI) for acute low back pain (LBP) has been associated with increased costs, greater health care utilization, and longer disability duration in workers' compensation claimants. OBJECTIVES: To assess the impact of a state policy implemented in June 2010 that required prospective utilization review (UR) for early MRI among workers' compensation claimants with LBP. RESEARCH DESIGN: Interrupted time series. SUBJECTS: In total, 76,119 Washington State workers' compensation claimants with LBP between 2006 and 2014. MEASURES: Proportion of workers receiving imaging per month (MRI, computed tomography, radiographs) and lumbosacral injections and surgery; mean total health care costs per worker; mean duration of disability per worker. Measures were aggregated monthly and attributed to injury month. RESULTS: After accounting for secular trends, decreases in early MRI [level change: -5.27 (95% confidence interval, -4.22 to -6.31); trend change: -0.06 (-0.01 to -0.12)], any MRI [-4.34 (-3.01 to -5.67); -0.10 (-0.04 to -0.17)], and injection [trend change: -0.12 (-0.06 to -0.18)] utilization were associated with the policy. Radiograph utilization

increased in parallel [level change: 2.46 (1.24-3.67)]. In addition, the policy resulted in significant decreasing changes in mean costs per claim, mean disability duration, and proportion of workers who received disability benefits. The policy had no effect on computed tomography or surgery utilization. CONCLUSIONS: The UR policy had discernable effects on health care utilization, costs, and disability. Integrating evidence-based guidelines with UR can improve quality of care and patient outcomes, while reducing use of low-value health services.

33. Hollingworth, W., Gray, D. T., Martin, B. I., Sullivan, S. D., Deyo, R. A., & Jarvik, J. G. (2003). Rapid magnetic resonance imaging for diagnosing cancer-related low back pain. J Gen Intern Med, 18(4), 303-312.

OBJECTIVES: This study compared the relative efficiency of lumbar X-ray and rapid magnetic resonance (MR) imaging for diagnosing cancer-related low back pain (LBP) in primary care patients. DESIGN: We developed a decision model with Markov state transitions to calculate the cost per case detected and cost per quality-adjusted life year (QALY) of rapid MR imaging. Model parameters were estimated from the medical literature. The costs of X-ray and rapid MR were calculated in an activity-based costing study. SETTING AND PATIENTS: A hypothetical cohort of primary care patients with LBP referred for imaging to exclude cancer as the cause of their pain. MAIN RESULTS: The rapid MR strategy was more expensive due to higher initial imaging costs and larger numbers of patients requiring conventional MR and biopsy. The overall sensitivity of the rapid MR strategy was higher than that of the X-ray strategy (62% vs 55%). However, because of low pre-imaging prevalence of cancer-related LBP, this generates <1 extra case per 1,000 patients imaged. Therefore, the incremental cost per case detected using rapid MR was high ($213,927). The rapid MR strategy resulted in a small increase in quality-adjusted survival (0.00043 QALYs). The estimated incremental cost per QALY for the rapid MR strategy was $296,176. CONCLUSIONS: There is currently not enough evidence to support the routine use of rapid MR to detect cancer as a cause of LBP in primary care patients.

34. Hourcade, S., & Treves, R. (2002). Computed tomography in low back pain and sciatica. A retrospective study of 132 patients in the Haute-Vienne district of France. Joint Bone Spine, 69(6), 589-596.

AIMS: To evaluate physician compliance with the guidelines of the National Agency for Accreditation and Health Evaluation (ANAES) and the Consensus Conference on the use of medical imagery in low back pain and sciatica. METHODS: We performed a retrospective study of 132 computed tomography scans (CTs) of the lumbar spine performed in one public and one private healthcare facility in the Haute-Vienne district, France. For each patent, the clinical findings, results of other investigations, prescriptions, and procedures reimbursed by the universal health insurance system were recorded. RESULTS: Guidelines on imagery were followed in 2% of patients with chronic nonspecific low back pain. In 72% of patients, CT results had no influence on the subsequent clinical management. The guidelines were followed more often in patients with sciatica: 85% underwent CT more than 4 weeks after the initial painful episode. However, before CT was ordered, only 54% received appropriate initial treatment with analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or muscle relaxants. Among these patients, 25% also received second-line medical therapy consisting of facet joint injection, conventional traction and, after the initial acute phase, physical therapy. In 39% of the sciatica patients, the imaging results had no effect on subsequent management. Among these patients, 12% underwent surgery for disk herniation. CONCLUSIONS: Ten years after the consensus conference and despite the publication of the ANAES guidelines, there is still a wide gap between observed practice and recommendations for optimal management. The consequences of this extend beyond unnecessary expenses for the universal health insurance system to include important deleterious effects on the patients. In particular, prompt appropriate management may help to avoid progression to chronic low back pain and unnecessary imaging studies and surgical procedures, which often have devastating social and occupational consequences.

35. Jensen, R. K., Claus, M., & Leboeuf-Yde, C. (2010). Routine versus needs-based MRI in patients with prolonged low back pain: a comparison of duration of treatment, number of clinical contacts and referrals to surgery. Chiropr Osteopat, 18(2), 19. doi:10.1186/1746-1340-18-19

BACKGROUND: The routine use of radiology is normally discouraged in patients with low back pain (LBP). Magnetic Resonance Imaging (MRI) provides clinicians and patients with detailed knowledge of spinal structures and has no known physical side effects. It is possible that insight into the pathological changes in LBP patients could affect patient management. However, to our knowledge, this has never been tested. Until June 2006, all patients at our specialised out-patient public clinic were referred for MRI on the basis of clinical indications, economic constraints, and availability of MRI (the "needs-based MRI" group). As a new approach, we now refer all patients who meet certain criteria for routine up-front MRI before the clinical examination (the "routine MRI" group). OBJECTIVES: The aims of this study were to investigate if these two MRI approaches resulted in differences in: (1) duration of treatment, (2) number of contacts with clinicians, and (3) referral for surgery. DESIGN: Comparison of two retrospective clinical cohorts. METHOD: Files were retrieved from consecutive patients in both groups. Criteria for referral were: (1) LBP or leg pain of at least 3 on an 11-point Numeric Rating Scale, (2) duration of present symptoms from 2 to12 months and (3) age above 18 years. A comparison was made between the "needs-based MRI" and "routine MRI" groups on the outcomes of duration of treatment and use of resources. RESULTS: In all, 169 "needs-based MRI" and 208 "routine MRI" patient files were identified. The two groups were similar in age, sex, and severity of LBP. However, the median duration of treatment for the "needs-based MRI" group was 160 versus 115 days in the "routine MRI" group ($p = 0.0001$). The median number of contacts with clinicians for the "needs-based MRI" group was 4 versus 3 for the "routine MRI" group ($p = 0.003$). There was no difference between the two approaches in frequency of referral for back surgery ($p = 0.81$). When the direct clinical costs were compared, the "routine MRI" group was less costly but only by euro11. CONCLUSION: In our clinic, the management strategy of routinely performing an up-front MRI at the start of treatment did reduce the duration of treatment and number of contacts with clinicians, and did not increase the rate of referral for back surgery. Also, the direct costs were not increased.

Lurie, J. D., Birkmeyer, N. J., & Weinstein, J. N. (2003). Rates of advanced spinal imaging and spine surgery. Spine (Phila Pa 1976), 28(6), 616-620. doi:10.1097/01.Brs.0000049927.37696.Dc STUDY DESIGN: Small area analysis. OBJECTIVES: To determine the association between the rates of advanced spinal imaging and spine surgery across geographic areas. SUMMARY OF BACKGROUND DATA: The rates of spine surgery in the United States have increased along with a concurrent rise in the use of advanced spinal imaging: CT and MRI. Spine surgery rates vary six-fold across geographic areas of the United States. Differences in patient populations and health care supply have explained only about 10% of this variation. METHODS: We used a random 5% sample of Medicare's National Claims History Part B files for 1996 and 1997 to determine procedure rates across 306 Hospital Referral Regions. We analyzed the association between spinal imaging and spine surgery using linear regression. Main outcome measures were rates of procedures and coefficients of determination (R2). RESULTS: The rates of advanced spinal imaging (CT and MRI combined) varied 5.5-fold across geographic areas. Areas with higher rates of MRI had higher rates of spine surgery overall ($r = 0.46$) and spinal stenosis surgery specifically ($r = 0.37$). The rates of advanced spinal imaging accounted for 22% of the variability in overall spine surgery rates ($R2 = 0.22$, $P < 0.001$) and 14% of the variability in lumbar stenosis surgery rates ($R2 = 0.14$, $P < 0.001$). A simulation model showed that MRIs obtained in the patients undergoing surgery accounted for only a small part of the correlation between MRI and total spine surgery rates. CONCLUSIONS: A significant proportion of the variation in rates of spine surgery can be explained by differences in the rates of advanced spinal imaging. The indications for advanced spinal imaging are not firmly agreed on, and the appropriateness of many of these imaging studies has been questioned. Improved consensus on the use and interpretation of advanced spinal imaging studies could have an important effect on variation in spine surgery rates.

36. Miller, P., Kendrick, D., Bentley, E., & Fielding, K. (2002). Cost-effectiveness of lumbar spine radiography in primary care patients with low back pain. Spine (Phila Pa 1976), 27(20), 2291-2297. doi:10.1097/01.BRS.0000029264.83803.74

STUDY DESIGN: Fifty-two practices in the East Midlands, United Kingdom, were included. OBJECTIVES: To test the hypothesis that referral for lumbar spine radiography is cost-effective in primary care patients with low back pain of at least 6 weeks' duration compared with usual care in which referral is not routine. SUMMARY OF BACKGROUND DATA: Lumbar spine radiography is commonly used in the management of low back pain, although the yield of findings that alter clinical management is low. Evidence is needed on the cost-effectiveness of lumbar spine radiographs in patients with low back pain. METHODS: A prospective economic analysis alongside a randomized controlled trial was used. Outcomes included the Roland disability score, pain, health status scale, EuroQol, satisfaction, direct health care costs (primary, secondary, and community care; prescribed and over-the-counter medicines; special equipment), and indirect costs (informal care, extra expenses, welfare benefits, loss of earnings and productivity). RESULTS A total of 210 participants were randomly assigned to lumbar spine radiography, and 211, to usual care. At 9 months' postrandomization, no difference between the groups was found in any health outcomes other than satisfaction. The intervention group had a higher overall satisfaction score (21 19, < 0.01). The intervention group had higher direct costs (150 pounds sterling vs 109 pounds sterling, < 0.01). Cost-effectiveness analysis shows that patient satisfaction can be increased using lumbar radiography but at an additional cost (point estimate 20 pounds sterling per point on satisfaction scale). The simulated distribution based on trial data shows that only when a 1-point increase in satisfaction is valued at more than 50 pounds sterling can it be claimed that radiography is cost-effective in these terms (incremental net monetary benefit mean = 116 pounds sterling, 95% CI pound 7, 225 pounds sterling). CONCLUSIONS: Radiography is likely to be cost-effective only when satisfaction is valued relatively highly. Strategies to enhance satisfaction for patients with low back pain without using lumbar radiography should be pursued.

37. Shreibati, J. B., & Baker, L. C. (2011). The relationship between low back magnetic resonance imaging, surgery, and spending: impact of physician self-referral status. Health Serv Res, 46(5), 1362-1381. doi:10.1111/j.1475-6773.2011.01265.x

OBJECTIVE: To examine the relationship between use of magnetic resonance imaging (MRI) and receipt of surgery for patients with low back pain. DATA SOURCES: Medicare claims for a 20 percent sample of beneficiaries from 1998 to 2005. STUDY DESIGN: We identify nonradiologist physicians who appear to begin self-referral arrangements for MRI between 1999 and 2005, as well as their patients who have a new episode of low back pain care during this time. We focus on regression models that identify the relationship between receipt of MRI and subsequent use of back surgery and health care spending. Receipt of MRI may be endogenous, so we use physician acquisition of MRI as an instrument for receipt of MRI. The models adjust for demographic and socioeconomic covariates as well as month, year, and physician fixed effects. DATA COLLECTION/EXTRACTION METHODS: We include traditional, fee-for-service Medicare beneficiaries with a visit to an orthopedist or primary care physician for nonspecific low back pain, and no claims for low back pain in the year prior. PRINCIPAL FINDINGS: In the first stage, acquisition of MRI equipment is a strongly correlated with patients receiving MRI scans. Among patients of orthopedists, receipt of an MRI scan increases the probability of having surgery by 34 percentage points. Among patients of primary care physicians, receiving a low back MRI is not statistically significantly associated with subsequent surgery receipt. CONCLUSIONS: Orthopedists and primary care physicians who begin billing for the performance of MRI procedures, rather than referring patients outside of their practice for MRI, appear to change their practice patterns such that they use more MRI for their patients with low back pain. These increases in MRI use appear to lead to increases in low back surgery receipt and health care spending among patients of orthopedic surgeons, but not of primary care physicians.

38. Webster, B. S., & Cifuentes, M. (2010). Relationship of early magnetic resonance imaging for work-related acute low back pain with disability and medical utilization outcomes. J Occup Environ Med, 52(9), 900-907. doi:10.1097/JOM.0b013e3181ef7e53

OBJECTIVE: To examine early magnetic resonance imaging (MRI) utilization for workers compensation cases with acute, disabling low back pain and further, to examine low or high

propensity to undergo early MRI with disability duration, medical costs, and surgery. METHODS: Two-year follow-up of 3264 cases. Cox regression and generalized linear models were used to examine the association between both early MRI (first 30 days postonset) and propensity of belonging to the early MRI group (estimated by demographic and severity indicators) with outcomes. RESULTS: A total of 21.7% cases had early MRI. After controlling for covariates, cases that had early MRI and simultaneously had a low propensity to undergo early MRI were more likely to have worse outcomes. CONCLUSIONS: The majority of cases had no early MRI indications. Results suggest that iatrogenic effects of early MRI are worse disability and increased medical costs and surgery, unrelated to severity.

39. Webster, B. S., Bauer, A. Z., Choi, Y., Cifuentes, M., & Pransky, G. S. (2013). Iatrogenic consequences of early magnetic resonance imaging in acute, work-related, disabling low back pain. Spine (Phila Pa 1976), 38(22), 1939-1946. doi:10.1097/BRS.0b013e3182a42eb6

STUDY DESIGN: Retrospective cohort study. OBJECTIVE: To determine the effect of early (receipt </=30 d postonset) magnetic resonance imaging (MRI) on disability and medical cost outcomes in patients with acute, disabling, work-related low back pain (LBP) with and without radiculopathy. SUMMARY OF BACKGROUND DATA: Evidence-based guidelines suggest that, except for "red flags," MRI is indicated to evaluate patients with persistent radicular pain, after 1 month of conservative management, who are candidates for surgery or epidural steroid injections. Prior research has suggested an independent iatrogenic effect of nonindicated early MRI, but it had limited clinical information and/or patient populations. METHODS: A nationally representative sample of workers with acute, disabling, occupational LBP was randomly selected, oversampling those with radiculopathy diagnoses (N = 1000). Clinical information from medical reports was used to exclude cases for which early MRI might have been indicated, or MRI occurred more than 30 days postonset (final cohort = 555). Clinical information was also used to categorize cases into "nonspecific LBP" and "radiculopathy" groups and further divided into "early-MRI" and "no-MRI" subgroups. The Cox proportional hazards model examined the association of early MRI with duration of the first episode of disability. Multivariate linear regression models examined the association with medical costs. All models adjusted for demographic and medical severity measures. RESULTS: In our sample, 37% of the nonspecific LBP and 79.9% of the radiculopathy cases received early MRI. The early-MRI groups had similar outcomes regardless of radiculopathy status: much lower rates of going off disability and, on average, $12,948 to $13,816 higher medical costs than the no-MRI groups. Even in a subgroup with relatively minimal disability impact (</=30 d of total lost time post-MRI), medical costs were, on average, $7643 to $8584 higher in the early-MRI groups. CONCLUSION: Early MRI without indication has a strong iatrogenic effect in acute LBP, regardless of radiculopathy status. Providers and patients should be made aware that when early MRI is not indicated, it provides no benefits, and worse outcomes are likely. LEVEL OF EVIDENCE: 3.

40. Webster, B. S., Choi, Y. S., Bauer, A. Z., Cifuentes, M., & Pransky, G. (2014). The Cascade of Medical Services and Associated Longitudinal Costs Due to Nonadherent Magnetic Resonance Imaging for Low Back Pain. Spine (Phila Pa 1976), 39(17), 1433-1440. doi:10.1097/Brs.0000000000000408

Study Design. Retrospective cohort study. Objective. To compare type, timing, and longitudinal medical costs incurred after adherent versus nonadherent magnetic resonance imaging (MRI) for work-related low back pain. Summary of Background Data. Guidelines advise against MRI for acute uncomplicated low back pain, but is an option for persistent radicular pain after a trial of conservative care. Yet, MRI has become frequent and often nonadherent. Few studies have documented the nature and impact of medical services (including type and timing) initiated by nonadherent MRI. Methods. A longitudinal, workers' compensation administrative data source was accessed to select low back pain claims filed between January 1, 2006 and December 31, 2006. Cases were grouped by MRI timing (early, timely, no MRI) and subgrouped by severity ("less severe," "more severe") (final cohort = 3022). Health care utilization for each subgroup was evaluated at 3, 6, 9, and 12 months post-MRI. Multivariate logistic regression models examined risk of receiving subsequent diagnostic studies and/or treatments, adjusting for pain indicators and demographic covariates. Results. The adjusted relative risks for MRI group cases to receive electromyography, nerve conduction testing, advanced imaging, injections, and surgery within 6 months post-MRI risks in the range from 6.5 (95% CI: 2.20-19.09) to 54.9

(95% CI: 22.12-136.21) times the rate for the referent group (no MRI less severe). The timely and early MRI less severe subgroups had similar adjusted relative risks to receive most services. The early MRI more severe subgroup cases had generally higher adjusted relative risks than timely MRI more severe subgroup cases. Medical costs for both early MRI subgroups were highest and increased the most over time. Conclusion. The impact of nonadherent MRI includes a wide variety of expensive and potentially unnecessary services, and occurs relatively soon post-MRI. Study results provide evidence to promote provider and patient conversations to help patients choose care that is based on evidence, free from harm, less costly, and truly necessary.

Stress testing for stable coronary disease

45. Bertoldi, E. G., Stella, S. F., Rohde, L. E. P., & Polanczyk, C. A. (2017). Cost-effectiveness of anatomical and functional test strategies for stable chest pain: public health perspective from a middle-income country. BMJ Open, 7(4), e012652. doi:10.1136/bmjopen-2016-012652

OBJECTIVES: The aim of this research is to evaluate the relative cost-effectiveness of functional and anatomical strategies for diagnosing stable coronary artery disease (CAD), using exercise (Ex)-ECG, stress echocardiogram (ECHO), single-photon emission CT (SPECT), coronary CT angiography (CTA) or stress cardiacmagnetic resonance (C-MRI). SETTING: Decision-analytical model, comparing strategies of sequential tests for evaluating patients with possible stable angina in low, intermediate and high pretest probability of CAD, from the perspective of a developing nation's public healthcare system. PARTICIPANTS: Hypothetical cohort of patients with pretest probability of CAD between 20% and 70%. PRIMARY AND SECONDARY OUTCOME MEASURES: The primary outcome is cost per correct diagnosis of CAD. Proportion of false-positive or false-negative tests and number of unnecessary tests performed were also evaluated. RESULTS: Strategies using Ex-ECG as initial test were the least costly alternatives but generated more frequent false-positive initial tests and false-negative final diagnosis. Strategies based on CTA or ECHO as initial test were the most attractive and resulted in similar cost-effectiveness ratios (I$ 286 and I$ 305 per correct diagnosis, respectively). A strategy based on C-MRI was highly effective for diagnosing stable CAD, but its high cost resulted in unfavourable incremental cost-effectiveness (ICER) in moderate-risk and high-risk scenarios. Non-invasive strategies based on SPECT have been dominated. CONCLUSIONS: An anatomical diagnostic strategy based on CTA is a cost-effective option for CAD diagnosis. Functional strategies performed equally well when based on ECHO. C-MRI yielded acceptable ICER only at low pretest probability, and SPECT was not cost-effective in our analysis.

46. Marwick, T. H., Shaw, L., Case, C., Vasey, C., & Thomas, J. D. (2003). Clinical and economic impact of exercise electrocardiography and exercise echocardiography in clinical practice. Eur Heart J, 24(12), 1153-1163.

BACKGROUND: Patients with known or suspected coronary disease are often investigated to facilitate risk assessment. We sought to examine the cost-effectiveness of strategies based on exercise echocardiography and exercise electrocardiography. METHODS AND RESULTS: We studied 7656 patients undergoing exercise testing; of whom half underwent exercise echocardiography. Risk was defined with the Duke treadmill score for those undergoing exercise electrocardiography alone, and by the extent of ischaemia by exercise echocardiography. Cox proportional hazards models, risk adjusted for pretest likelihood of coronary artery disease, were used to estimate time to cardiac death or myocardial infarction. Costs (including diagnostic and revascularisation procedures, hospitalisations, and events) were calculated, inflation-corrected to year 2000 using Medicare trust fund rates and discounted at a rate of 5%. A decision model was employed to assess the marginal cost effectiveness (cost/life year saved) of exercise echo compared with exercise electrocardiography. Exercise echocardiography identified more patients as low-risk (51% vs 24%, $p<0.001$), and fewer as intermediate- (27% vs 51%, $p<0.001$) and high-risk (22% vs 4%); survival was greater in low- and intermediate-risk and less in high-risk patients. Although initial procedural costs and revascularisation costs (in intermediate-high risk patients) were greater, exercise echocardiography was associated with a greater incremental life expectancy (0.2 years) and a lower use of additional diagnostic procedures when compared with exercise electrocardiography (especially in lower risk patients). Using decision analysis, exercise echocardiography (in 2615/life year saved) was more cost effective than exercise

electrocardiography. CONCLUSION: Exercise echocardiography may enhance cost-effectiveness for the detection and management of at risk patients with known or suspected coronary disease.

47. Shaw, L. J., Mieres, J. H., Hendel, R. H., Boden, W. E., Gulati, M., Veledar, E., . . . Investigators, W. T. (2011). Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. Circulation, 124(11), 1239-1249. doi:10.1161/CIRCULATIONAHA.111.029660

BACKGROUND: There is a paucity of randomized trials regarding diagnostic testing in women with suspected coronary artery disease (CAD). It remains unclear whether the addition of myocardial perfusion imaging (MPI) to the standard ECG exercise treadmill test (ETT) provides incremental information to improve clinical decision making in women with suspected CAD. METHODS AND RESULTS: We randomized symptomatic women with suspected CAD, an interpretable ECG, and >/=5 metabolic equivalents on the Duke Activity Status Index to 1 of 2 diagnostic strategies: ETT or exercise MPI. The primary end point was 2-year incidence of major adverse cardiac events, defined as CAD death or hospitalization for an acute coronary syndrome or heart failure. A total of 824 women were randomized to ETT or exercise MPI. For women randomized to ETT, ECG results were normal in 64%, indeterminate in 16%, and abnormal in 20%. By comparison, the exercise MPI results were normal in 91%, mildly abnormal in 3%, and moderate to severely abnormal in 6%. At 2 years, there was no difference in major adverse cardiac events (98.0% for ETT and 97.7% for MPI; P=0.59). Compared with ETT, index testing costs were higher for exercise MPI (P<0.001), whereas downstream procedural costs were slightly lower (P=0.0008). Overall, the cumulative diagnostic cost savings was 48% for ETT compared with exercise MPI (P<0.001). CONCLUSIONS: In low-risk, exercising women, a diagnostic strategy that uses ETT versus exercise MPI yields similar 2-year posttest outcomes while providing significant diagnostic cost savings. The ETT with selective follow-up testing should be considered as the initial diagnostic strategy in symptomatic women with suspected CAD. CLINICAL TRIAL REGISTRATION: http://www.clinicaltrials.gov. Unique identifier: NCT00282711.

48. Thom, H., West, N. E., Hughes, V., Dyer, M., Buxton, M., Sharples, L. D., . . . group, C. E. s. (2014). Cost-effectiveness of initial stress cardiovascular MR, stress SPECT or stress echocardiography as a gate-keeper test, compared with upfront invasive coronary angiography in the investigation and management of patients with stable chest pain: mid-term outcomes from the CECaT randomised controlled trial. BMJ Open, 4(2), e003419. doi:10.1136/bmjopen-2013-003419

OBJECTIVES: To compare outcomes and cost-effectiveness of various initial imaging strategies in the management of stable chest pain in a long-term prospective randomised trial. SETTING: Regional cardiothoracic referral centre in the east of England. PARTICIPANTS: 898 patients (69% man) entered the study with 869 alive at 2 years of follow-up. Patients were included if they presented for assessment of stable chest pain with a positive exercise test and no prior history of ischaemic heart disease. Exclusion criteria were recent infarction, unstable symptoms or any contraindication to stress MRI. PRIMARY OUTCOME MEASURES: The primary outcomes of this follow-up study were survival up to a minimum of 2 years post-treatment, quality-adjusted survival and cost-utility of each strategy. RESULTS: 898 patients were randomised. Compared with angiography, mortality was marginally higher in the groups randomised to cardiac MR (HR 2.6, 95% CI 1.1 to 6.2), but similar in the single photon emission CT-methoxyisobutylisonitrile (SPECT-MIBI; HR 1.0, 95% CI 0.4 to 2.9) and ECHO groups (HR 1.6, 95% CI 0.6 to 4.0). Although SPECT-MIBI was marginally superior to other non-invasive tests there were no other significant differences between the groups in mortality, quality-adjusted survival or costs. CONCLUSIONS: Non-invasive cardiac imaging can be used safely as the initial diagnostic test to diagnose coronary artery disease without adverse effects on patient outcomes or increased costs, relative to angiography. These results should be interpreted in the context of recent advances in imaging technology. TRIAL REGISTRATION: ISRCTN 47108462, UKCRN 3696.

49. Zacharias, K., Ahmed, A., Shah, B. N., Gurunathan, S., Young, G., Acosta, D., & Senior, R. (2017). Relative clinical and economic impact of exercise echocardiography vs. exercise electrocardiography, as first line investigation in patients without known coronary artery disease and new stable angina: a randomized prospective study. Eur Heart J Cardiovasc Imaging, 18(2), 195-202. doi:10.1093/ehjci/jew049

AIMS: Exercise electrocardiography (ExECG) is widely used in suspected stable angina (SA) as the initial test for the evaluation of coronary artery disease (CAD). We hypothesized that exercise stress echo (ESE) would be efficacious with cost advantage over ExECG when utilized as the initial test. METHODS AND RESULTS: Consecutive patients with suspected SA, without known CAD were randomized into ExECG or ESE. Patients with positive tests were offered coronary angiography (CA) and with inconclusive tests were referred for further investigations. All patients were followed-up for cardiac events (death, myocardial infarction, and unplanned revascularization). Cost to diagnosis of CAD was calculated by adding the cost of all investigations, up to and including CA. In the 194 and 191 patients in the ExECG vs. ESE groups, respectively, pre-test probability of CAD was similar (34 +/- 23 vs. 35 +/- 25%, P = 0.6). Results of ExECG were: 108 (55.7%) negative, 14 (7.2%) positive, 72 (37.1%) inconclusive and of ESE were 181 (94.8%) negative, 9 (4.7%) positive, 1 (0.5%) inconclusive, respectively. Patients with obstructive CAD following positive ESE vs. Ex ECG were 9/9 vs. 9/14, respectively (P = 0.04). Cost to diagnosis of CAD was pound266 for ESE vs. pound327 for ExECG (P = 0.005). Over a mean follow-up period of 21 +/- 5 months, event rates were similar between the two groups. CONCLUSION: In this first randomized study, ESE was more efficacious and demonstrated superior cost-saving, compared with ExECG when used as the initial investigation for the evaluation of CAD in patients with new-onset suspected SA without known CAD.

Percutaneous coronary intervention with balloon angioplasty or stent placement for stable coronary disease

50. Abdelnoor, M., Andersen, J. G., Arnesen, H., & Johansen, O. (2017). Early discharge compared with ordinary discharge after percutaneous coronary intervention - a systematic review and meta-analysis of safety and cost. Vasc Health Risk Manag, 13, 101-109. doi:10.2147/VHRM.S122951

AIM: We aimed to summarize the pooled effect of early discharge compared with ordinary discharge after percutaneous coronary intervention (PCI) on the composite endpoint of re-infarction, revascularization, stroke, death, and incidence of rehospitalization. We also aimed to compare costs for the two strategies. METHODS: The study was a systematic review and a meta-analysis of 12 randomized controlled trials including 2962 patients, followed by trial sequential analysis. An estimation of cost was considered. Follow-up time was 30 days. RESULTS: For early discharge, pooled effect for the composite endpoint was relative risk of efficacy (RRe)=0.65, 95% confidence interval (CI) (0.52-0.81). Rehospitalization had a pooled effect of RRe=1.10, 95% CI (0.88-1.38). Early discharge had an increasing risk of rehospitalization with increasing frequency of hypertension for all populations, except those with stable angina, where a decreasing risk was noted. Advancing age gave increased risk of revascularization. Early discharge had a cost reduction of 655 Euros per patient compared with ordinary discharge. CONCLUSION: The pooled effect supports the safe use of early discharge after PCI in the treatment of a heterogeneous population of patients with coronary artery disease. There was an increased risk of rehospitalization for all subpopulations, except patients with stable angina. Clinical trials with homogeneous populations of acute coronary syndrome are needed to be conclusive on this issue.

51. Amin, A. P., Spertus, J. A., Cohen, D. J., Chhatriwalla, A., Kennedy, K. F., Vilain, K., . . . Yeh, R. W. (2012). Use of drug-eluting stents as a function of predicted benefit: clinical and economic implications of current practice. Arch Intern Med, 172(15), 1145-1152. doi:10.1001/archinternmed.2012.3093

BACKGROUND: Benefits of drug-eluting stents (DES) in percutaneous coronary intervention (PCI) are greatest in those at the highest risk of target-vessel revascularization (TVR). Drug-eluting stents cost more than bare-metal stents (BMS) and necessitate prolonged dual antiplatelet therapy (DAPT), which increases costs, bleeding risk, and risk of complications if DAPT is prematurely discontinued. Our objective was to assess whether DES are preferentially used in patients with higher predicted TVR risk and to estimate if lower use of DES in low-TVR-risk

patients would be more cost-effective than the existing DES use pattern. METHODS: We analyzed more than 1.5 million PCI procedures in the National Cardiovascular Data Registry (NCDR) CathPCI registry from 2004 through 2010 and estimated 1-year TVR risk with BMS using a validated model. We examined the association between TVR risk and DES use and the cost-effectiveness of lower DES use in low-TVR-risk patients (50% less DES use among patients with <10% TVR risk) compared with existing DES use. RESULTS: There was marked variation in physicians' use of DES (range 2%-100%). Use of DES was high across all predicted TVR risk categories (73.9% in TVR risk <10%; 78.0% in TVR risk 10%-20%; and 83.2% in TVR risk >20%), with a modest relationship between TVR risk and DES use (relative risk, 1.005 per 1% increase in TVR risk [95% CI, 1.005-1.006]). Reducing DES use by 50% in low-TVR-risk patients was projected to lower US health care costs by $205 million per year while increasing the overall TVR event rate by 0.5% (95% CI, 0.49%-0.51%) in absolute terms. CONCLUSIONS: Use of DES in the United States varies widely among physicians, with only a modest correlation to patients' risk of restenosis. Less DES use among patients with low risk of restenosis has the potential for significant cost savings for the US health care system while minimally increasing restenosis events.

52. Beresniak, A., Caruba, T., Sabatier, B., Juilliere, Y., Dubourg, O., & Danchin, N. (2015). Cost-effectiveness modelling of percutaneous coronary interventions in stable coronary artery disease. World J Cardiol, 7(10), 594-602. doi:10.4330/wjc.v7.i10.594

The objective of this study is to develop a cost-effectiveness model comparing drug eluting stents (DES) vs bare metal stent (BMS) in patients suffering of stable coronary artery disease. Using a 2-years time horizon, two simulation models have been developed: BMS first line strategy and DES first line strategy. Direct medical costs were estimated considering ambulatory and hospital costs. The effectiveness endpoint was defined as treatment success, which is the absence of major adverse cardiac events. Probabilistic sensitivity analyses were carried out using 10000 Monte-Carlo simulations. DES appeared slightly more efficacious over 2 years (60% of success) when compared to BMS (58% of success). Total costs over 2 years were estimated at 9303 euro for the DES and at 8926 euro for bare metal stent. Hence, corresponding mean cost-effectiveness ratios showed slightly lower costs ($P < 0.05$) per success for the BMS strategy (15520 euro/success), as compared to the DES strategy (15588 euro/success). Incremental cost-effectiveness ratio is 18850 euro for one additional percent of success. The sequential strategy including BMS as the first option appears to be slightly less efficacious but more cost-effective compared to the strategy including DES as first option. Future modelling approaches should confirm these results as further comparative data in stable coronary artery disease and long-term evidence become available.

53. Bonaventura, K., Leber, A. W., Sohns, C., Roser, M., Boldt, L. H., Kleber, F. X., . . . Dorenkamp, M. (2012). Cost-effectiveness of paclitaxel-coated balloon angioplasty and paclitaxel-eluting stent implantation for treatment of coronary in-stent restenosis in patients with stable coronary artery disease. Clin Res Cardiol, 101(7), 573-584. doi:10.1007/s00392-012-0428-2

BACKGROUND: Recent studies have demonstrated the safety and efficacy of drug-coated balloon (DCB) angioplasty for the treatment of coronary in-stent restenosis (ISR). The cost-effectiveness of this practice is unknown. METHODS: A Markov state-transition decision analytic model accounting for varying procedural efficacy rates, complication rates, and cost estimates was developed to compare DCB angioplasty with drug-eluting stent (DES) placement in patients with bare-metal stent (BMS)-ISR. Data on procedural outcomes associated with both treatment strategies were derived from the literature, and the cost analysis was conducted from a health care payer perspective. Effectiveness was expressed as life-years gained. RESULTS: In the base-case analysis, initial procedure costs amounted to euro3,604.14 for DCB angioplasty and to euro3,309.66 for DES implantation. Over a 12-month time horizon, the DCB strategy was found to be less costly (euro4,130.38 vs. euro5,305.30) and slightly more effective in terms of life expectancy (0.983 vs. 0.976 years) than the DES strategy. Extensive sensitivity analyses indicated that, in comparison with DES implantation, the cost advantage of the DCB strategy was robust to clinically plausible variations in the values of key model input parameters. The variables with the greatest impact on base-case results were the duration of dual antiplatelet therapy with acetylsalicylic acid and clopidogrel after DCB angioplasty, the use of generic clopidogrel, and variations in the costs associated with the DCB device. CONCLUSION: DCB angioplasty is a cost-

effective treatment option for coronary BMS-ISR. The higher initial costs of DCB are more than offset by later cost-savings, predominantly as a result of reduced medication costs.

54. Brophy, J. M., & Erickson, L. J. (2005). Cost-effectiveness of drug-eluting coronary stents in Quebec, Canada. Int J Technol Assess Health Care, 21(3), 326-333.

OBJECTIVES: The aim of this investigation was to assess the incremental cost-effectiveness of replacing bare metal coronary stents (BMS) with drug-eluting stents (DES) in the Province of Quebec, Canada. METHODS: The strategy used was a cost-effectiveness analysis from the perspective of the health-care provider, in the province of Quebec, Canada (population 7.5 million). The main outcome measure was the cost per avoided revascularization intervention. RESULTS: Based on the annual Quebec rate of 14,000 angioplasties with an average of 1.7 stents per procedure and a purchase cost of $2,600 Canadian dollar (CDN) for DES, 100 percent substitution of BMS with DES would require an additional $45.1 million CDN of funding. After the benefits of reduced repeat revascularization interventions are included, the incremental cost would be $35.2 million CDN. The cost per avoided revascularization intervention (18 percent coronary artery bypass graft, 82 percent percutaneous coronary intervention [PCI]) would be $23,067 CDN. If DES were offered selectively to higher risk populations, for example, a 20 percent subgroup with a relative restenosis risk of 2.5 times the current bare metal rate, the incremental cost of the program would be $4.9 million CDN at a cost of $7,800 per avoided revascularization procedure. Break-even costs for the program would occur at DES purchase cost of $1,161 for 100 percent DES use and $1,627 for selective 20 percent DES use for high-risk patients for restenosis (RR = 2.5). Univariate and Monte Carlo sensitivity analyses indicate that the parameters most affecting the analysis are the capacity to select patients at high risk of restenosis, the average number of stents used per PCI, baseline restenosis rates for BMS, the effectiveness ratio of restenosis prevention for DES versus BMS, the cost of DES, and the revascularization rate after initial PCI. Sensitivity analyses suggest little additional health benefits but escalating cost-effectiveness ratios once a DES penetration of 40 percent has been attained. CONCLUSIONS: Under current conditions in Quebec, Canada, selective use of DES in high-risk patients is the most acceptable strategy in terms of cost-effectiveness. Results of such an analysis would be expected to be similar in other countries with key model parameters similar to those used in this model. This model provides an example of how to evaluate the cost-effectiveness of selective use of a new technology in high-risk patients.

55. Brophy, J. M., Belisle, P., & Joseph, L. (2003). Evidence for use of coronary Stents - A hierarchical Bayesian meta-analysis. Ann Intern Med, 138(10), 777-786. doi:10.7326/0003-4819-138-10-200305200-00005

Background: Coronary stents are widely used in interventionall cardiology, but a current quantitative systematic overview comparing routine coronary stenting with standard percutaneous transluminal coronary angioplasty (PTCA) and restricted stenting (provisional stenting) has not been published. Purpose: To summarize results from all randomized clinical trials comparing routine coronary stenting with standard PTCA. Data Sources: Electronic databases were searched by using the key words angioplasty and stent. References from identified articles were also reviewed. In addition, several prominent general medical and cardiology journals were searched and agencies known to perform systematic reviews were consulted. Study Selection: All comparative randomized clinical trials were included, except those involving primary angioplasty for the treatment of acute myocardial infarction. Data Extraction: A specified protocol was followed, and two of the authors independently extracted the data. Outcomes assessed were total mortality, myocardial infarction, angiographic restenosis, coronary artery bypass surgery, repeated PTCA, and freedom from angina. Data Synthesis: The results were synthesized by using a Bayesian hierarchical random-effects model. A total of 29 trials involving 9918 patients were identified. There was no evidence for a difference between routine coronary stenting and standard PTCA in terms of deaths or myocardial infarctions (odds ratio, 0.90 [95% credible interval [CrI], 0.72 to 1.11]) or the need for coronary artery bypass surgery (odds ratio, 1.01 [CrI, 0.79 to 1.31]). Coronary stenting reduced the rate of restenosis (odds ratio, 0.52 [CrI, 0.37 to 0.69]) and the need for repeated PTCA (odds ratio, 0.59 [CrI, 0.50 to 0.68]). The trials showed a wide range of crossover rates from PTCA to stenting. By use of a multiplicative model, each 10% increase in crossover rate decreased the need for repeated angioplasty by approximately 8% (odds ratio multiplying factor, 1.08 [CrI, 0.98 to 1.18]). Routine stenting probably reduces the need for repeated angioplasty by fewer than 4 to 5 per

100 treated persons compared with PTCA with provisional stenting. Studies were not blinded and suggest a bias with a possible overestimation of this benefit. Conclusions: in the controlled environment of randomized clinical trials, routine coronary stenting is safe but probably not associated with important reductions in rates of mortality, acute myocardial infarction, or coronary artery bypass surgery compared with standard PTCA with provisional stenting. Coronary stenting is associated with substantial reductions in angiographic restenosis rates and the subsequent need for repeated PTCA, although this benefit may be overestimated because of trial designs. The incremental benefit of routine stenting for reducing repeated angioplasty diminishes as the crossover rate of stenting with conventional PTCA increases.

56. Brunner-La Rocca, H. P., Kaiser, C., Bernheim, A., Zellweger, M. J., Jeger, R., Buser, P. T., . . . Investigators, B. (2007). Cost-effectiveness of drug-eluting stents in patients at high or low risk of major cardiac events in the Basel Stent KostenEffektivitats Trial (BASKET): an 18-month analysis. Lancet, 370(9598), 1552-1559. doi:10.1016/S0140-6736(07)61660-2

BACKGROUND: Our aim was to determine whether drug-eluting stents are good value for money in long-term, everyday practice. METHODS: We did an 18-month cost-effectiveness analysis of the Basel Stent KostenEffektivitats Trial (BASKET), which randomised 826 patients 2:1 to drug-eluting stents (n=545) or to bare-metal stents (281). We used non-parametric bootstrap techniques to determine incremental cost-effectiveness ratios (ICERs) of drug-eluting versus bare-metal stents, to compare low-risk (> or =3.0 mm stents in native vessels; n=558, 68%) and high-risk patients (<3.0 mm stents/bypass graft stenting; n=268, 32%), and to do sensitivity analyses by altering costs and event rates in the whole study sample and in predefined subgroups. Quality-adjusted life-years (QALYs) were assessed by EQ-5D questionnaire (available in 703/826 patients). FINDINGS: Overall costs were higher for patients with drug-eluting stents than in those with bare-metal stents (11,808 euros [SD 400] per patient with drug-eluting stents and 10,450 euros [592] per patient with bare-metal stents, mean difference 1358 euros [717], p<0.0001), due to higher stent costs. We calculated an ICER of 64,732 euros to prevent one major adverse cardiac event, and of 40,467 euros per QALY gained. Stent costs, number of events, and QALYs affected ICERs most, but unrealistic alterations would have been required to achieve acceptable cost-effectiveness. In low-risk patients, the probability of drug-eluting stents achieving an arbitrary ICER of 10,000 euros or less to prevent one major adverse cardiac event was 0.016; by contrast, it was 0.874 in high-risk patients. INTERPRETATION: If used in all patients, drug-eluting stents are not good value for money, even if prices were substantially reduced. Drug-eluting stents are cost effective in patients needing small vessel or bypass graft stenting, but not in those who require large native vessel stenting.

57. Caruba, T., Katsahian, S., Schramm, C., Charles Nelson, A., Durieux, P., Begue, D., . . . Sabatier, B. (2014). Treatment for stable coronary artery disease: a network meta-analysis of cost-effectiveness studies. PLoS One, 9(6), e98371. doi:10.1371/journal.pone.0098371

INTRODUCTION AND OBJECTIVES: Numerous studies have assessed cost-effectiveness of different treatment modalities for stable angina. Direct comparisons, however, are uncommon. We therefore set out to compare the efficacy and mean cost per patient after 1 and 3 years of follow-up, of the following treatments as assessed in randomized controlled trials (RCT): medical therapy (MT), percutaneous coronary intervention (PCI) without stent (PTCA), with bare-metal stent (BMS), with drug-eluting stent (DES), and elective coronary artery bypass graft (CABG). METHODS: RCT comparing at least two of the five treatments and reporting clinical and cost data were identified by a systematic search. Clinical end-points were mortality and myocardial infarction (MI). The costs described in the different trials were standardized and expressed in US $ 2008, based on purchasing power parity. A network meta-analysis was used to compare costs. RESULTS: Fifteen RCT were selected. Mortality and MI rates were similar in the five treatment groups both for 1-year and 3-year follow-up. Weighted cost per patient however differed markedly for the five treatment modalities, at both one year and three years (P<0.0001). MT was the least expensive treatment modality: US $3069 and 13 864 after one and three years of follow-up, while CABG was the most costly: US $27 003 and 28 670 after one and three years. PCI, whether with plain balloon, BMS or DES came in between, but was closer to the costs of CABG. CONCLUSIONS: Appreciable savings in health expenditures can be achieved by using MT in the management of patients with stable angina.

58. Clavijo, L. C., Cortes, G. A., Jolly, A., Tun, H., Mehra, A., Gaglia, M. A., Jr., . . . Matthews, R. V. (2016). Same-day discharge after coronary stenting and femoral artery device closure: A randomized study in stable and low-risk acute coronary syndrome patients. Cardiovasc Revasc Med, 17(3), 155-161. doi:10.1016/j.carrev.2016.03.003

OBJECTIVE: To compare same-day (SD) vs. delayed hospital discharge (DD) after single and multivessel coronary stenting facilitated by femoral closure device in patients with stable angina and low-risk acute coronary syndrome (ACS). METHODS: University of Southern California patients were screened and coronary stenting was performed in 2480 patients. Four hundred ninety-three patients met screening criteria and consented. Four hours after percutaneous coronary intervention, 100 were randomized to SD (n=50) or DD (n=50). Patients were followed for one year; outcomes-, patient satisfaction-, and cost analyses were performed. RESULTS: Groups were well distributed, with similar baseline demographic and angiographic characteristics. Mean age was 58.1+/-8.8years and 86% were male. Non-ST-elevation myocardial infarction and unstable angina were the clinical presentations in 30% and 44% of the SD and DD groups, respectively (p=0.2). Multivessel stenting was performed in 36% and 30% of SD and DD groups, respectively (p=0.14). At one year, two patients from each group (4%) required unplanned revascularization and one patient in the SD group had a gastrointestinal bleed that required a blood transfusion. Six SD and four DD patients required repeat hospitalization (p=0.74). There were no femoral artery vascular complications in either group. Patient satisfaction scores were equivalent. SD discharge was associated with $1200 savings per patient. CONCLUSIONS: SD discharge after uncomplicated single and multivessel coronary stenting of patients with stable, low-risk ACS, via the femoral approach facilitated by a closure device, is associated with similar clinical outcomes, patient satisfaction, and cost savings compared to overnight (DD) hospital stay.

59. Cohen, D. J., Lavelle, T. A., Van Hout, B., Li, H., Lei, Y., Robertus, K., . . . Kappetein, A. P. (2012). Economic outcomes of percutaneous coronary intervention with drug-eluting stents versus bypass surgery for patients with left main or three-vessel coronary artery disease: one-year results from the SYNTAX trial. Catheter Cardiovasc Interv, 79(2), 198-209. doi:10.1002/ccd.23147

OBJECTIVES: To evaluate the cost-effectiveness of alternative approaches to revascularization for patients with three-vessel or left main coronary artery disease (CAD). BACKGROUND: Previous studies have demonstrated that, despite higher initial costs, long-term costs with bypass surgery (CABG) in multivessel CAD are similar to those for percutaneous coronary intervention (PCI). The impact of drug-eluting stents (DES) on these results is unknown. METHODS: The SYNTAX trial randomized 1,800 patients with left main or three-vessel CAD to either CABG (n = 897) or PCI using paclitaxel-eluting stents (n = 903). Resource utilization data were collected prospectively for all patients, and cumulative 1-year costs were assessed from the perspective of the U.S. healthcare system. RESULTS: Total costs for the initial hospitalization were $5,693/patient higher with CABG, whereas follow-up costs were $2,282/patient higher with PCI due mainly to more frequent revascularization procedures and higher outpatient medication costs. Total 1-year costs were thus $3,590/patient higher with CABG, while quality-adjusted life expectancy was slightly higher with PCI. Although PCI was an economically dominant strategy for the overall population, cost-effectiveness varied considerably according to angiographic complexity. For patients with high angiographic complexity (SYNTAX score > 32), total 1-year costs were similar for CABG and PCI, and the incremental cost-effectiveness ratio for CABG was $43,486 per quality-adjusted life-year gained. CONCLUSIONS: Among patients with three-vessel or left main CAD, PCI is an economically attractive strategy over the first year for patients with low and moderate angiographic complexity, while CABG is favored among patients with high angiographic complexity.

60. Escarcega, R. O., Perez-Alva, J. C., Jimenez-Hernandez, M., Mendoza-Pinto, C., Perez, R. S., Porras, R. S., & Garcia-Carrasco, M. (2010). Transradial percutaneous coronary intervention without on-site cardiac surgery for stable coronary disease and myocardial infarction: preliminary report and initial experience in 174 patients. Isr Med Assoc J, 12(10), 592-597.

BACKGROUND: On-site cardiac surgery is not widely available in developing countries despite a high prevalence of coronary artery disease. OBJECTIVES: To analyze the safety, feasibility and

cost-effectiveness of transradial percutaneous coronary intervention without on-site cardiac surgery in a community hospital in a developing country. METHODS: Of the 174 patients who underwent PCI for the first time in our center, we analyzed two groups: stable coronary disease and acute myocardial infarction. The primary endpoint was the rate of complications during the first 24 hours after PCI. We also analyzed the length of hospital stay and the rate of hospital readmission in the first week after PCI, and compared costs between the radial and femoral approaches. RESULTS: The study group comprised 131 patients with stable coronary disease and 43 with acute MI. Among the patients with stable coronary disease 8 (6.1%) had pulse loss, 12 (9.16%) had on-site hematoma, and 3 (2.29%) had bleeding at the site of the puncture. Among the patients with acute MI, 3 (6.98) had pulse loss and 5 (11.63%) had bleeding at the site of the puncture. There were no cases of atriovenous fistula or nerve damage. In the stable coronary disease group, 130 patients (99%) were discharged on the same day (2.4 +/- 2 hours). In the acute MI group, the length of stay was 6.6 +/- 2.5 days with at least 24 hours in the intensive care unit. There were no hospital readmissions in the first week after the procedure. The total cost, which includes equipment related to the specific approach and recovery room stay, was significantly lower with the radial approach compared to the femoral approach (US$ 500 saving per intervention). CONCLUSIONS: The transradial approach was safe and feasible in a community hospital in a developing country without on-site cardiac surgery backup. The radial artery approach is clearly more cost-effective than the femoral approach.

61. Favarato, D., Hueb, W., Gersh, B. J., Soares, P. R., Cesar, L. A., da Luz, P. L., . . . First Year Follow-Up of, M. I. I. S. (2003). Relative cost comparison of treatments for coronary artery disease: the First Year Follow-Up of MASS II Study. Circulation, 108 Suppl 1, II21-23. doi:10.1161/01.cir.0000087381.98299.7b

BACKGROUND: Prior comparisons of costs following CABG and PTCA have demonstrated higher initial costs after CABG but following PTCA, recurrent symptoms and repeat revascularization result in increased late costs and over time their costs equilibrate. The MASS II trial provides an opportunity to compare the costs of CABG and PTCA in addition to a strategy of medical therapy. METHODS: We studied the 611 patients of MASS II [Medical (203), Angioplasty (205), or Surgery (203) Study], a randomized study to compare treatments for multivessel CAD and preserved left ventricle function. The costs were: CABG 10,650.00 US dollars; PTCA 6400.00 US dollars; new AMI hospitalization AMI 2550 US dollars; angiography not followed-up of PTCA 1900.00 US dollars; and medication 1200.00 US dollars for medical, and 1000.00 US dollars for the other groups. We did adjustment for average event-free time, and angina-free proportion. The statistical analysis carried out was chi-square, t test, and analysis of variance. RESULTS: After 1 year, 49% Medical, 79% PTCA, and 88% CABG became angina-free; P<0.0001. There were 26 coronary angiograms (5 medical, 17 PTCA, and 4 CABG), 23 AMI (8 medical, 17 PTCA, and 6 CABG; P=0.03); PTCA was performed in 7 Medical, 17 PTCA, and 1 CABG, (P=0.0003), CABG was performed in 15 Medical, 8 PTCA, and zero CABG; P=0.002. The event-free and event and angina-free-costs in the first year were 2453.50 US dollars and 5006.32 US dollars for Medical; 10348,43 US dollars; and 13,099.31 US dollars for PTCA; and 12,404.21 US dollars and 14,095.09 US dollars for CABG group. An increase from expected costs of 317%, 77%, and 21%, respectively. CONCLUSIONS: PTCA effective costs were similar to CAGB costs, Medical treatment presented the lowest cost, and however, the greatest increment, and CABG presented the most stable costs.

62. Fearon, W. F., Nishi, T., De Bruyne, B., Boothroyd, D. B., Barbato, E., Tonino, P., . . . Investigators, F. T. (2018). Clinical Outcomes and Cost-Effectiveness of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease: Three-Year Follow-Up of the FAME 2 Trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). Circulation, 137(5), 480-487. doi:10.1161/CIRCULATIONAHA.117.031907

BACKGROUND: Previous studies found that percutaneous coronary intervention (PCI) does not improve outcome compared with medical therapy (MT) in patients with stable coronary artery disease, but PCI was guided by angiography alone. FAME 2 trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) compared PCI guided by fractional flow reserve with best MT in patients with stable coronary artery disease to assess clinical outcomes and cost-effectiveness. METHODS: A total of 888 patients with stable single-vessel or multivessel coronary artery disease with reduced fractional flow reserve were randomly assigned to PCI plus MT

(n=447) or MT alone (n=441). Major adverse cardiac events included death, myocardial infarction, and urgent revascularization. Costs were calculated on the basis of resource use and Medicare reimbursement rates. Changes in quality-adjusted life-years were assessed with utilities determined by the European Quality of Life-5 Dimensions health survey at baseline and over follow-up. RESULTS: Major adverse cardiac events at 3 years were significantly lower in the PCI group compared with the MT group (10.1% versus 22.0%; P<0.001), primarily as a result of a lower rate of urgent revascularization (4.3% versus 17.2%; P<0.001). Death and myocardial infarction were numerically lower in the PCI group (8.3% versus 10.4%; P=0.28). Angina was significantly less severe in the PCI group at all follow-up points to 3 years. Mean initial costs were higher in the PCI group ($9944 versus $4440; P<0.001) but by 3 years were similar between the 2 groups ($16 792 versus $16 737; P=0.94). The incremental cost-effectiveness ratio for PCI compared with MT was $17 300 per quality-adjusted life-year at 2 years and $1600 per quality-adjusted life-year at 3 years. The above findings were robust in sensitivity analyses. CONCLUSIONS: PCI of lesions with reduced fractional flow reserve improves long-term outcome and is economically attractive compared with MT alone in patients with stable coronary artery disease. CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01132495.

63. Fearon, W. F., Shilane, D., Pijls, N. H., Boothroyd, D. B., Tonino, P. A., Barbato, E., . . . Fractional Flow Reserve Versus Angiography for Multivessel Evaluation, I. (2013). Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. Circulation, 128(12), 1335-1340. doi:10.1161/CIRCULATIONAHA.113.003059

BACKGROUND: The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) 2 trial demonstrated a significant reduction in subsequent coronary revascularization among patients with stable angina and at least 1 coronary lesion with a fractional flow reserve </=0.80 who were randomized to percutaneous coronary intervention (PCI) compared with best medical therapy. The economic and quality-of-life implications of PCI in the setting of an abnormal fractional flow reserve are unknown. METHODS AND RESULTS: We calculated the cost of the index hospitalization based on initial resource use and follow-up costs based on Medicare reimbursements. We assessed patient utility using the EQ-5D health survey with US weights at baseline and 1 month and projected quality-adjusted life-years assuming a linear decline over 3 years in the 1-month utility improvements. We calculated the incremental cost-effectiveness ratio based on cumulative costs over 12 months. Initial costs were significantly higher for PCI in the setting of an abnormal fractional flow reserve than with medical therapy ($9927 versus $3900, P<0.001), but the $6027 difference narrowed over 1-year follow-up to $2883 (P<0.001), mostly because of the cost of subsequent revascularization procedures. Patient utility was improved more at 1 month with PCI than with medical therapy (0.054 versus 0.001 units, P<0.001). The incremental cost-effectiveness ratio of PCI was $36 000 per quality-adjusted life-year, which was robust in bootstrap replications and in sensitivity analyses. CONCLUSIONS: PCI of coronary lesions with reduced fractional flow reserve improves outcomes and appears economically attractive compared with best medical therapy among patients with stable angina.

64. Gada, H., Whitlow, P. L., & Marwick, T. H. (2012). Establishing the cost-effectiveness of percutaneous coronary intervention for chronic total occlusion in stable angina: a decision-analytic model. Heart, 98(24), 1790-1797. doi:10.1136/heartjnl-2012-302581

BACKGROUND: In the setting of chronic stable angina, successful percutaneous coronary intervention (PCI) of chronic total occlusions (CTO) has been shown to produce significant symptom improvement with some evidence for survival benefit. However, the economic basis for this procedure has not been established compared with optimal medical treatment (OMT) of chronic stable angina. OBJECTIVE: The aim of this study was to determine the cost-effectiveness of CTO-PCI in chronic stable angina using a Markov model. DESIGN: The transition probabilities, utilities and costs related to CTO-PCI and OMT used to inform the model were derived from literature and our experience. Implications with respect to cost and quality of life were calculated. Sensitivity analyses were based on factors noted to influence model outcome. RESULTS: In the reference case, mean age 60 years, rate of successful CTO-PCI 67.9%, and mean transition probabilities, utilities and costs as defined by literature and clinical experience, the strategy of CTO-PCI incurred higher costs relative to OMT (US$31 512 vs US$27 805), but also accumulated greater quality-adjusted life-years (QALYs) (2.38 vs 1.99), yielding a cost-effectiveness ratio of

US$9505 per QALY. Sensitivity analyses showed the utility of OMT and utilities postsuccessful and postunsuccessful CTO-PCI to be the most influential drivers of outcome. Procedural success held limited influence over model outcome at particular utility threshold values. CONCLUSIONS: On the basis of the supporting evidence, this decision-analytic model suggests that CTO-PCI is cost-effective in a patient population with severe symptoms. Quality-of-life metrics should be employed in future appropriateness criteria developed for CTO-PCI.

65. Gaster, A. L., Slothuus Skjoldborg, U., Larsen, J., Korsholm, L., von Birgelen, C., Jensen, S., . . . Haghfelt, T. H. (2003). Continued improvement of clinical outcome and cost effectiveness following intravascular ultrasound guided PCI: insights from a prospective, randomised study. Heart, 89(9), 1043-1049.

OBJECTIVE: To investigate in a prospective randomised study both long term clinical effects and cost effectiveness of percutaneous coronary interventions (PCI) with or without intravascular ultrasound (IVUS) guidance. METHODS: 108 male patients with stable angina referred for PCI of a significant coronary lesion were randomly assigned to IVUS guided PCI or conventional PCI. Individual accumulated costs of the entire follow up period were calculated and compared in the randomisation groups. Effectiveness of treatment was measured by freedom from major adverse cardiac events. RESULTS: Cost effectiveness of IVUS guided PCI that was noted at six months was maintained and even accentuated at long term follow up (median 2.5 years). The cumulated cost level was found to be lower for the IVUS guided group, with a cumulated cost of &163 672 in the IVUS guided group versus &313 706 in the coronary angiography group (p = 0.01). Throughout the study, mean cost per day was lower in the IVUS guided PCI group (&2.7 v & 5.2; p = 0.01). In the IVUS group, 78% were free from major adverse cardiac events versus 59% in the coronary angiography group (p = 0.04) with an odds ratio of 2.5 in favour of IVUS guidance. CONCLUSION: IVUS guidance results in continued improvement of long term clinical outcome and cost effectiveness. The results of this study suggest that IVUS guidance may be used more liberally in PCI.

66. Hambrecht, R., Walther, C., Mobius-Winkler, S., Gielen, S., Linke, A., Conradi, K., . . . Schuler, G. (2004). Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. Circulation, 109(11), 1371-1378. doi:10.1161/01.CIR.0000121360.31954.1F

BACKGROUND: Regular exercise in patients with stable coronary artery disease has been shown to improve myocardial perfusion and to retard disease progression. We therefore conducted a randomized study to compare the effects of exercise training versus standard percutaneous coronary intervention (PCI) with stenting on clinical symptoms, angina-free exercise capacity, myocardial perfusion, cost-effectiveness, and frequency of a combined clinical end point (death of cardiac cause, stroke, CABG, angioplasty, acute myocardial infarction, and worsening angina with objective evidence resulting in hospitalization). METHODS AND RESULTS: A total of 101 male patients aged < or =70 years were recruited after routine coronary angiography and randomized to 12 months of exercise training (20 minutes of bicycle ergometry per day) or to PCI. Cost efficiency was calculated as the average expense (in US dollars) needed to improve the Canadian Cardiovascular Society class by 1 class. Exercise training was associated with a higher event-free survival (88% versus 70% in the PCI group, P=0.023) and increased maximal oxygen uptake (+16%, from 22.7+/-0.7 to 26.2+/-0.8 mL O2/kg, P<0.001 versus baseline, P<0.001 versus PCI group after 12 months). To gain 1 Canadian Cardiovascular Society class, 6956 dollars was spent in the PCI group versus 3429 dollars in the training group (P<0.001). CONCLUSIONS: Compared with PCI, a 12-month program of regular physical exercise in selected patients with stable coronary artery disease resulted in superior event-free survival and exercise capacity at lower costs, notably owing to reduced rehospitalizations and repeat revascularizations.

67. Hlatky, M. A., Boothroyd, D. B., Melsop, K. A., Kennedy, L., Rihal, C., Rogers, W. J., . . . Bypass Angioplasty Revascularization Investigation 2 Diabetes Study, G. (2009). Economic outcomes of treatment strategies for type 2 diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial. Circulation, 120(25), 2550-2558. doi:10.1161/CIRCULATIONAHA.109.912709

BACKGROUND: The economic outcomes of clinical management strategies are important in assessing their value to patients. METHODS AND RESULTS: Bypass Angioplasty Revascularization

Investigation 2 Diabetes (BARI 2D) randomized patients with type 2 diabetes mellitus and angiographically documented, stable coronary disease to strategies of (1) prompt revascularization versus medical therapy with delayed revascularization as needed to relieve symptoms and (2) insulin sensitization versus insulin provision. Before randomization, the physician declared whether coronary artery bypass grafting or percutaneous coronary intervention would be used if the patient were assigned to revascularization. We followed 2005 patients for medical utilization and costs and assessed the cost-effectiveness of these management strategies. Medical costs were higher for revascularization than medical therapy, with a significant interaction with the intended method of revascularization (P<0.0001). In the coronary artery bypass grafting stratum, 4-year costs were $80 900 for revascularization versus $60 600 for medical therapy (P<0.0001). In the percutaneous coronary intervention stratum, costs were $73 400 for revascularization versus $67 800 for medical therapy (P<0.02). Costs also were higher for insulin sensitization ($71 300) versus insulin provision ($70 200). Other factors that significantly (P<0.05) and independently increased cost included insulin use and dose at baseline, female sex, white race, body mass index > or =30, and albuminuria. Cost-effectiveness based on 4-year data favored the strategy of medical therapy over prompt revascularization and the strategy of insulin provision over insulin sensitization. Lifetime projections of cost-effectiveness showed that medical therapy was cost-effective compared with revascularization in the percutaneous coronary intervention stratum ($600 per life-year added) with high confidence. Lifetime projections suggest that revascularization may be cost-effective in the coronary artery bypass grafting stratum ($47 000 per life-year added) but with lower confidence. CONCLUSIONS: Prompt coronary revascularization significantly increases costs among patients with type 2 diabetes mellitus and stable coronary disease. The strategy of medical therapy (with delayed revascularization as needed) appears to be cost-effective compared with the strategy of prompt coronary revascularization among patients identified a priori as suitable for percutaneous coronary intervention.

68. Hung, C. S., Cheng, C. L., Chao, C. L., Kao, H. L., Chen, M. F., & Lin, N. P. (2011). Cost-effectiveness of drug-eluting stents in patients with stable coronary artery disease. J Formos Med Assoc, 110(2), 109-114. doi:10.1016/S0929-6646(11)60017-X

BACKGROUND/PURPOSE: Drug-eluting stents (DESs) have been shown to reduce in-stent restenosis and target vessel revascularization (TVR) in large clinical trials. We conducted this study to elucidate the differences in the cost and clinical outcome of DESs and bare metal stents (BMSs). METHODS: We retrospectively analyzed the clinical data and costs of patients with stable angina treated with coronary stents from September 2003 to January 2005 at the National Taiwan University Hospital, Taipei, Taiwan. RESULTS: We enrolled 186 patients treated with DESs and 194 patients treated with BMSs. The use of DESs is associated with a lower rate of TVR compared with that with BMSs (12%vs. 22%, p = 0.011). Compared with the BMS group, the overall costs were significantly higher in the DES group (NT$352,495 +/- 140,408 vs. NT$298,947 +/- 131,289, p<0.001). The incremental cost to avoid one TVR at 2 years was NT$546,444 (95% confidence interval: NT$151,071-2,565,793). CONCLUSION: The use of DESs reduces the rate of TVR at 2 years after intervention, but is probably not cost-effective compared with BMSs in patients with stable coronary artery disease.

69. Kuukasjärvi, P., Räsänen, P., Malmivaara, A., Aronen, P., & Sintonen, H. (2007). Economic evaluation of drug-eluting stents: a systematic literature review and model-based cost–utility analysis. International journal of technology assessment in health care, 23(4), 473-479.

Objectives: The aim of this study was to systematically review economic analyses comparing drug-eluting stents (DES) to bare metal stents (BMS) in patients who undergo percutaneous coronary intervention to form an overall view about cost-effectiveness of DES and to construct a simple decision analysis model to evaluate the cost–utility of DES. Methods: Electronic databases searched from January 2004 to January 2006 were Cochrane Database of Systematic Reviews; DARE, HTA, EED (NHS CRD); MEDLINE(R) In-Process, Other Non-Indexed Citations, MEDLINE(R). References of the papers identified were checked. We included randomized controlled trials (RCT) or model-based cost-effectiveness analyses comparing DES to BMS in patients with coronary artery disease. The methodological quality of the papers was assessed by Drummond's criteria. Baseline characteristics and results of the studies were extracted and data synthesized descriptively. A decision tree model was constructed to evaluate the cost–utility of DES in

comparison to BMS, where health-related quality of life was measured by the 15D. Results: We identified thirteen good-quality economic evaluations. In two of these based on RCTs, DES was found cost-effective. In six studies, it was concluded that DES might probably be a cost-effective strategy in some circumstances, but not as a single strategy, and four studies concluded that DES is not cost-effective. One study did not draw a clear conclusion. In our analysis, the overall incremental cost-effectiveness ratio was €98,827 per quality-adjusted life-years gained. Avoiding one revascularization with DES would cost €4,794, when revascularization with BMS costs €3,260. Conclusions: The evidence is inconsistent of whether DES would be a cost-effective treatment compared with BMS in any healthcare system where evaluated. A marked restenosis risk reduction should be achieved before use of DES is justifiable at present prices. When considering adoption of a new health technology with a high incremental cost within a fixed budget, opportunity cost in terms of untreated patients should be seriously considered as a question of collective ethics.

70. Lee, S., Baek, K., & Chun, K. (2014). Cost-effectiveness of drug-eluting vs. bare-metal stents in patients with coronary artery disease from the Korean National Health Insurance Database. Yonsei Med J, 55(6), 1533-1541. doi:10.3349/ymj.2014.55.6.1533

PURPOSE: The aim of this study was to evaluate the cost-effectiveness of the use of drug-eluting stents (DESs), as compared with bare-metal stents (BMSs) in Korea. MATERIALS AND METHODS: A retrospective cohort study was conducted between January 2000 and December 2007. Subjects were stent-treated for the first time between 2004 and 2005, with four years of follow-up (2004-2007) (n=43674). The incremental cost-effectiveness ratio (ICER) was used to calculate the costs of DESs compared with BMSs among patients with coronary artery disease (CAD). Cost-effectiveness was assessed with effectiveness defined as a reduction in major adverse cardiac events after six months and after one, two, three, and four years. RESULTS: The total costs of a DESs were 674108 Korean won (KRW) higher than that of a BMSs at the end of the follow-up; 13635 thousand KRW per patient treated with DESs and 12960 thousand KRW per patient treated with BMSs. The ICER was 256315 per KRW/death avoided and 293090 per KRW/re-stenting avoided among the CAD patients at the end of the follow-up. CONCLUSION: The ICER for the high-risk patients was lower than that for the low-risk patients. The use of DESs is clinically more useful than the use of BMSs for CAD and myocardial infarction patients, especially for those considered to be high-risk patients in Korea.

71. Mark, D. B., Pan, W., Clapp-Channing, N. E., Anstrom, K. J., Ross, J. R., Fox, R. S., . . . Occluded Artery Trial, I. (2009). Quality of life after late invasive therapy for occluded arteries. N Engl J Med, 360(8), 774-783. doi:10.1056/NEJMoa0805151

BACKGROUND: The open-artery hypothesis postulates that late opening of an infarct-related artery after myocardial infarction will improve clinical outcomes. We evaluated the quality-of-life and economic outcomes associated with the use of this strategy. METHODS: We compared percutaneous coronary intervention (PCI) plus stenting with medical therapy alone in high-risk patients in stable condition who had a totally occluded infarct-related artery 3 to 28 days after myocardial infarction. In 951 patients (44% of those eligible), we assessed quality of life by means of a battery of tests that included two principal outcome measures, the Duke Activity Status Index (DASI) (which measures cardiac physical function on a scale from 0 to 58, with higher scores indicating better function) and the Medical Outcomes Study 36-Item Short-Form Mental Health Inventory 5 (which measures psychological well-being). Structured quality-of-life interviews were performed at baseline and at 4, 12, and 24 months. Costs of treatment were assessed for 458 of 469 patients in the United States (98%), and 2-year cost-effectiveness was estimated. RESULTS: At 4 months, the medical-therapy group, as compared with the PCI group, had a clinically marginal decrease of 3.4 points in the DASI score (P=0.007). At 1 and 2 years, the differences were smaller. No significant differences in psychological well-being were observed. For the 469 patients in the United States, cumulative 2-year costs were approximately $7,000 higher in the PCI group (P<0.001), and the quality-adjusted survival was marginally longer in the medical-therapy group. CONCLUSIONS: PCI was associated with a marginal advantage in cardiac physical function at 4 months but not thereafter. At 2 years, medical therapy remained significantly less expensive than routine PCI and was associated with marginally longer quality-adjusted survival. (ClinicalTrials.gov number, NCT00004562.)

72. Maud, A., Vazquez, G., Nyman, J. A., Lakshminarayan, K., Anderson, D. C., & Qureshi, A. I. (2010). Cost-effectiveness analysis of protected carotid artery stent placement versus endarterectomy in high-risk patients. J Endovasc Ther, 17(2), 224-229. doi:10.1583/09-2938.1

PURPOSE: To determine the cost-effectiveness of carotid angioplasty with stent placement (CAS) under emboli protection versus carotid endarterectomy (CEA) in patients with severe carotid stenosis considered to be at high surgical risk for CEA. METHODS: The probabilities of various outcomes were adopted from the SAPPHIRE trial results. The quality-adjusted life year (QALYs) associated with each treatment modality were estimated by using the frequencies of various quality-adjusted outcomes (QALY weights of ipsilateral stroke, myocardial infarction, and death). Total cost associated with each intervention was computed using the frequency of stroke, myocardial infarction, and death in each group. Costs are expressed in 2006 US$. Incremental cost-effectiveness ratios (ICERs) were estimated for a 1-year postprocedure period. RESULTS: The mean (range) estimated net costs at 1 year for patients treated with CAS and CEA were $12,782 ($12,205-$13,563) and $8,916 ($8,267-$9,766), respectively. Overall QALYs for the CAS and CEA groups were 0.753 and 0.701 [within a range of 0.0 (meaning death) to 0.815 (meaning no adverse events)]. The mean cost per QALY gained for CAS was $16,223 ($15,315-$17,474) and the mean cost per QALY gained for CEA was $12,745 ($11,372-$14,605). The estimated median ICER for CAS versus CEA treatment was $67,891 (-$129,372 to $379,661). CONCLUSION: The proven non-inferiority of CAS versus CEA in high-surgical-risk patients with severe carotid stenosis might provide a marginal benefit that is offset by the higher cost associated with this procedure.

73. Morgan, K. P., Leahy, M. G., Butts, J. N., & Beatt, K. J. (2010). The cost effectiveness of primary angioplasty compared to thrombolysis in the real world: one year results from West London. EuroIntervention, 6(5), 596-603. doi:10.4244/EIJV6I5A100

AIMS: The aim of this study is to use real-world data from West London to compare the cost-effectiveness of a contemporary primary angioplasty (PPCI) service to thrombolysis which it superseded over a time horizon of one year. Previous studies have depended on randomised trials and economic modelling. METHODS AND RESULTS: Resource and outcome data were collected on 400 consecutive patients treated for ST segment elevation myocardial infarction (STEMI) at the hub and two spoke sites over three years. After the first 200 received thrombolysis, the PPCI service was introduced providing treatment for the next 200 cases. The incidence of major adverse cardiac events was significantly less in the PPCI group at 30 days (46.2% versus 7.0%, adjusted odds ratio (AOR) 12 p<0.001) and one year (57.4% versus 13.2%, AOR 8.6 p<0.001) driven by reductions in mortality and ischaemia driven revascularisations. Mean index and one year cumulative costs did not differ significantly between thrombolysis and PPCI (pound7,016 versus pound6,802; p=0.653 and pound8442 versus pound7,731; p=0.213 respectively). Initial angioplasty costs were significantly higher in the PPCI group offset by reduced hospital stay (8.5 versus 4 days; p<0.001). CONCLUSIONS: This model of PPCI delivery is associated with larger than expected benefits and is cost-neutral when compared to thrombolysis.

74. Polanczyk, C. A., Wainstein, M. V., & Ribeiro, J. P. (2007). Cost-effectiveness of sirolimus-eluting stents in percutaneous coronary interventions in Brazil. Arq Bras Cardiol, 88(4), 464-474.

OBJECTIVES: To compare the cost-effectiveness ratios of sirolimus-eluting stents (SES) with bare-metal stents (BMS) under two perspectives: the "supplementary medical system" (health plans and private patients) and the public health (SUS) system. METHODS: A decision-analytic model using three different therapeutic strategies for coronary lesions: percutaneous coronary intervention (PCI) with BMS; with SES; or with BMS followed by SES to treat symptomatic restenosis. Study endpoints were one-year event-free survival and life expectancy. Decision trees were constructed using the results of published registries and clinical trials. RESULTS: One-year restenosis-free survival was 92.7% with SES and 78.8% with BMS. Estimated life expectancy was very similar for all the strategies, ranging from 18.5 to 19 years. Under a nonpublic perspective, the cost difference in the first year between BMS and SES was R$3,816, with an incremental cost-effectiveness ratio of R$27,403 per event avoided in one year. Under the SUS perspective, the cost per event avoided in one year was R$47,529. In the sensitivity analysis, probability of

restenosis, risk reduction expected with SES, the price of the stent and cost of treating restenosis were all important predictors. In the Monte Carlo simulation, data per years of life saved showed very high cost-effectiveness ratios. CONCLUSION: In the Brazilian model, the cost-effectiveness ratios for SES were elevated. The use of SES was more favorable for patients with high risk of restenosis, as it is associated with elevated costs in restenosis management of and under a nonpublic perspective.

75. Saadi, R., Cohen, S., Banko, D., Thompson, M., Duong, M., & Ferko, N. (2011). Cost analysis of four major drug-eluting stents in diabetic populations. In.

AIM: To use an indirect comparisons approach and conduct a cost analysis comparing four drug-eluting stents (DES) from a United States (US) payer (i.e., fixed-fee reimbursement) perspective. METHODS AND RESULTS: Studies were chosen that randomised two or more DES in diabetic patients. A one-year target lesion revascularisation (TLR) risk for Taxus was first derived. Risk Ratios (RRs) for each DES versus Taxus were calculated through meta-analyses. The RRs were multiplied by the average TLR risk for Taxus to estimate DES TLR risks. Estimates were added to a budget-impact model, along with utilisation and reimbursement rates for diagnosis-related groups. Budgets were calculated, assuming 100% stent use and 200,000 diabetic beneficiaries. One-year TLR risks were estimated to be 3.2%, 7.1%, 6.9% and 7.9% for Cypher, Endeavor, Taxus and Xience respectively. By substituting Cypher for DES with higher TLR, results predicted annual cost-savings greater than $146 million per population ($ 733 per patient). Results were comparable when assuming no difference in TLR risk between Endeavor, Taxus and Xience. CONCLUSIONS: When outcomes from trials of diabetic populations are analysed and used in a budget-impact model from a US payer perspective, the use of Cypher is associated with lower TLR rates, which translates into large potential cost savings.

76. Serruys, P. W., Unger, F., Sousa, J. E., Jatene, A., Bonnier, H. J., Schonberger, J. P., . . . Arterial Revascularization Therapies Study, G. (2001). Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med, 344(15), 1117-1124. doi:10.1056/NEJM200104123441502

BACKGROUND: The recent recognition that coronary-artery stenting has improved the short- and long-term outcomes of patients treated with angioplasty has made it necessary to reevaluate the relative benefits of bypass surgery and percutaneous interventions in patients with multivessel disease. METHODS: A total of 1205 patients were randomly assigned to undergo stent implantation or bypass surgery when a cardiac surgeon and an interventional cardiologist agreed that the same extent of revascularization could be achieved by either technique. The primary clinical end point was freedom from major adverse cardiac and cerebrovascular events at one year. The costs of hospital resources used were also determined. RESULTS: At one year, there was no significant difference between the two groups in terms of the rates of death, stroke, or myocardial infarction. Among patients who survived without a stroke or a myocardial infarction, 16.8 percent of those in the stenting group underwent a second revascularization, as compared with 3.5 percent of those in the surgery group. The rate of event-free survival at one year was 73.8 percent among the patients who received stents and 87.8 percent among those who underwent bypass surgery ($P<0.001$ by the log-rank test). The costs for the initial procedure were $4,212 less for patients assigned to stenting than for those assigned to bypass surgery, but this difference was reduced during follow-up because of the increased need for repeated revascularization; after one year, the net difference in favor of stenting was estimated to be $2,973 per patient. CONCLUSION: As measured one year after the procedure, coronary stenting for multivessel disease is less expensive than bypass surgery and offers the same degree of protection against death, stroke, and myocardial infarction. However, stenting is associated with a greater need for repeated revascularization.

77. Shrive, F. M., Manns, B. J., Galbraith, P. D., Knudtson, M. L., Ghali, W. A., & Investigators, A. (2005). Economic evaluation of sirolimus-eluting stents. Cmaj, 172(3), 345-351. doi:10.1503/cmaj.1041062

BACKGROUND: Sirolimus-eluting stents have recently been shown to reduce the risk of restenosis among patients who undergo percutaneous coronary intervention (PCI). Given that sirolimus-eluting stents cost about 4 times as much as conventional stents, and considering the volume of PCI procedures, the decision to use sirolimus-eluting stents has large economic

implications. METHODS: We performed an economic evaluation comparing treatment with sirolimus-eluting and conventional stents in patients undergoing PCI and in subgroups based on age and diabetes mellitus status. The probabilities of transition between clinical states and estimates of resource use and health-related quality of life were derived from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database. Information on effectiveness was based on a meta-analysis of randomized controlled clinical trials (RCTs) comparing sirolimus-eluting and conventional stents. RESULTS: Cost per quality-adjusted life year (QALY) gained in the baseline analysis was Can58,721 dollars. Sirolimus-eluting stents were more cost-effective in patients with diabetes and in those over 75 years of age, the costs per QALY gained being 44,135 dollars and 40,129 dollars, respectively. The results were sensitive to plausible variations in the cost of stents, the estimate of the effectiveness of sirolimus-eluting stents and the assumption that sirolimus-eluting stents would prevent the need for cardiac catheterizations in the subsequent year when no revascularization procedure was performed to treat restenosis. INTERPRETATION: The use of sirolimus-eluting stents is associated with a cost per QALY that is similar to or higher than that of other accepted medical forms of therapy and is associated with a significant incremental cost. Sirolimus-eluting stents are more economically attractive for patients who are at higher risk of restenosis or at a high risk of death if a second revascularization procedure were to be required.

78. Takura, T., Tachibana, K., Isshiki, T., Sumitsuji, S., Kuroda, T., Mizote, I., . . . Nanto, S. (2017). Preliminary report on a cost-utility analysis of revascularization by percutaneous coronary intervention for ischemic heart disease. Cardiovasc Interv Ther, 32(2), 127-136. doi:10.1007/s12928-016-0401-5

Few socioeconomic studies have so far reported on revascularization for stable ischemic heart disease in Japan. This study aimed to validate the sensitivity of the health-related quality of life (HRQOL) scale for determining the pathology and medical technology to be used and to validate the application of a cost-utility analysis model. We studied 32 patients who had undergone percutaneous coronary intervention (PCI) (mean age 67.9 +/- 7.3 years). For HRQOL, utility and quality of life (QOL) were examined using the EuroQol 5 Dimension (EQ-5D) and EuroQol Visual Analogue Scale (EQ-VAS), respectively. The changes in the utility index before and after PCI were compared between the PCI and coronary angiography (CAG) groups to determine the sensitivity of the EQ-5D that was used to calculate quality-adjusted life years (QALY). Additionally, to estimate the cost-utility of PCI 120 months after the procedure, we analyzed our study results and the results of previous reports using the Markov chain model. The utility index was found to improve in the PCI group (0.08 +/- 0.15), whereas it decreased in the CAG group (-0.02 +/- 0.11) ($p = 0.049$). The estimated result of the cost-utility analysis as the increase in utility above baseline level was the expected value, that is, 70,000 US$/QALY. Our findings suggest that QALY may be valid as a utility index in the clinical and economic evaluation of PCI in Japan.

79. van Hout, B. A., Serruys, P. W., Lemos, P. A., van den Brand, M. J., van Es, G. A., Lindeboom, W. K., & Morice, M. C. (2005). One year cost effectiveness of sirolimus eluting stents compared with bare metal stents in the treatment of single native de novo coronary lesions: an analysis from the RAVEL trial. Heart, 91(4), 507-512. doi:10.1136/hrt.2004.034454

OBJECTIVE: To assess the balance between costs and effects of the sirolimus eluting stent in the treatment of single native de novo coronary lesions in the RAVEL (randomised study with the sirolimus eluting Bx Velocity balloon expandable stent in the treatment of patients with de novo native coronary artery lesions) study. DESIGN: Multicentre, double blind, randomised trial. SETTING: Percutaneous coronary intervention for single de novo coronary lesions. PATIENTS: 238 patients with stable or unstable angina. INTERVENTIONS: Randomisation to sirolimus eluting stent or bare stent implantation. MAIN OUTCOME MEASURES: Patients were followed up to one year and the treatment effects were expressed as one year survival free of major adverse cardiac events (MACE). Costs were estimated as the product of resource utilisation and Dutch unit costs. RESULTS: At one year, the absolute difference in MACE-free survival was 23% in favour of the sirolimus eluting stent group. At the index procedure, sirolimus eluting stent implantation had an estimated additional procedural cost of 1286. At one year, however, the estimated additional cost difference had decreased to 54 because of the reduction in the need for repeat revascularisations in the sirolimus group (0.8% v 23.6%; $p < 0.01$). After adjustment of actual results for the consequences of angiographic follow up (correction based on data from the BENESTENT (Belgium

Netherlands stent) II study), the difference in MACE-free survival was estimated at 11.1% and the additional one year costs at 166. CONCLUSIONS: The one year data from RAVEL suggest an attractive balance between costs and effects for sirolimus eluting stents in the treatment of single native de novo coronary lesions. The cost effectiveness of drug eluting stents in more complex lesion subsets remains to be determined.

80. Weaver, W. D., Reisman, M. A., Griffin, J. J., Buller, C. E., Leimgruber, P. P., Henry, T., . . . Every, N. R. (2000). Optimum percutaneous transluminal coronary angioplasty compared with routine stent strategy trial (OPUS-1): a randomised trial. Lancet, 355(9222), 2199-2203.

BACKGROUND: Whether routine implantation of coronary stents is the best strategy to treat flow-limiting coronary stenoses is unclear. An alternative approach is to do balloon angioplasty and provisionally use stents only to treat suboptimum results. We did a multicentre trial to compare the outcomes of patients treated with these strategies. METHODS: We randomly assigned 479 patients undergoing single-vessel coronary angioplasty routine stent implantation or initial balloon angioplasty and provisional stenting. We followed up patients for 6 months to determine the composite rate of death, myocardial infarction, cardiac surgery, and target-vessel revascularisation. RESULTS: Stents were implanted in 227 (98.7%) of the patients assigned routine stenting. 93 (37%) patients assigned balloon angioplasty had at least one stent placed because of suboptimum angioplasty results. At 6 months the composite endpoint was significantly lower in the routine stent strategy (14 events, 6.1%) than with the strategy of balloon angioplasty with provisional stenting (37 events, 14.9%, p=0.003). The cost of the initial revascularisation procedure was higher than when a routine stent strategy was used (US$389 vs $339, p<0.001) but at 6 months, average per-patient hospital costs did not differ ($10,206 vs $10,490). Bootstrap replication of 6-month cost data showed continued economic benefit of the routine stent strategy. INTERPRETATION: Routine stent implantation leads to better acute and long-term clinical outcomes at a cost similar to that of initial balloon angioplasty with provisional stenting.

81. Weintraub, W. S., Boden, W. E., Zhang, Z., Kolm, P., Zhang, Z., Spertus, J. A., . . . Study, C. (2008). Cost-effectiveness of percutaneous coronary intervention in optimally treated stable coronary patients. Circ Cardiovasc Qual Outcomes, 1(1), 12-20. doi:10.1161/CIRCOUTCOMES.108.798462

BACKGROUND: The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluations) trial compared the effect of percutaneous coronary intervention (PCI) plus optimal medical therapy with optimal medical therapy alone on cardiovascular events in 2287 patients with stable coronary disease. After 4.6 years, there was no difference in the primary end point of death or myocardial infarction, although PCI improved quality of life. The present study evaluated the relative cost and cost-effectiveness of PCI in the COURAGE trial. METHODS AND RESULTS: Resource use was assessed by diagnosis-related group for hospitalizations and by current procedural terminology code for outpatient visits and tests and then converted to costs by use of 2004 Medicare payments. Medication costs were assessed with the Red Book average wholesale price. Life expectancy beyond the trial was estimated from Framingham survival data. Utilities were assessed by the standard gamble method. The incremental cost-effectiveness ratio was expressed as cost per life-year and cost per quality-adjusted life-year gained. The added cost of PCI was approximately $10,000, without significant gain in life-years or quality-adjusted life-years. The incremental cost-effectiveness ratio varied from just over $168,000 to just under $300,000 per life-year or quality-adjusted life-year gained with PCI. A large minority of the distributions found that medical therapy alone offered better outcome at lower cost. The costs per patient for a significant improvement in angina frequency, physical limitation, and quality of life were $154,580, $112,876, and $124,233, respectively. CONCLUSIONS: The COURAGE trial did not find the addition of PCI to optimal medical therapy to be a cost-effective initial management strategy for symptomatic, chronic coronary artery disease.

82. Weintraub, W. S., Mahoney, E. M., Zhang, Z., Chu, H., Hutton, J., Buxton, M., . . . De Cock, E. (2004). One year comparison of costs of coronary surgery versus percutaneous coronary intervention in the stent or surgery trial. Heart, 90(7), 782-788. doi:10.1136/hrt.2003.015057

OBJECTIVES: To compare initial and one year costs of coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) in the stent or surgery trial. DESIGN: Prospective, unblinded, randomised trial. SETTING: Multicentre study. PATIENTS: 988 patients with multivessel disease. INTERVENTIONS: CABG and stent assisted PCI. MAIN OUTCOME MEASURES: Initial hospitalisation and one year follow up costs. RESULTS: At one year mortality was 2.5% in the PCI arm and 0.8% in the CABG arm (p = 0.05). There was no difference in the composite of death or Q wave myocardial infarction (6.9% for PCI v 8.1% for CABG, p = 0.49). There were more repeat revascularisations with PCI (17.2% v 4.2% for CABG). There was no significant difference in utility between arms at six months or at one year. Quality adjusted life years were similar 0.6938 for PCI v 0.6954 for PCI, Delta = 0.00154, 95% confidence interval (CI) -0.0242 to 0.0273). Initial length of stay was longer with CABG (12.2 v 5.4 days with PCI, p < 0.0001) and initial hospitalisation costs were higher (7321 pounds sterling v 3884 pounds sterling for PCI, Delta = 3437 pounds sterling, 95% CI 3040 pounds sterling to 3848 pounds sterling). At one year the cost difference narrowed but costs remained higher for CABG (8905 pounds sterling v 6296 pounds sterling for PCI, Delta = 2609 pounds sterling, 95% CI 1769 pounds sterling to 3314 pounds sterling). CONCLUSIONS: Over one year, CABG was more expensive and offered greater survival than PCI but little added benefit in terms of quality adjusted life years. The additional cost of CABG can be justified only if it offers continuing benefit at no further increase in cost relative to PCI over several years.

83. Wijeysundera, H. C., Tomlinson, G., Ko, D. T., Dzavik, V., & Krahn, M. D. (2013). Medical therapy v. PCI in stable coronary artery disease: a cost-effectiveness analysis. Med Decis Making, 33(7), 891-905. doi:10.1177/0272989X13497262

BACKGROUND: Percutaneous coronary intervention (PCI) with either drug-eluting stents (DES) or bare metal stents (BMS) reduces angina and repeat procedures compared with optimal medical therapy alone. It remains unclear if these benefits are sufficient to offset their increased costs and small increase in adverse events. OBJECTIVE: Cost utility analysis of initial medical therapy v. PCI with either BMS or DES. DESIGN: . Markov cohort decision model. Data Sources. Propensity-matched observational data from Ontario, Canada, for baseline event rates. Effectiveness and utility data obtained from the published literature, with costs from the Ontario Case Costing Initiative. TARGET POPULATION: Patients with stable coronary artery disease, confirmed after angiography, stratified by risk of restenosis based on diabetic status, lesion size, and lesion length. Time Horizon. Lifetime. Perspective. Ontario Ministry of Health and Long Term Care. Interventions. Optimal medical therapy, PCI with BMS or DES. OUTCOME MEASURES: Lifetime costs, quality-adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER). RESULTS: of Base Case Analysis. In the overall population, medical therapy had the lowest lifetime costs at $22,952 v. $25,081 and $25,536 for BMS and DES, respectively. Medical therapy had a quality-adjusted life expectancy of 10.1 v. 10.26 QALYs for BMS, producing an ICER of $13,271/QALY. The DES strategy had a quality-adjusted life expectancy of only 10.20 QALYs and was dominated by the BMS strategy. This ranking was consistent in all groups stratified by restenosis risk, except diabetic patients with long lesions in small arteries, in whom DES was cost-effective compared with medical therapy (ICER of $18,826/QALY). Limitations. There is the possibility of residual unobserved confounding. CONCLUSIONS: In patients with stable coronary artery disease, an initial BMS strategy is cost-effective.

84. Zeymer, U., Uebis, R., Vogt, A., Glunz, H. G., Vohringer, H. F., Harmjanz, D., . . . Group, A. L.-S. (2003). Randomized comparison of percutaneous transluminal coronary angioplasty and medical therapy in stable survivors of acute myocardial infarction with single vessel disease: a study of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte. Circulation, 108(11), 1324-1328. doi:10.1161/01.CIR.0000087605.09362.0E

BACKGROUND: Percutaneous transluminal coronary angioplasty of the infarct-related artery in stable survivors of acute myocardial infarction is often performed, even in patients without any symptoms or residual ischemia. Despite the lack of randomized studies, it is widely believed that

this intervention will improve the clinical outcome of these patients. METHODS AND RESULTS: Three hundred patients with single vessel disease of the infarct vessel and no or minor angina pectoris in the subacute phase (1 to 6 weeks) after an acute myocardial infarction were randomized to angioplasty (n=149) or medical therapy (n=151). Primary end point was the survival free of reinfarction, (re)intervention, coronary artery bypass surgery, or readmission for severe angina pectoris at 1 year. The event-free survival at 1 year was 82% in the medical group and 90% in the angioplasty group (P=0.06). This difference was mainly driven by the difference in the need for (re)interventions (20 versus 8, P=0.03). At long-term follow-up (mean, 56 months), survival was 89% and 96% (P=0.02). Survival free of reinfarction, (re)intervention, or coronary artery bypass surgery was 66% and 80% in the medically and interventionally treated patients, respectively (P=0.05). The use of nitrates was significantly lower in the angioplasty group, both at 1 year (38% versus 67%, P=0.001) and at long-term follow-up (36% versus 55%, P=0.006). CONCLUSIONS: Percutaneous revascularization of the infarct-related coronary artery in stable patients with single vessel disease improves clinical outcome at long-term follow-up and reduces the use of nitrates. The results of our study should be reproduced in a confirmatory study with a larger sample size before percutaneous coronary intervention in this low-risk patient subgroup, after myocardial infarction can be recommended as routine treatment in clinical practice.

85. Zhang, Z., Kolm, P., Boden, W. E., Hartigan, P. M., Maron, D. J., Spertus, J. A., . . . Weintraub, W. S. (2011). The cost-effectiveness of percutaneous coronary intervention as a function of angina severity in patients with stable angina. Circ Cardiovasc Qual Outcomes, 4(2), 172-182. doi:10.1161/CIRCOUTCOMES.110.940502

BACKGROUND: The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial compared percutaneous coronary intervention (PCI) plus optimal medical therapy (OMT) to OMT alone in reducing the risk of cardiovascular events in 2287 patients with stable coronary disease. We examined the cost-effectiveness of PCI as a function of angina severity at the time of randomization. METHODS AND RESULTS: Angina severity was assessed with the Seattle Angina Questionnaire (SAQ). Patients were grouped into tertiles based on the distribution of baseline scores such that higher tertiles represented better health status. Clinically significant improvement from baseline within individual patients was defined as score increases of >8 for physical limitation, >20 for angina frequency, and >16 for quality-of-life domains. The incremental cost-effectiveness ratio for PCI was calculated as the difference in costs divided by the difference in proportion of patients with clinically significant improvement. Improvement in angina severity was significantly greater for PCI patients in the lowest and middle tertiles. The number of patients needed to treat was much larger for the highest tertile. The added in-trial cost of PCI ranged from $7300 to $13 000. Incremental cost-effectiveness ratios ranged from $80 000 to $330 000 for the lowest and middle tertiles and from $520 000 to >$3 million for the highest tertile for 1 additional patient to achieve significant clinical improvement in health status. CONCLUSIONS: The incremental cost of PCI to provide meaningful clinical benefit above that achieved by OMT alone was lower for patients with severe angina than for those with mild or no angina. However, it is uncertain that at any level of angina severity that PCI as an initial strategy would achieve a socially acceptable cost threshold. Clinical Trial Registration- URL: http://www.clinicaltrials.gov. Unique identifier: NCT00007657.

86. Zhang, Z., Kolm, P., Grau-Sepulveda, M. V., Ponirakis, A., O'Brien, S. M., Klein, L. W., . . . Weintraub, W. S. (2015). Cost-effectiveness of revascularization strategies: the ASCERT study. J Am Coll Cardiol, 65(1), 1-11. doi:10.1016/j.jacc.2014.09.078

BACKGROUND: ASCERT (American College of Cardiology Foundation and the Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies) was a large observational study designed to compare the long-term effectiveness of coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) to treat coronary artery disease (CAD) over 4 to 5 years. OBJECTIVES: This study examined the cost-effectiveness of CABG versus PCI for stable ischemic heart disease. METHODS: The Society of Thoracic Surgeons and American College of Cardiology Foundation databases were linked to the Centers for Medicare and Medicaid Services claims data. Costs for the index and observation period (2004 to 2008) hospitalizations were assessed by diagnosis-related group Medicare reimbursement rates; costs beyond the observation period were estimated from average Medicare participant per capita expenditure. Effectiveness was measured via mortality and life-expectancy data. Cost and

effectiveness comparisons were adjusted using propensity score matching with the incremental cost-effectiveness ratio expressed as cost per quality-adjusted life-year gained. RESULTS: CABG patients (n = 86,244) and PCI patients (n = 103,549) were at least 65 years old with 2- or 3-vessel coronary artery disease. Adjusted costs were higher for CABG for the index hospitalization, study period, and lifetime by $10,670, $8,145, and $11,575, respectively. Patients undergoing CABG gained an adjusted average of 0.2525 and 0.3801 life-years relative to PCI over the observation period and lifetime, respectively. The life-time incremental cost-effectiveness ratio of CABG compared to PCI was $30,454/QALY gained. CONCLUSIONS: Over a period of 4 years or longer, patients undergoing CABG had better outcomes but at higher costs than those undergoing PCI.

87. Zhang, Z., Spertus, J. A., Mahoney, E. M., Booth, J., Nugara, F., Stables, R. H., & Weintraub, W. S. (2005). The impact of acute coronary syndrome on clinical, economic, and cardiac-specific health status after coronary artery bypass surgery versus stent-assisted percutaneous coronary intervention: 1-year results from the stent or surgery (SoS) trial. Am Heart J, 150(1), 175-181. doi:10.1016/j.ahj.2005.01.019

BACKGROUND: Data are limited regarding the impact of acute coronary syndromes (ACSs) on the relative benefits of coronary artery bypass grafting (CABG) versus stent-assisted percutaneous coronary intervention (PCI). METHODS: The SoS trial compared patients with multivessel disease who were randomly assigned to CABG (n = 500) or stent-assisted PCI (n = 488). The impact of treatment on 1-year outcomes was compared in ACS (n = 126, CABG; n = 116, PCI) and non-ACS (n = 374, CABG; n = 372, PCI) subgroups. RESULTS: Baseline characteristics were similar between treatment groups within ACS and non-ACS groups, as was the 1-year composite incidence of mortality and myocardial infarction (ACS, 5.2% for PCI vs 5.6% for CABG, P = .89; non-ACS, 7.0% vs 8.3%, P = .50). The need for repeat revascularizations was higher after PCI versus CABG within each subgroup (ACS, 15.5% vs 7.1%, P = .04; non-ACS, 18.0% vs 3.2%, P < .001). At 6 and 12 months, scores on the Seattle Angina Questionnaire improved significantly in patients with and without ACS. In patients without ACS, CABG was associated with greater improvement in physical limitation, angina frequency, and quality of life at 6 and 12 months. In patients with ACS, there was only a nonsignificant slight trend toward greater improvement with CABG at 1 year. The total 1-year costs for PCI and CABG in patients without ACS were 5760 pound sterling and 8509 pound sterling (Delta = 2749 pound sterling, 95% CI 1890 pound sterling - 3409 pound sterling), and in patients with ACS, 8014 pound sterling and 10080 pound sterling (Delta = 2066 pound sterling, 95% CI -690 pound sterling to 3487 pound sterling). CONCLUSIONS: In patients with and without ACS, CABG had similar clinical outcomes, less need for repeat revascularization and higher costs compared to PCI. The benefit of CABG relative to PCI in improving patients' health status tended to be greater in patients without ACS than in patients with ACS.

Carotid endarterectomy for asymptomatic patients

93. Dakour-Aridi, H., Nejim, B., Locham, S., Alshaikh, H., Obeid, T., & Malas, M. B. (2018). Complication-Specific In-Hospital Costs After Carotid Endarterectomy vs Carotid Artery Stenting. J Endovasc Ther, 25(4), 514-521. doi:10.1177/1526602818781580

PURPOSE: To quantify and compare the incremental cost associated with in-hospital stroke, death, and myocardial infarction (MI) after carotid endarterectomy (CEA) vs carotid artery stenting (CAS). METHODS: A retrospective analysis was performed of 100,185 patients (mean age 70.7+/-9.5 years; 58.3% men) who underwent CEA (n=86,035) or CAS (n=14,150) between 2009 and 2015 and were entered into the Premier Healthcare Database. Multivariate logistic models and generalized linear models were used to analyze binary outcomes and hospitalization costs, respectively. Outcomes are presented as the adjusted odds ratio (aOR) and 95% confidence interval (CI). RESULTS: CAS was associated with 1.6 times higher adjusted odds of stroke [aOR 1.55 (95% CI 1.36 to 1.77), p<0.001] and with 2.6 times higher odds of death [aOR 2.60 (95% CI 2.14 to 3.17), p<0.001] compared with CEA. There was no significant difference in MI risk between the 2 procedures. The adjusted incremental cost of death and MI were similar between the 2 procedures. However, the adjusted incremental cost of stroke was significantly higher in CEA compared with CAS by an estimated $2000. When stratified with respect to symptomatic status, the increased adjusted incremental cost of stroke in CEA was mainly seen in

asymptomatic patients ($5284 vs $2932, p<0.01). CONCLUSION: The incremental cost of in-hospital stroke is relatively higher in CEA compared to CAS. However, CEA remains a more cost-effective carotid intervention due to lower complication rates and baseline costs compared with CAS. Long-term cost-effectiveness studies are needed before definite conclusions are made.

94. Henriksson, M., Lundgren, F., & Carlsson, P. (2008). Cost-effectiveness of endarterectomy in patients with asymptomatic carotid artery stenosis. Br J Surg, 95(6), 714-720. doi:10.1002/bjs.6157

BACKGROUND: Long-term health outcomes and costs are important when deciding whether a strategy of carotid endarterectomy in addition to best medical management should be recommended for patients with asymptomatic carotid artery stenosis. This study investigated the cost-effectiveness of such a strategy compared with a strategy of best medical management alone. METHODS: Based on data from the randomized Asymptomatic Carotid Surgery Trial (ACST), a national vascular database and other published sources, expected costs and health outcomes in terms of quality-adjusted life years (QALYs) of both treatment strategies were estimated using decision-analytical modelling. Cost-effectiveness was established for a Swedish setting from a societal perspective. RESULTS: Base-case analysis showed that the incremental cost per QALY of a strategy with carotid endarterectomy for 65- and 75-year-old men (women) was 34,557 euros (311,133 euros) and 58,930 euros (779,776 euros) respectively. Sensitivity analyses indicated that the duration of the treatment effect after 5 years of follow-up in the ACST was important for the cost-effectiveness results. CONCLUSION: Carotid endarterectomy in addition to best medical management can be considered cost-effective in men aged 73 years or less but is less likely to be cost-effective in older men or in women.

95. Illig, K. A., Shortell, C. K., Zhang, R. Y., Sternbach, Y., Rhodes, J. M., Davies, M. G., . . . Green, R. M. (2003). Carotid endarterectomy then and now: Outcome and cost-effectiveness of modern practice. Surgery, 134(4), 705-711. doi:10.1016/S0039-6060(03)00333-7

Background. During the past decade, our practice of performing carotid endarterectomy (CEA) has changed dramatically, most notably by an abrupt shift from routine to selective preoperative angiography, reliance on defined care plans with full-time nurse practitioner oversight, and increasing reliance on eversion endarterectomy and cervical block anesthesia. This study was designed to determine whether these shafts in policy have been associated with lower costs without sacrificing clinical outcome. Methods. All patients undergoing CEA from July 1993 to December 2000 were identified, and inpatient and outpatient charts were reviewed. Cost data were obtained from the central hospital accounting system and converted to 2001 dollars. Thirty-day outcomes and costs were quantified each year and compared between each of 2 temporally well-defined groups: those undergoing "routine" versus "selective" angiography and those cared for before and after defined patient care protocols were instituted. Results. A total of 1168 CEAs were analyzed. Thirty-day combined stroke and death rate was 3.1%, and no trends or significant differences over time were seen. From 1993 to 2000 the cost of CEA fell from $9302 to $6216 (P < .0002), and length of stay was reduced I full day (P = .005). Institution of "selective" angiography was associated with an immediate cost savings of approximately $2000 per case (P < .0001), and nurse practitioner oversight along with institution of defined clinical protocols with a $530 (P < .05) decline in nonoperating room-related costs. Conclusions. Changes in policy from routine to selective angiography, reliance on defined postoperative care pathways, eversion endarterectomy, and cervical block anesthesia have been associated with significant cost savings, with no compromise in clinical outcome at our institution.

96. Jain, S., Jain, K. M., Kumar, S. D., Munn, J. S., & Rummel, M. C. (2007). Operative intervention for carotid restenosis is safe and effective. Eur J Vasc Endovasc Surg, 34(5), 561-568. doi:10.1016/j.ejvs.2007.06.003

Carotid stenting has been proposed as an alternative to reoperative carotid endarterectomy (rCEA) for recurrent carotid stenosis. The purpose of this study is to prove the safety, effectiveness and durability of reoperation in long term follow up of 18 years in a community hospital setting. From March 1988 to April 2005 80 patients, 46 men and 34 women (mean age: 64.1 years) underwent a total of 83 operations. Symptomatic recurrent stenosis (>70%) was the indication in 32, asymptomatic high-grade stenosis (>80%) in 49, intimal flap in one and

fibromuscular dysplasia (F.M.D), in one. The initial operation was carotid endarterectomy with primary closure in 60 and prosthetic patch in 23. The mean recurrences were at 23.3 months in 33 with myointimal hyperplasia, 105.4 months in 29 with recurrent atherosclerosis, 61.4 months in 19 with both hyperplasia and atherosclerosis, 2 months in one with intimal flap and 8 months in one with F.M.D bands. Reoperation utilized primary closure (3), vein patch (14), prosthetic patch (55), Gore-Tex interposition grafts (7), vein interposition grafts (3) and intraoperative dilation (1). No perioperative strokes or deaths occurred. One patient died from cardiac complications following combined rCEA and coronary artery bypass grafting. Operative morbidity consisted of reversible nerve injury (5), irreversible recurrent laryngeal nerve injury (1) and hematoma requiring evacuation (3). During follow up (3-153 months; mean: 50.9) carotid occlusion resulted in mild ipsilateral stroke in one patient, and one non-hemispheric stroke. There were 26 late deaths due to all causes, one due to CVA. Eight patients required reoperation (mean 53.4 months). Seven of these were hypertensive. Kaplan-Meier analysis of long-term follow up shows relatively high stroke free rates; at 153 months (12.75 years) the hemispheric stroke free rate was 98.67% and the all-stroke free rate was 95.85%. The survival estimate following redo surgery was 69.97% at 5 years and 40.23% at 10 years. We found that individuals on statin therapy (p-value=0.0042), and those on combination of statin and aspirin (p-value=0.0320), had significantly increased interval between primary and secondary operation. Increased age was correlated to a decreased time to redo surgery (p-value=<0.0001). We conclude that reoperation for recurrent carotid stenosis using standard vascular techniques is safe, effective, durable and cost effective. It should continue to be the mainstay of treatment when secondary intervention is required. Statins have a salutary effect on durability of the procedure and should be used when indicated.

97. Kilaru, S., Korn, P., Kasirajan, K., Lee, T. Y., Beavers, F. P., Lyon, R. T., . . . Kent, K. C. (2003). Is carotid angioplasty and stenting more cost effective than carotid endarterectomy? J Vasc Surg, 37(2), 331-339.

Objective: Carotid angioplasty and stenting (CAS) has been advocated as a minimally invasive and inexpensive alternative to carotid endarterectomy (CEA). However, a precise comparative analysis of the immediate and long-term costs associated with these two procedures has not been performed. To accomplish this, a Markov decision analysis model was created to evaluate the relative cost effectiveness of these two interventions. Methods: Procedural morbidity/mortality rate for CEA and costs (not charges) were derived from a retrospective review of consecutive patients treated at New York Presbyterian Hospital/Cornell (n = 447). Data for CAS were obtained from the literature. We incorporated into this model both the immediate procedural costs and the long-term cost of morbidities, such as stroke (major stroke in the first year = $52,019; in subsequent years = $27,336/y; minor stroke = $9419). We determined long-term survival rate in quality-adjusted life years and lifetime costs for a hypothetic cohort of 70-year-old patients undergoing either CEA or CAS. Our measure of outcome was the cost-effectiveness ratio. Results: The immediate procedural costs of CEA and CAS were $7871 and $10,133 respectively. We assumed major plus minor stroke rates for CEA and CAS of 0.9% and 5%, respectively. We assumed a 30-day mortality rate of 0% for CEA and 1.2% for CAS. In our base case analysis, CEA was cost saving (lifetime savings = $7017/patient; increase in quality-adjusted life years saved = 0.16). Sensitivity analysis revealed major stroke and death rates as the major contributors to this differential in cost effectiveness. Procedural costs were less important, and minor stroke rates were least important. CAS became cost effective only if its major stroke and mortality rates were made equivalent to those of CEA. Conclusion: CEA is cost saving compared with CAS. This is related to the higher rate of stroke with CAS and the high cost of stents and protection devices. To be economically competitive, the mortality and major stroke rates of CAS must be at least equivalent if not less than those of CEA. (J Vasc Surg 2003;37:331-9.)

98. Kim, J. H., Choi, J. B., Park, H. K., Kim, K. H., & Kuh, J. H. (2014). Cost-Effectiveness of Carotid Endarterectomy versus Carotid Artery Stenting for Treatment of Carotid Artery Stenosis. Korean J Thorac Cardiovasc Surg, 47(1), 20-25. doi:10.5090/kjtcs.2014.47.1.20

BACKGROUND: Symptomatic or asymptomatic patients with significant carotid artery stenosis (range, 70% to 99%) generally undergo either carotid artery endarterectomy (CEA) or carotid artery stenting (CAS) to prevent stroke. In this study, we evaluated the cost effectiveness of

these two treatment modalities. METHODS: A total of 47 patients (mean age, 67.1+/-9.1 years; male, 87.2%) undergoing either CEA (n=28) or CAS (n=19) for the treatment of significant carotid artery stenosis were enrolled in this study. Hospitalization costs were subdivided into three parts, namely pre-procedure, procedure and resource, and post-procedure costs. RESULTS: Total hospitalization costs were similar in both groups of CEA and CAS (6,377 thousand won [TW] vs. 6,703 TW, p=0.255); however, the total cost minus the pre-procedure cost was higher in the CAS group than in the CEA group (4,948 TW vs. 5,941 TW, p<0.0001). The pre-procedure cost of the CEA group was higher than that of the CAS group (1,429 TW vs. 762 TW, p<0.0001). However, the procedure and resource cost was higher in the CAS group because the resource cost was approximately three times higher in the CAS group than in the CEA group. The post-procedure cost was higher in the CEA group because hospital stays were approximately two times longer. CONCLUSION: The total hospitalization cost was not different between the CEA and the CAS groups. The pre-procedure cost was high in the CEA group, but the cost from procedure onset to discharge, including the resource cost, was significantly lower in this group.

99. Luebke, T., & Brunkwall, J. (2016). Impact of Real-World Adherence with Best Medical Treatment on Cost-Effectiveness of Carotid Endarterectomy for Asymptomatic Carotid Artery Stenosis. Ann Vasc Surg, 30, 236-247. doi:10.1016/j.avsg.2015.06.098

BACKGROUND: To present a model of decision and cost-effectiveness analysis that allows assessing the trade-off between the short-term risks of performing a carotid endarterectomy (CEA) and the rate of preventable future events and the impact of real-world adherence of best medical treatment (BMT) on cost-effectiveness of both therapeutic options. METHODS: We used data from the current literature to define values for a base case and perform a sensitivity analysis. The primary end point was a comparison of the fatal and disabling stroke-free survival during a 5-year period in a cohort of hypothetical patients who presented asymptomatic severe carotid stenosis and were treated with either prophylactic CEA or adherent and nonadherent best medical treatment, respectively. RESULTS: The difference in estimated fatal and disabling stroke-free survival favoring endarterectomy in patients with asymptomatic severe carotid stenosis is 44 days over the course of 5 years in case of nonadherent best medical treatment. Over a 5-year time horizon, prophylactic CEA would be cost-effective in 50.8% of bootstrap replicates and nonpersistent BMT might be economically dominant in 11.1%. The probability that CEA would be cost-effective at a willingness-to-pay (WTP) threshold of Euro 50,000/quality-adjusted life year gained was 71.8%. In 17.9% prophylactic CEA would be more costly and effective than persistent BMT, but its incremental cost-effectiveness ratio was greater than the WTP, so persistent BMT would be optimal. CONCLUSIONS: In this model, in case of real-world drug adherence, it was likely that a strategy of early endarterectomy might be a cost-effective or even the dominant therapeutic option in comparison with a strategy of medical therapy alone (deferred surgery). If background any-territory stroke rates on contemporary medical therapy would fall substantially below 0.7%, surgery would cease to be cost-effective.

100. Pandya, A., Gupta, A., Kamel, H., Navi, B. B., Sanelli, P. C., & Schackman, B. R. (2015). Carotid artery stenosis: cost-effectiveness of assessment of cerebrovascular reserve to guide treatment of asymptomatic patients. Radiology, 274(2), 455-463. doi:10.1148/radiol.14140501

PURPOSE: To project and compare the lifetime health benefits, health care costs, and incremental cost-effectiveness of a decision rule based on assessment of cerebrovascular reserve (CVR) compared with medical therapy and immediate revascularization in asymptomatic patients with carotid artery stenosis for prevention of stroke. MATERIALS AND METHODS: The three strategies compared included immediate revascularization (carotid endarterectomy) and ongoing medical therapy (with antiplatelet, statin, and antihypertensive agents plus lifestyle modification), medical therapy-based treatment with revascularization only for patients who progressed, and use of a CVR-based decision rule for treatment in which patients with CVR impairment undergo immediate revascularization and all others receive medical therapy. A decision analytic model was developed to project lifetime quality-adjusted life years (QALYs) and costs for asymptomatic patients with carotid stenosis with 70%-89% carotid luminal narrowing at presentation. Risks of clinical events, costs, and quality-of-life values were estimated on the basis of those in published sources. The analysis was conducted from a health care system perspective, with health and cost outcomes discounted at 3%. Results Total costs per person and lifetime QALYs were lowest for the medical therapy-based strategy ($14 597, 9.848 QALYs), followed by CVR testing ($16 583,

9.934 QALYs) and immediate revascularization ($20 950, 9.940 QALYs). The incremental cost-effectiveness ratio for the CVR-based strategy compared with the medical therapy-based strategy was $23 000 per QALY and for the immediate revascularization versus the CVR-based strategy was $760 000 per QALY. RESULTS: were sensitive to variations in model inputs for revascularization costs and complication risks and baseline stroke risk. CONCLUSION: CVR testing can be a cost-effective tool to identify asymptomatic patients with carotid stenosis who are most likely to benefit from revascularization.

101. Thapar, A., Garcia Mochon, L., Epstein, D., Shalhoub, J., & Davies, A. H. (2013). Modelling the cost-effectiveness of carotid endarterectomy for asymptomatic stenosis. Br J Surg, 100(2), 231-239. doi:10.1002/bjs.8960

BACKGROUND: The aim of this study was to model the cost-effectiveness of carotid endarterectomy for asymptomatic stenosis versus medical therapy based on 10-year data from the Asymptomatic Carotid Surgery Trial (ACST). METHODS: This was a cost-utility analysis based on clinical effectiveness data from the ACST with UK-specific costs and stroke outcomes. A Markov model was used to calculate the incremental cost-effectiveness ratio (ICER, or cost per additional quality-of-life year) for a strategy of early endarterectomy versus medical therapy for the average patient and published subgroups. An exploratory analysis considered contemporary event rates. RESULTS: The ICER was pound7584 per additional quality-adjusted life-year (QALY) for the average patient in the ACST. At thresholds of pound20,000 and pound30,000 there was a 74 and 84 per cent chance respectively of early endarterectomy being cost-effective. The ICER for men below 75 years of age was pound3254, and that for men aged 75 years or above was pound71,699. For women aged under 75 years endarterectomy was less costly and more effective than medical therapy; for women aged 75 years or more endarterectomy was less effective and more costly than medical therapy. At contemporary perioperative event rates of 2.7 per cent and background any-territory stroke rates of 1.6 per cent, early endarterectomy remained cost-effective. CONCLUSION: In the ACST, early endarterectomy was predicted to be cost-effective in those below 75 years of age, using a threshold of pound20,000 per QALY. If background any-territory stroke rates fell below 1 per cent per annum, early endarterectomy would cease to be cost-effective.

102. Wallaert, J. B., Newhall, K. A., Suckow, B. D., Brooke, B. S., Zhang, M., Farber, A. E., . . . Vascular Quality, I. (2016). Relationships between 2-Year Survival, Costs, and Outcomes following Carotid Endarterectomy in Asymptomatic Patients in the Vascular Quality Initiative. Ann Vasc Surg, 35, 174-182. doi:10.1016/j.avsg.2016.01.024

BACKGROUND: Carotid endarterectomy (CEA) for asymptomatic patients with limited life expectancy may not be beneficial or cost-effective. The purpose of this study was to examine relationships among survival, outcomes, and costs within 2 years following CEA among asymptomatic patients. METHODS: Prospectively collected data from 3097 patients undergoing CEA for asymptomatic disease from Vascular Quality Initiative VQI registry were linked to Medicare. Models were used to identify predictors of 2-year mortality following CEA. Patients were classified as low, medium, or high risk of death based on this model. Next, we examined costs related to cerebrovascular care, occurrence of stroke, rehospitalization, and reintervention within 2 years following CEA across risk strata. RESULTS: Overall, 2-year mortality was 6.7%. Age, diabetes, smoking, congestive heart failure (CHF), chronic obstructive pulmonary disease, renal insufficiency, absence of statin use, and contralateral internal carotid artery (ICA) stenosis were independently associated with a higher risk of death following CEA. In-hospital costs averaged $7500 among patients defined as low risk for death, and exceeded $10,800 among high risk patients. Although long-term costs related to cerebrovascular disease were 2 times higher in patients deemed high risk for death compared with low risk patents ($17,800 vs. $8800, P = 0.001), high risk of death was not independently associated with a high probability of high cost. Predictors of high cost at 2 years were severe contralateral ICA stenosis, dialysis dependence, and American Society for Anesthesia Class 4. Both statin use and CHF were protective of high cost. CONCLUSIONS: Greater than 90% of patients undergoing CEA live long enough to realize the benefits of their procedure. Moreover, the long-term costs are supported by the effectiveness of this procedure at all levels of patient risk.

Appendix 2:
Additional Abstracts Identified Through Full Text Review

Percutaneous coronary intervention with balloon angioplasty or stent placement for stable coronary disease

1. **Babapulle, M. N., Joseph, L., Belisle, P., Brophy, J. M., & Eisenberg, M. J. (2004, Aug 14-20). A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet, 364*(9434), 583-591. http://dx.doi.org/10.1016/s0140-6736(04)16850-5**

   BACKGROUND: Drug-eluting stents (DES) are associated with lower restenosis rates than bare-metal stents (BMS), but the benefits and safety of the new devices have not been systematically quantified across different trials. We undertook a meta-analysis of randomised trials comparing BMS and stents eluting sirolimus or paclitaxel. METHODS: A systematic literature search aimed to identify all randomised clinical trials with 6-12 months of clinical follow-up. Results were pooled by a hierarchical Bayesian random-effects model with prespecified stratification for drug and the presence of carrier polymer. The primary outcomes examined were rates of death, myocardial infarction, target-lesion revascularisation, major adverse cardiac events (death, myocardial infarction, and target-vessel revascularisation), and angiographic restenosis. FINDINGS: We identified 11 eligible trials involving 5103 patients. The pooled mortality rates were low for both DES and BMS with no evidence of any difference between them (odds ratio 1.11 [95% credible interval 0.61-2.06]). Pooled rates of myocardial infarction showed no between-group difference (0.92 [0.65-1.25]). The rate of major adverse cardiac events was 7.8% with DES and 16.4% with BMS (0.42 [0.32-0.53]), and the angiographic restenosis rates were also lower for DES (8.9% vs 29.3%; 0.18 [0.06-0.40]). The pooled rates of major adverse cardiac events for each DES type and the respective BMS were: for sirolimus, 6.8% versus 21.0% (0.28 [0.17-0.41]); for polymer-based paclitaxel 8.7% versus 16.7% (0.47 [0.25-0.71]); and for non-polymer-based paclitaxel 7.7% versus 9.5% (0.64 [0.42-1.00]). We did not observe higher rates of edge restenosis, stent thrombosis, or late incomplete stent apposition with DES, although the credible intervals were wide. INTERPRETATION: Sirolimus-eluting and polymeric paclitaxel-eluting stents are effective at decreasing rates of angiographic restenosis and major adverse cardiac events compared with BMS. However, there is no evidence that they affect mortality or myocardial-infarction rates. They also appear to be safe in the short to medium term, although definitive conclusions are not possible. Larger studies with longer follow-up are needed to define better the role of these new devices.

2. **Caruba, T., Chevreul, K., Zarca, K., Cadier, B., Juilliere, Y., Dubourg, O., . . . Danchin, N. (2015, Nov). Annual cost of stable coronary artery disease in France: A modeling study. *Archives of Cardiovascular Disease, 108*(11), 576-588. http://dx.doi.org/10.1016/j.acvd.2015.06.006**

   BACKGROUND: Few studies have analyzed the cost of treatment of chronic angina pectoris, especially in European countries. AIM: To determine, using a modeling approach, the cost of care in 2012 for 1year of treatment of patients with stable angina, according to four therapeutic options: optimal medical therapy (OMT); percutaneous coronary intervention with bare-metal stent (PCI-BMS); PCI with drug-eluting stent (PCI-DES); and coronary artery bypass graft (CABG). METHODS: Six different clinical scenarios that could occur over 1year were defined: clinical success; recurrence of symptoms without hospitalization; myocardial infarction (MI); subsequent revascularization; death from non-cardiac cause; and cardiac death. The probability of a patient being in one of the six clinical scenarios, according to the therapeutic options used, was determined from a literature search. A direct medical cost for each of the therapeutic options was calculated from the perspective of French statutory health insurance. RESULTS: The annual costs per patient for each strategy, according to their efficacy results, were, in our models, euro1567 with OMT, euro5908 with PCI-BMS, euro6623 with PCI-DES and euro16,612 with

CABG. These costs were significantly different (P<0.05). A part of these costs was related to management of complications (recurrence of symptoms, MI and death) during the year (between 3% and 38% depending on the therapeutic options studied); this part of the expenditure was lowest with the CABG therapeutic option. CONCLUSION: OMT appears to be the least costly option, and, if reasonable from a clinical point of view, might achieve appreciable savings in health expenditure.

3. **Denvir, M. A., Lee, A. J., Rysdale, J., Prescott, R. J., Eteiba, H., Starkey, I. R., . . . Walker, A. (2007, Feb). Effects of changing clinical practice on costs and outcomes of percutaneous coronary intervention between 1998 and 2002. Heart, 93(2), 195-199.** http://dx.doi.org/10.1136/hrt.2006.090134

   Aim: To assess the effect of changing clinical practice on the costs and outcomes of percutaneous coronary intervention (PCI) between 1998 and 2002. Setting: Two tertiary interventional centres. Patients: Consecutive patients undergoing PCI over a 12-month period between 1998 and 2002. Design: Comparative observational study of costs and 12- month clinical outcomes of consecutive PCI procedures in 1998 (n = 1047) and 2002 (n = 1346). Clinical data were recorded in the Scottish PCI register. Repeat PCI, coronary artery bypass graft and mortality were obtained by record linkage. Costs of equipment were calculated using a computerised bar- code system and standard National Health Service reference costs. Results: Between 1998 and 2002, the use of bare metal stents increased from 44% to 81%, and the use of glycoprotein IIB/IIIA inhibitors increased from 0% to 14% of cases. During this time, a significant reduction was observed in repeat target-vessel PCI (from 8.4% to 5.1%, p = 0.001), any repeat PCI (from 11.7% to 9.2%, p = 0.05) and any repeat revascularisation (from 15.1% to 11.3%, p = 0.009) within 12 months. Significantly higher cost per case in 2002 compared with 1998 (mean (standard deviation) 2311 (1158) v 1785 pound (907), p < 0.001) was mainly due to increased contribution from bed-day costs in 2002 (45.0% (16.3%) v 26.2% (12.6%), p = 0.01) associated with non-elective cases spending significantly longer in hospital (6.22 (4.3) v 4.6 (4.3) days, p = 0.01). Conclusions: Greater use of stents and glycoprotein IIb/IIIa inhibitors between 1998 and 2002 has been accompanied by a marked reduction in the need for repeat revascularisation. Longer duration of hospital stay for non-elective cases is mainly responsible for increasing costs. Strategies to reduce the length of stay could considerably reduce the costs of PCI.

4. **Fischell, T. A., Attia, T., Rane, S., & Salman, W. (2006, Oct). High-dose, single-bolus eptifibatide: A safe and cost-effective alternative to conventional glycoprotein IIb/IIIa inhibitor use for elective coronary interventions. Journal of Invasive Cardiology, 18(10), 487-491.**

   BACKGROUND: Adjunctive pharmacotherapy with eptifibatide, a glycoprotein (GP) IIb/IIIa inhibitor, as an intravenous bolus followed by infusion has been shown to improve outcomes in elective coronary interventions (PCI). However, bleeding complications and costs have limited the routine adoption of this regimen. PURPOSE: The goal of this study was to examine the safety, efficacy and cost-effectiveness of high-dose, single-bolus eptifibatide, without post-intervention infusion, in "real-world" patients undergoing elective PCI. METHODS: We studied 401 patients with stable and unstable angina who were treated with a high-dose (20 mg), single bolus of eptifibatide plus heparin prior to the start of elective PCI. Exclusion criteria included recent MI, stenting of bypass graft(s), rotational atherectomy and/or brachytherapy. The primary study endpoints were major adverse clinical events (MACE), defined as the in-hospital and 30-day incidence of death from any cause, Q-wave or non-Q-wave MI, repeat target vessel revascularization and/or major bleeding complications. RESULTS: Relevant demographic and procedural characteristics included mean age: 66.4 +/- 11.2; male gender: 242/401 (61%); number of vessels treated per patient: 1.46 +/- 0.42; and number of stents deployed per patient: 1.82 +/- 0.65. In-hospital non-Q-wave MI (CPK and/or CPK-MB > 3 times the upper limit of normal) occurred in 7/401 patients (1.75%) and MACE was 2.25%. Major bleeding complications were seen in 2/401 patients (0.49%). There were 4 additional MACE events at 30-day follow up (total MACE and bleeding = 3.25%). The average anticoagulation cost was 66 dollars/patient. CONCLUSIONS: Intravenous eptifibatide, administered as a high-dose (20 mg)

single-vial bolus, is a safe, effective and highly cost-effective alternative to the conventional regimens of bolus plus prolonged intravenous GP IIb/IIIa inhibitor infusion for patients undergoing elective PCI.

5. **Glaser, R., Gertz, Z., Matthai, W. H., Wilensky, R. L., Weiner, M., Kolansky, D., . . . Herrmann, H. (2009, Sep). Patient satisfaction is comparable to early discharge versus overnight observation after elective percutaneous coronary intervention. Journal of Invasive Cardiology, 21(9), 464-467.**

   BACKGROUND: Previous investigation has suggested that early discharge after percutaneous coronary intervention (PCI) is feasible and safe, but these studies have utilized largely radial approaches or been conducted in non-U.S. cohorts. We sought to assess patient satisfaction, safety and cost of a strategy of selective early discharge in U.S. patients undergoing PCI via a femoral approach with contemporary adjunctive pharmacologic and hemostasis agents. METHODS AND RESULTS: Patients with stable coronary artery disease undergoing elective PCI were prospectively recruited and randomized to either routine care, with an overnight hospital stay, versus early discharge 2 hours following successful PCI with adjunctive bivalirudin therapy and a femoral arterial closure device at the end of the procedure. The primary endpoints were safety and patient satisfaction as measured by a validated patient satisfaction survey during the index hospital stay and at 30 days. A total of 39 patients were randomized, with 20 to routine care and 19 to early discharge. There was no difference in major safety endpoints including death, non-fatal MI, urgent target lesion revascularization and thrombolysis in myocardial infarction (TIMI) major bleeding, with none in either group. Mean patient satisfaction scores were similar and high in both groups (89.6 for early discharge patients and 90.7 for routine care patients, p = 0.68). There was lower cost in the early discharge group, with a mean cost of 8,604 USD versus 10,565 USD in the routine care group (mean difference 1,961 USD, 95% confidence interval, -96 USD to 4,017 USD). CONCLUSION: Patients undergoing elective PCI for stable coronary artery disease may have similar safety and satisfaction with early discharge when using a careful strategy that incorporates optimal stent and hemostasis results and contemporary adjunctive anticoagulation therapy, with lower cost. This strategy may serve as a basis for a larger-scale randomized trial.

6. **Jabara, R., Gadesam, R., Pendyala, L., Chronos, N., Crisco, L. V., King, S. B., & Chen, J. P. (2008, Dec). Ambulatory discharge after transradial coronary intervention: Preliminary US single-center experience (Same-day TransRadial Intervention and Discharge Evaluation, the STRIDE Study). American Heart Journal, 156(6), 1141-1146.** http://dx.doi.org/10.1016/j.ahj.2008.07.018

   BACKGROUND: Although the safety and cost-effectiveness of same-day discharge after uncomplicated transradial percutaneous coronary intervention (TR-PCI) is well established in Europe and Asia, such data are not available for US patients. METHODS: All patients who underwent TR-PCI at our high-volume US medical center between 2004 and 2007 were included in this study. The primary end point was in-hospital adverse clinical outcomes between 6 and 24 hours postprocedure. RESULTS: A total of 450 patients were included in this study (aged 59 +/- 11 years). Of these, 13% were female, 27% were diabetic, 6% had peripheral vascular disease, and 5% had chronic kidney disease. Procedural indications included stable angina (49%), unstable angina (31%), non-ST elevation myocardial infarction (NSTEMI) (17%), and ST elevation myocardial infarction (STEMI) (3%). All patients received an intra-arterial cocktail of heparin, verapamil, and nitroglycerin, and 13% of patients received glycoprotein IIb/IIIa inhibitors. Seven percent of patients had 3-vessel disease, 3% had bypass grafts stenoses, and 20% had class B(2)/C lesions. Procedural success rate was 96%. A total of 24 (5.3%) postprocedural complications were observed; however, none occurred between hours 6 to 24, the time differential between same-day and next-day discharge. Thirteen patients (2.9%) experienced significant complications within the first 6 hours (MI, urgent repeat revascularization, and ventricular tachycardia). Eleven (2.4%) spontaneously resolved minor access complications developed. There were 12 same-day discharges according to the operators' discretion; none required readmission. CONCLUSIONS: Although a low incidence of complications did occur, none

would have been impacted by same-day discharge. Those observed before 6 hours would have prevented early discharge, and those occurring after 24 hours would have been unaffected by routine next-day discharge. This observational study demonstrated the safety and feasibility for a prospective evaluation of ambulatory TR-PCI in an American practice setting.

7. **SoS Investigators. (2002). Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): A randomised controlled trial. Lancet, 360(9338), 965-970.**

   BACKGROUND: Results of trials, comparing percutaneous transluminal coronary angioplasty (PTCA) with coronary artery bypass grafting (CABG), indicate that rates of death or myocardial infarction are similar with either treatment strategy. Management with PTCA is, however, associated with an increased requirement for subsequent, additional revascularisation. Coronary stents, used as an adjunct to PTCA, reduce restenosis and the need for repeat revascularisation. The aim of the Stent or Surgery (SoS) trial was to assess the effect of stent-assisted percutaneous coronary intervention (PCI) versus CABG in the management of patients with multivessel disease. METHODS: In 53 centres in Europe and Canada, symptomatic patients with multivessel coronary artery disease were randomised to CABG (n=500) or stent-assisted PCI (n=488). The primary outcome measure was a comparison of the rates of repeat revascularisation. Secondary outcomes included death or Q-wave myocardial infarction and all-cause mortality. Analysis was by intention to treat. FINDINGS: All patients were followed-up for a minimum of 1 year and the results are expressed for the median follow-up of 2 years. 21% (n=101) of patients in the PCI group required additional revascularisation procedures compared with 6% (n=30) in the CABG group (hazard ratio 3.85, 95% CI 2.56-5.79, p<0.0001). The incidence of death or Q-wave myocardial infarction was similar in both groups (PCI 9% [n=46], CABG 10% [n=49]; hazard ratio 0.95, 95% CI 0.63-1.42, p=0.80). There were fewer deaths in the CABG group than in the PCI group (PCI 5% [n=22], CABG 2% [n=8]; hazard ratio 2.91, 95% CI 1.29-6.53, p=0.01). INTERPRETATION: The use of coronary stents has reduced the need for repeat revascularisation when compared with previous studies that used balloon angioplasty, though the rate remains significantly higher than in patients managed with CABG. The apparent reduction in mortality with CABG requires further investigation.

8. **Varani, E., Guastaroba, P., Di Tanna, G. L., Saia, F., Balducelli, M., Campo, G., . . . Marzocchi, A. (2010, Apr). Long-term clinical outcomes and cost-effectiveness analysis in multivessel percutaneous coronary interventions: Comparison of drug-eluting stents, bare-metal stents and a mixed approach in patients at high and low risk of repeat revascularisation. EuroIntervention, 5(8), 953-961.** http://dx.doi.org/10.4244/

   AIMS: To evaluate the long-term effectiveness and cost-efficacy of drug-eluting stents (DES) in a real world setting of multivessel percutaneous coronary intervention (PCI). METHODS AND RESULTS: We evaluated the 2-year outcome of all multivessel PCI in de novo lesions enrolled in a prospective web-based multicentre registry from July 2003 to December 2006. Among the 2,898 eligible patients, 1,315 were treated with bare-metal stent (BMS) alone, 657 with DES alone, and 926 with both. At 2-years, use of DES was associated with a lower propensity score adjusted incidence of major adverse cardiac events (MACE), death and myocardial infarction, and target vessel revascularisation (TVR) compared with BMS but only in patients at high risk of TVR. No difference was apparent between "pure" DES and the mixed approach. The matched cost-effectiveness analysis revealed DES to be more costly and more effective with a reasonable incremental cost-efficacy ratio for any MACE avoided only in patients with a high risk of TVR and only in comparison with "pure" BMS patients. CONCLUSIONS: In this real-world multivessel PCI registry, the use of DES and a mixed approach were associated with a 2-year reduction of adverse clinical outcomes in comparison with BMS especially in patients with a high risk of TVR. DES were cost-effective only in patients at high risk of TVR.

Appendix 3:
Rating Tools by Study Type

Rating tools were developed to assess each of the domains (study limitations, directness, precision, and suspected reporting bias). A separate tool was developed for each of the three main study types assessed.

RCT

Adapted from the "Quality Assessment of Controlled Intervention Studies" and "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies"
https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Study limitations

1. Was the study objective clearly defined? Was the objective of the study to measure downstream service utilization or spending after a low-value services?
2. Was the study population clearly specified and defined? Did the study adequately describe how patients were included and excluded from the study?
3. Did the study adequately describe how participants were randomized?
4. Were the treatment and control groups shown to be similar at baseline on key characteristics?
5. Was the outcome measure clearly defined and measured consistently for the entire study population?
6. Was the follow-up period appropriate for the low-value care measure?
7. Were sensitivity analyses conducted?
8. Were limitations and generalizability of findings discussed?

Precision

1. Was the primary comparison of interest (intervention vs no intervention/medical therapy) tested using a statistical test?
2. Was the sample size large enough to detect a statistically significant effect (if an analysis of interest was conducted)? Do the authors present power calculations if sample sizes are small?
3. Was uncertainty in the estimates calculated/expressed? Were significance tests were used?

Directness

1. Were data measuring the low-value service and the outcome drawn from the same source/study? If not, were data sources sufficiently comparable to measure the relationship of interest?

Suspected reporting bias

1. Were the funding sources (if any) reported?
2. Were there any potential conflicts of interest between the authors and the funding source?

Observational Studies

Adapted from the "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Study limitations

1. Was the study objective clearly defined? Was the objective of the study to measure downstream service utilization or spending after a low-value services?
2. Was the study population, inclusion, and exclusion clearly specified and defined?
3. Does the included study population align with the measure of low-value care?
4. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between the low-value care measure and the outcome(s) (if an analysis of interest was conducted)?
5. Was the outcome measure clearly defined and implemented consistently for the entire study population?
6. Was the follow-up period appropriate for the low-value care measure?
7. Were sensitivity analyses conducted?
8. Were limitations and generalizability of findings discussed?

Precision

1. Was the primary comparison of interest (intervention vs no intervention/medical therapy) tested using a statistical test?
2. Was the sample size large enough to detect a statistically significant effect (if an analysis of interest was conducted)? Do the authors present power calculations if sample sizes are small?
3. Were measures of uncertainty (e.g., p-values, confidence intervals) used to quantify uncertainty in the estimates of interest?

Directness

1. Were data measuring the low-value service and the outcome measured in the same population? If not, were the data sources sufficiently comparable to measure the relationship of interest?

Suspected reporting bias

1. Were the funding sources (if any) reported?
2. Were there any potential conflicts of interest between the authors and the funding source?

Evidence Syntheses and Economic Analyses

Adapted from the ISPOR CHEERS checklist (Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.)

Study limitations

1. Was the study objective clearly defined? Was the objective of the study to measure downstream service utilization or spending after a low-value services?
2. Were the population of interest and data sources clearly specified and defined?
3. What type(s) of studies were the population/model inputs drawn from (e.g., RCT vs. cohort, cross-sectional)?
4. Was the perspective of the analysis/model clearly described?
5. Are the interventions or strategies being compared clearly described?
6. Do the authors clearly state how were the costs or services downstream to the low-value care measure defined or estimated?
7. Was the currency and year of reported costs reported? If costs were converted, is the methodology sufficiently described?
8. Was the type of decision analytical model (if applicable) clearly defined?
9. Are there any structural or other assumptions that the analysis makes?
10. Was the follow-up period/time horizon appropriate for the low-value care measure?
11. Was a discount rate reported/used?
12. Were deterministic sensitivity analyses conducted to test the effects of varying model parameters? (A deterministic sensitivity analysis is where model input parameters manually changed to determine if there is an impact on the outcome.)
13. Were limitations and generalizability of findings discussed?

Precision

1. Was the primary comparison of interest (intervention vs no intervention/medical therapy) tested using a statistical test?
2. If the study was based off of a single study, was the sample size large enough to detect an effect (if an analysis of interest was conducted)?
3. Were probabilistic sensitivity analyses was conducted to attempt to quantify the uncertainty of model estimates? Were the results of these analyses sufficiently described? Note: We considered model derived estimates of downstream spending or service utilization precise if probabilistic sensitivity analyses were used to quantify their uncertainty even absent a relevant control group. (A probabilistic sensitivity analysis is a technique to quantify the level of confidence in the model output; distributions around point estimates are often tested.)

Directness

1. Were data measuring the low-value service and the outcome drawn from the same source/study? If not, were data sources sufficiently comparable to measure the relationship of interest?

Suspected reporting bias

1. Were the funding sources (if any) reported?
2. Were there any potential conflicts of interest between the authors and the funding source?

Appendix 4:
Evidence Tables

Appendix 4.1: Evidence Table for PSA Testing

Table App 4.1-1. Evidence Table for PSA Testing

	Benoit et al., 2001	Heijnsdijk et al., 2015	Heijnsdijk et al., 2016	Heijnsdijk et al., 2009
Study design	Economic Evaluation/Evidence Synthesis	Economic Evaluation/Evidence Synthesis	Economic Evaluation/Evidence Synthesis	Economic Evaluation/Evidence Synthesis
Country	United States and Sweden	United States	Europe	Europe
Key population of interest	Men 50–70 years of age	Men 55–69 years of age (Rotterdam and Goteborg data)	Men 55–69 years of age (Rotterdam and Goteborg data)	Men 55–70 years of age
Key treatments of interest (n)	PSA only (100,000) vs. PSA + digital rectal exam (DRE; 100,000)	PSA at different intervals; No screening (10 million men cohort with 80% participation in screening)	PSA only vs. PSA + Beckman Coulter Prostate Health Index; No screening (10 million, participation not specified)	PSA at different intervals; No screening (100,000 men cohort with 100% participation in screening)
Treatments not included	N/A	N/A	N/A	N/A
Quality rating	Low	Moderate	Moderate	Moderate
Examines Cost				
Currency, cost year	USD, year NR (used 1992)	USD, 2008	Euro, 2008	Euro, 2008
Cost follow-up time	Lifetime	Lifetime	Lifetime	Lifetime
Units	Per 100,000 men	Per 1,000 men	Per 1,000 men	Per 100,000 men
Costs included	Initial screening, treatment, complications	Initial screening, diagnosis, primary treatment, follow-up, palliative care	Initial screening, diagnosis, primary treatment, follow-up, palliative care	Initial screening, staging, follow-up, radical prostatectomy, radiation therapy, active surveillance
Mean per patient, ≥ 70 years (2018 USD)	NR	NR	NR	NR
Annual cost to a health care system, ≥ 75 years (2018 USD)	NR	NR	NR	NR
Mean per patient, 40–74 years (2018 USD)	50–59 years: PSA + DRE: $53,614,208–$68,888,726 ($95,592,307–$124,111,149) 50–69 years: PSA + DRE: $83,494,828–$108,111,846 ($150,425,761–$194,776,217) 60–69 years: PSA + DRE: $106,907,986–$138,806,659 ($192,607,322–$250,076,536) 50–70 years: PSA only: $44,116,797 ($79,481,603)	Ranges from $2,652 (55 years, 1 screen; $3,326) to $4,842 (55–75 years, screen every year; $6,072) No screening: $2,531 ($3,174)	50–75 years, screen every 4 years PSA only: €2,893 ($4,136) PSA + Beckman Coulter Prostate Health Index: €2,860 ($4,089) No screening: €2,016 ($2,882)	Ranges from €60,695,000 (55–70 years, screen every 4 years; $86,773,987) to €83,391,000 (55–75 years, screen every 4 years; $119,221,840) No screening: €30,284,000 ($43,296,209)

(continued)

Table App 4.1-1. Evidence Table for PSA Testing (continued)

	Benoit et al., 2001	Heijnsdijk et al., 2015	Heijnsdijk et al., 2016	Heijnsdijk et al., 2009
Annual cost to a health care system, 50–74 years (2018 USD)	NR	NR	NR	NR
Incremental cost per patient, 40–74 years (2018 USD)	NR	NR	NR	NR
Examines Services				
Service follow-up time	NR	NR	NR	Lifetime
Units	NR	NR	NR	Per 100,000 men
Prostate biopsy	NR	NR	NR	55–70 years, screen every 4 years: 19,946 55–70 years, screen every year: 24,488 55–70 years, screen every 2 years: 23,759 55–75 years, screen every 4 years: 29,954 55–70 years, no screening: 6,642
Ultrasound	NR	NR	NR	NR
Imaging	NR	NR	NR	NR
Any treatment	NR	NR	NR	NR
Active surveillance/conservative management	NR	NR	NR	55–70 years, screen every 4 years: 1,310 55–70 years, screen every year: 1,714 55–70 years, screen every 2 years: 1,614 55–75 years, screen every 4 years: 1,942 55–70 years, no screening: 438
Radical prostatectomy	NR	NR	NR	55–70 years, screen every 4 years: 1,559 55–70 years, screen every year: 1,792 55–70 years, screen every 2 years: 1,779 55–75 years, screen every 4 years: 2,214 55–70 years, no screening: 716
Radiation therapy	NR	NR	NR	55–70 years, screen every 4 years: 1,786 55–70 years, screen every year: 2,099 55–70 years, screen every 2 years: 2,065 55–75 years, screen every 4 years: 2,608 55–70 years, no screening: 708
Hormone therapy	NR	NR	NR	NR
Outpatient visit	NR	NR	NR	NR

(continued)

Table App 4.1-1. Evidence Table for PSA Testing (continued)

	Benoit et al., 2001	Heijnsdijk et al., 2015	Heijnsdijk et al., 2016	Heijnsdijk et al., 2009
Palliative therapy	NR	NR	NR	Palliative therapy: 55–70 years, screen every 4 years: 301 55–70 years, screen every year: 245 55–70 years, screen every 2 years: 251 55–75 years, screen every 4 years: 217 55–70 years, no screening: 514 Palliative therapy after primary treatment: 55–70 years, screen every 4 years: 267 55–70 years, screen every year: 218 55–70 years, screen every 2 years: 246 55–75 years, screen every 4 years: 277 55–70 years, no screening: 241
Repeat PSA	NR	NR		NR

(continued)

Table App 4.1-1. Evidence Table for PSA Testing (continued)

	Keller et al., 2017	Ma et al., 2014	Martin et al., 2013	Pataky et al., 2014
Study design	Economic Evaluation/Evidence Synthesis	Observational	Economic Evaluation/Evidence Synthesis	Economic Evaluation/Evidence Synthesis
Country	Australia	United States	United States	Canada
Key population of interest	Men 50–69 years of age	Men 66–99 years of age (Medicare)	50-year-old men, screen every 4 years	Men ≥ 40 years of age
Key treatments of interest (n)	Base case (NR): treatment based on cancer risk and patient preference (current practice) Optimized active surveillance (NR): low-risk prostate cancer treated with active surveillance Opportunistic screening (NR)	PSA (94,652; includes those not screened)	PSA (NR)	PSA; No screening (NR)
Treatments not included	N/A	N/A	N/A	
Quality rating	High	Moderate	Low	Moderate
Examines Cost				
Currency, cost year	AUD, 2015	USD, 2009	AUD, 2012	CAD, 2010
Cost follow-up time	20 years	Follow-up PSA within 180 days of the screening PSA, biopsy within 180 days, hospitalization within 30 days of biopsy	10 years	50 years
Units	Per patient	Annual cost per beneficiary (denominator includes men not screened)	Per patient by risk for prostate cancer	Per capita
Costs included	Initial screening, diagnosis, treatment, follow-up, palliative/end-of-life care	Initial screening, biopsy, hospitalizations	Routine and additional PSA screening, lifetime treatment (excluding terminal care), confirming cancer diagnosis, biopsy, urology visits, terminal care, and mortality	Initial screening, diagnosis, treatment, follow-up, end-of-life care
Mean per patient, ≥ 70 years (2018 USD)	NR	85–99 years: $14 ($17) 75–84 years: $31 ($38)	NR	70 years, 1 screen: 571 CAD ($520)
Annual cost to a health care system, ≥ 75 years (2018 USD)	NR	85–99 years: $18 million ($22.1 million) 75–84 years: $127 million ($155.7 million)	NR	NR

(continued)

Table App 4.1-1. Evidence Table for PSA Testing (continued)

	Keller et al., 2017	Ma et al., 2014	Martin et al., 2013	Pataky et al., 2014
Mean per patient, 40–74 years (2018 USD)	50–69 years Base case: 5481.47 AUD ($4,224) Opportunistic screening for Base case: 4664.17 AUD ($3,594) Optimized active surveillance: 5085.59 AUD ($3,919) Opportunistic screening for Optimized active surveillance: 4524.92 AUD ($3,487)	66–74 years: $43 ($53) 66–99 years: $36 ($44)	NR	Ranges from 469 CAD (50 years, 1 screen; $427) to 1,445 CAD (40–74 years, screen every 2 years; $1,316) No screening: 438 CAD ($399)
Annual cost to a health care system, 50–74 years (2018 USD)	NR	66–74 years: $301 million ($369.0 million) 66–99 years: $447 million ($548.0 million)	NR	NR
Incremental cost per patient, 40–74 years (2018 USD)	NR	NR	Average risk: 2185 AUD ($1,802) High risk: 2519 AUD ($2,078) Very high risk: 2755 AUD ($2,272)	NR
Examines Services				
Service follow-up time	NR	180 days	NR	NR
Units	NR	Median rate	NR	NR
Prostate biopsy	NR	1.10%	NR	NR
Ultrasound	NR	NR	NR	NR
Imaging	NR	NR	NR	NR
Any treatment	NR	NR	NR	NR
Active surveillance/conservative management	NR	NR	NR	NR
Radical prostatectomy	NR	NR	NR	NR
Radiation therapy	NR	NR	NR	NR
Hormone therapy	NR	NR	NR	NR
Outpatient visit	NR	NR	NR	NR
Palliative therapy	NR	NR	NR	NR
Repeat PSA	NR	NR	NR	NR

(continued)

Table App 4.1-1. Evidence Table for PSA Testing (continued)

	Richter et al., 2001	Roth et al., 2016	Sennfalt et al., 2004	Shao et al., 2011
Study design	Observational	Economic Evaluation/Evidence Synthesis	Economic Evaluation/Evidence Synthesis	Observational
Country	United States	United States	Sweden	United States
Key population of interest	NR (whole database for Veterans Affairs-New Jersey from 1996–1998)	Men ≥ 40 years of age	1,492 screened, men 50–69 years of age	22,047 who were ≥ 70 years of age and previously diagnosed with prostate cancer (Medicare)
Key treatments of interest (n)	PSA	Contemporary: all cases receive treatment by age and cancer stage/grade Selective: low-risk receive conservative management; others follow contemporary treatment No screening	PSA	Number of annual PSA screenings (0, 1, 2, 3, 4–6)
Treatments not included	N/A	N/A	7,679 with no screening	No screening
Quality rating	Low	Moderate	Low	Moderate
Examines Cost				
Currency, cost year	NR	USD, 2014	Swedish SEK, 1999	NR
Cost follow-up time	NR	Lifetime	Lifetime	NR
Units	NR	Per patient	Per man	NR
Costs included	NR	Initial screening, diagnosis, treatment, follow-up, end-of-life care	Initial screening, diagnosis, treatment, follow-up, palliative care	NR
Mean per patient, ≥ 70 years (2018 USD)	NR	NR	NR	NR
Annual cost to a health care system, ≥ 75 years (2018 USD)	NR	NR	NR	NR
Mean per patient, 40–74 years (2018 USD)	NR	Contemporary: ranges $5,022 (55–69 years, screen every 4 years; $5,498) to $6,079 (50–74 years, screen every year; $6,655) Selective: ranges from $4,971 (55–69 years, screen every 4 years; $5,422) to $5,411 (50–74 years, screen every year; $5,924) No screening: $4,708 ($5,154)	50–69 years: 10,260 SEK ($1,735)	NR
Annual cost to a health care system, 50–74 years (2018 USD)	NR	NR	NR	NR
Incremental cost per patient, 40–74 years (2018 USD)	NR	NR	NR	NR

(continued)

Table App 4.1-1. Evidence Table for PSA Testing (continued)

	Richter et al., 2001	Roth et al., 2016	Sennfalt et al., 2004	Shao et al., 2011
Examines Services				
Service follow-up time	NR	NR	NR	180 days
Units	Number of biopsies/number of PSAs	NR	NR	Percentages stratified by # of PSA screenings
Prostate biopsy	1996: 309/8,000 *(3.9%)* 1997: 434/9,410 *(4.6%)* 1998: 507/23,684 *(2.1%)*	NR	NR	
Ultrasound	NR	NR	NR	
Imaging	NR	NR	NR	
Any treatment	NR	NR	NR	
Active surveillance/conservative management	NR	NR	NR	1 PSA: 26% 2 PSAs: 25% 3 PSAs: 24% 4–6 PSAs: 23%
Radical prostatectomy	NR	NR	NR	1 PSA: 6% 2 PSAs: 8% 3 PSAs: 9% 4–6 PSAs: 10%
Radiation therapy	NR	NR	NR	1 PSA: 35% 2 PSAs: 40% 3 PSAs: 44% 4–6 PSAs: 47%
Hormone therapy	NR	NR	NR	1 PSA: 33% 2 PSAs: 27% 3 PSAs: 23% 4–6 PSAs: 20%
Outpatient visit	NR	NR	NR	NR
Palliative therapy	NR	NR	NR	NR
Repeat PSA	NR	NR	NR	NR

(continued)

Table App 4.1-1. Evidence Table for PSA Testing (continued)

	Stone et al., 2005	Tawfik, 2015	Walter et al., 2013	Zanwar et al., 2016
Study design	Cost effectiveness model with Monte Carlo simulation	Cost analysis	Longitudinal cohort study	Retrospective cohort study
Country	Australia	Canada	United States	United States
Key population of interest	Australian men	Asymptomatic men ≥ 40 years of age (Canada)	295,645 men ≥ 65 years of age (Veterans Affairs)	46,782 men ≥ 75 years of age with a PCP (Texas Medicare)
Key treatments of interest (n)	Status quo: guidelines for < 50 years, 50–69 years, ⩾ 70 years Scenario 1: PSA test ineffective in men > 70 years Scenario 2: PSA test effective in men > 70 years	Opportunistic screening men ≥ 40 years (current; OP1) Opportunistic screening men 50–74 years (OP2) Population-based screening men 50–74 years (Pop) No screening	PSA	PCP with low PSA testing rate vs. PCP with high PSA testing rate (PSA testing higher or lower than the mean testing rate)
Treatments not included	N/A	N/A	N/A	N/A
Quality rating	Low	Moderate	Moderate	High
Examines Cost				
Currency, cost year	AUD, 1996	CAD, 2012	NR	USD, 2010–2011
Cost follow-up time	NR	1 year	NR	2 years
Units	Cost of program	Cost to the government	NR	Annual per beneficiary payment associated with prostate cancer (denominator includes men not screened)
Costs included	Initial screening, diagnosis, treatment, follow-up, palliative/end-of-life care	Initial screening, diagnosis, staging, treatment	NR	Initial screening, diagnosis, staging, treatment
Mean per patient, ≥ 70 years (2018 USD)	NR	NR	NR	Low-rate PCP, unadjusted: $90.72 ($109) High-rate PCP, unadjusted: $63.51 ($76) Low-rate PCP, adjusted: $80.63 ($97) High-rate PCP, adjusted: $55.01 ($66)
Annual cost to a health care system, ≥ 75 years (2018 USD)	NR	NR	NR	NR
Mean per patient, 40–74 years (2018 USD)	NR	NR	NR	NR

(continued)

Table App 4.1-1. Evidence Table for PSA Testing (continued)

	Stone et al., 2005	Tawfik, 2015	Walter et al., 2013	Zanwar et al., 2016
Annual cost to a health care system, 50–74 years (2018 USD)	Net cost of Scenario 1: 6.6 million AUD ($7.8 million) Net cost of Scenario 2: 7.1 million AUD ($8.4 million) Gross cost of national program: 12.5 million AUD ($14.8 million)	OP1: 119,235,088 CAD ($103,804,634) OP2: 97,263,991 CAD ($84,676,861) Pop: 149,374,169 CAD ($130,043,355) No screening: 0 CAD ($0)	NR	NR
Incremental cost per patient, 40–74 years (2018 USD)	NR	NR	NR	NR
Examines Services				
Service follow-up time	NR	NR	5 years	2 years
Units	NR	NR	Number of events (Percentage of men screened)	Percentage of patients by PCP PSA ordering rate (denominator includes men not screened)
Prostate biopsy	NR	NR	8,313 *(2.8%)*	Low-rate PCP: 2.4% High-rate PCP: 2.1%
Ultrasound	NR	NR	NR	Low-rate PCP: 3.4% High-rate PCP: 2.9%
Imaging	NR	NR	NR	Low-rate PCP: 0.9% High-rate PCP: 0.7%
Any treatment	NR	NR	NR	Low-rate PCP: 1.2% High-rate PCP: 1.1%
Active surveillance/conservative management	NR	NR	NR	NR
Radical prostatectomy	NR	NR	648 *(0.2%)*	Low-rate PCP: 0.1% High-rate PCP: 0.1%
Radiation therapy	NR	NR	2,387 *(0.8%)*	Low-rate PCP: 0.7% High-rate PCP: 0.5%
Hormone therapy	NR	NR	1,249 *(0.4%)*	Low-rate PCP: 0.7% High-rate PCP: 0.7%
Outpatient visit	NR	NR	NR	Outpatient visit for prostate cancer: Low-rate PCP: 1.8% High-rate PCP: 1.5% Outpatient visit to urologist: Low-rate PCP: 35.4% High-rate PCP: 35.2%
Palliative therapy	NR	NR	NR	NR
Repeat PSA	NR	NR	14,654 *(5.0%)*	NR

Note: Italicized estimates were calculated for the literature review.

AUD: Australian dollars; CAD: carotid artery disease; N/A: not applicable; NR: not reported; PCP: primary care physician; PSA: prostate-specific antigen; USD: U.S. dollars

Appendix 4.2:
Evidence Table for Back Imaging for Low Back Pain

Table App 4.2-1. Evidence Table for Back Imaging for Low Back Pain

	Aaronson et al., 2017	Fried et al., 2018	Gilbert et al., 2004b
Study design	Observational	Observational	RCT
Country	United States	United States	UK
Key population of interest	Emergency department patients for LBP	Patients referred to lumbar spine MRI because of uncomplicated LBP or radiculopathy	New patients presenting with symptomatic lumbar spine disorders (LBP and/or sciatica)
Key treatments of interest (n)	Receipt of MRI (797) No MRI (5,297)	MRI for uncomplicated LBP or radiculopathy (188 no LBP statement, 187 LBP statement)	Early imaging (imaging performed as soon as practical; 393) Delayed/selective imaging (389)
Treatments not included	N/A	N/A	N/A
Quality rating	High	Low	High
Examines Cost			
Currency, cost year	NR	NR	USD, 2001–2002
Patients included	NR	NR	All patients by treatment
Cost follow-up time	NR	NR	2 years
Costs included	NR	NR	Initial imaging, hospital-based services, primary care services, other test and devices
Unadjusted mean per patient (2018 USD)	NR	NR	Early: $701 ($1,030) Delayed: $614 ($638) Difference was not significant
Adjusted mean per patient (2018 USD)	NR	NR	NR
Examines Services			
Patients included	All patients by treatment arm	All patients by treatment arm	All patients by treatment arm
Service follow-up time	NR	NR	2 years
Units	Percentage	Percentage	Percentage
Physical therapy (or referral)	NR	No statement: 48% Statement: 44%	Early: 63.1% Delayed: 59.9%
Primary care/outpatient visit	NR	NR	Primary care: Early: 83.5% Delayed: 67.9% Outpatient: Early: 70.7% Delayed: 70.1%

(continued)

Table App 4.2-1. Evidence Table for Back Imaging for Low Back Pain (continued)

	Aaronson et al., 2017	Fried et al., 2018	Gilbert et al., 2004b
Repeat/advance imaging	NR	Repeat imaging: No statement: 11% Statement: 4% Imaging-based intervention: No statement: 38% of patients referred to spine specialist Statement: 47% of patients referred to spine specialist	NR
Injection	NR	Lumbar epidural steroid injection: No statement: 25% of patients referred to spine specialist Statement: 37% of patients referred to spine specialist Lumbar nerve root block No statement: 16% of patients referred to spine specialist Statement: 20% of patients referred to spine specialist	Early: 17.8% Delayed: 17.5%
Synovial cyst rupture	NR	No statement: 1% of patients referred to spine specialist Statement: 2% of patients referred to spine specialist	NR
Surgery (or referral)	NR	No statement: 13% Statement: 9%	Early: 6.9% Delayed: 5.1%
Electromyography/nerve conduction velocity	NR	NR	NR
Narcotic prescription	NR	No statement: 28% Statement: 29%	NR
Referred to spine specialist	NR	No statement: 85% Statement: 73%	NR
Hospital admission	NR	NR	Early: 7.9% Delayed: 6.7%
Return to emergency department within 7 days	MRI: 4.3% No MRI: 4.6% Difference was not significant	NR	NR

(continued)

Table App 4.2-1. Evidence Table for Back Imaging for Low Back Pain (continued)

	Jensen et al., 2010	Miller et al., 2002	Shreibati & Baker, 2011
Study design	Observational	RCT	Observational
Country	Denmark	UK	United States
Key population of interest	Patients with back problems with or without radiculopathy (patients with LBP or leg pain with symptoms for 2–12 months)	Patients with lumbar spine x-ray for LBP (LBP for ≥ 6 weeks and < 6 months)	Medicare Fee-For-Service beneficiaries with an outpatient visit with LBP as primary diagnosis
Key treatments of interest (n)	Routine MRI (208) Needs-based MRI group (169)	Receipt of lumbar spine X-ray (210) Usual care (211)	Patient episodes (orthopedist = 78,914, primary care = 661,553)
Treatments not included	N/A	N/A	N/A
Quality rating	Moderate	High	High
Examines Cost			
Currency, cost year	Euro, 2007	UK pound, NR (used 2001)	USD, NR (used 2005)
Patients included	All patients by treatment	All patients by treatment	Patients by type of physician
Cost follow-up time	Up to 9 months	9 months	6 months
Costs included	Initial imaging, clinic visits	Initial imaging, direct medical costs (including inpatient visits, outpatient visits, equipment, travel, work-loss costs) and indirect costs (including extra expenses, welfare benefits, loss of earnings and productivity)	Initial imaging; inpatient, outpatient, and physician claims
Unadjusted mean per patient (2018 USD)	Routine: €956.83 ($1,399) Needs-based: €967.62 ($1,416)	Direct medical costs X-ray: £150 ($287) Usual care: £109 ($208) (p<0.001) Total costs (direct and indirect) X-ray: £590 ($1,127) Usual care: £507 ($969) (p<0.001)	NR
Adjusted mean per patient (2018 USD)	NR	NR	Primary care: $1,179 ($1,583) Orthopedist: $4,161 ($5,585) Costs of orthopedist patients receiving an MRI were significantly different than those not receiving an MRI

(continued)

Table App 4.2-1. Evidence Table for Back Imaging for Low Back Pain (continued)

	Jensen et al., 2010	Miller et al., 2002	Shreibati & Baker, 2011
Examines Services			
Patients included	All patients by treatment arm	NR	Patients by type of physician
Service follow-up time	Up to 9 months	NR	6 months
Units	Median or percentage	NR	Probability of event given the receipt of MRI (instrumental variable coefficient)
Physical therapy (or referral)	NR	NR	NR
Primary care/outpatient visit	Routine: 3 (median) Needs-based: 4 (median) Difference was significant (p=0.003)	NR	NR
Repeat/advance imaging	NR	NR	NR
Injection	NR	NR	NR
Synovial cyst rupture	NR	NR	NR
Low back/spinal surgery (or referral)	Routine: 8% Needs-based: 9% Difference was not significant (p=0.81)	NR	Primary care: 5.6% Orthopedist: 34.1% Significant for orthopedist visit
Electromyography/nerve conduction velocity	NR	NR	NR
Narcotic prescription	NR	NR	NR
Referred to spine specialist	NR	NR	NR
Hospital admission	NR	NR	NR
Return to emergency department within 7 days	NR	NR	NR

(continued)

Table App 4.2-1. Evidence Table for Back Imaging for Low Back Pain (continued)

	Webster et al., 2013	Webster et al., 2014	Webster & Cifuentes, 2010
Study design	Observational	Observational	Observational
Country	United States	United States	United States
Key population of interest	Workers with acute, disabling, work-related LBP	Workers with acute, disabling, work-related LBP	Workers with acute, disabling, work-related LBP
Key treatments of interest (n)	Early MRI (≤ 30 days post-onset) (non-specific LBP = 123, radiculopathy = 178) No MRI (non-specific LBP = 209, radiculopathy = 45)	Early MRI (≤ 30 days post-onset) (less-severe = 458; more-severe = 324) Timely MRI (41 to 180 days) (less-severe = 214, more-severe = 209) No MRI (less-severe = 1,546, more-severe = 271)	Early MRI (≤ 30 days post-onset) (709) No MRI (1,861)
Treatments not included	N/A	N/A	N/A
Quality rating	High	High	Moderate
Examines Cost			
Currency, cost year	USD, NR (used 2006)		USD, NR (used 2006)
Patients included	All patients by treatment	All patients by treatment	All patients by treatment
Cost follow-up time	up to 2 years	3, 6, 9, 12 months	up to 2 years
Costs included	Post-imaging (MRI) medical costs	Post-imaging (MRI) medical costs	Post-imaging (MRI) medical costs
Unadjusted mean per patient (2018 USD)	Early MRI: Radiculopathy: $22,339 ($29,313) Non-specific LBP: $17,028 ($22,344) No MRI: Radiculopathy: $4,100 ($5,380) Non-specific LBP: $2,306 ($3,026)	Figure only	Early: $21,921 ($28,765) No MRI: $2,779 ($3,647)
Adjusted mean per patient (2018 USD)	Early MRI: Radiculopathy: $20,989 ($27,542) Non-specific LBP: $17,803 ($23,361) No MRI: Radiculopathy: $7,173 ($9,412) Non-specific LBP: $4,855 ($6,371) Difference between early and no MRI was significant for radiculopathy patients (p=0.03) and non-specific LBP patients (p<0.0001)		
Examines Services			
Patients included	NR	All patients by treatment	All patients by treatment
Service follow-up time	NR	3 months, 6 months	up to 2 years
Units	NR	Percentage; RR at 6 months post-MRI (ref is no MRI, less-severe)*	Percentage
Physical therapy (or referral)	NR	NR	NR

(continued)

Table App 4.2-1. Evidence Table for Back Imaging for Low Back Pain (continued)

	Webster et al., 2013	Webster et al., 2014	Webster & Cifuentes, 2010
Primary care/outpatient visit	NR	NR	NR
Repeat/advance imaging	NR	No MRI, less-severe: ▪ 3 months: 0.6%, 6 months: 0.8%; RR ref. No MRI, more-severe: ▪ 3 months: 0.4%, 6 months: 0.4%; RR 0.48 Timely MRI, less-severe: ▪ 3 months: 7.0%, 6 months: 13.1%; RR 16.6 Timely MRI, more-severe: ▪ 3 months: 5.3%, 6 months: 10.0%; RR 13.04 Early MRI, less-severe: ▪ 3 months: 7.6%, 6 months: 14.4%; RR 17.81 Early MRI, more-severe: ▪ 3 months: 8.6%, 6 months: 17.0%; RR 20.53	NR
Injection	NR	No MRI, less-severe: ▪ 3 months: 1.0%, 6 months: 1.4%; RR ref. No MRI, more-severe: ▪ 3 months: 2.6%, 6 months: 3.7%; RR 2.70 Timely MRI, less-severe: ▪ 3 months: 25.2%, 6 months: 35.5%; RR 25.17 Timely MRI, more-severe: ▪ 3 months: 27.8%, 6 months: 36.8%; RR: 26.24 Early MRI, less-severe: ▪ 3 months: 33.0%, 6 months: 38.9%; RR 27.40 Early MRI, more-severe: ▪ 3 months: 36.7%, 6 months: 46.6%; RR 32.70	NR
Synovial cyst rupture	NR	NR	NR
Surgery (or referral)	NR	No MRI, less-severe: ▪ 3 months: 0.2%, 6 months: 0.5%; RR ref. No MRI, more-severe: ▪ 3 months: 0.7%, 6 months: 0.7%; RR 1.64 Timely MRI, less-severe: ▪ 3 months: 0.9%, 6 months: 2.8%; RR 6.48 Timely MRI, more-severe: ▪ 3 months: 5.3%, 6 months: 8.6%; RR 20.07 Early MRI, less-severe: ▪ 3 months: 8.1%, 6 months: 13.3%; RR 28.35 Early MRI, more-severe: ▪ 3 months: 10.2%, 6 months: 16.0%; RR 33.80	MRI: 22% No MRI: 0.8%

(continued)

Table App 4.2-1. Evidence Table for Back Imaging for Low Back Pain (continued)

	Webster et al., 2013	Webster et al., 2014	Webster & Cifuentes, 2010
Electromyography/nerve conduction velocity	NR	No MRI, less-severe: ▪ 3 months: 0.1%, 6 months: 0.3%; RR ref. No MRI, more-severe: ▪ 3 months: 1.5%, 6 months: 1.5%; RR 4.59 Timely MRI, less-severe: ▪ 3 months: 6.1%, 6 months: 11.2%; RR 35.13 Timely MRI, more-severe: ▪ 3 months: 9.6%, 6 months: 13.9%; RR 42.77 Early MRI, less-severe: ▪ 3 months: 8.1%, 6 months: 12.2%; RR 38.08 Early MRI, more-severe: ▪ 3 months: 13.9%, 6 months: 17.6%; RR 54.89	NR
Narcotic prescription	NR	NR	NR
Referred to spine specialist	NR	NR	NR
Hospital admission	NR	NR	NR
Return to emergency department within 7 days	NR	NR	NR

Italicized estimates were calculated for the literature review.

LBP: low-back pain; MRI: magnetic resonance imaging; N/A: not applicable; NR: not reported; RCT: randomized controlled trial; RR: relative risk; USD: U.S. dollars

Severity based on International Classification of Diseases, Ninth Revision (ICD-9) severity codes (herniated disc, sciatica, spinal stenosis, etc.)

* Relative risk models adjusted for age, sex, job tenure, and use of early opioids.

Appendix 4.3: Evidence Table for PCI in Stable Coronary Disease

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease

	Babapulle et al., 2004	Beresniak et al., 2015	Brophy et al., 2003
Study design	Economic evaluation/evidence synthesis	Economic evaluation/evidence synthesis	Economic evaluation/evidence synthesis
Country	N/A	France	N/A
Key population of interest	11 trials with 510 PCI patients (likely mix of stable and unstable angina)	PCI patients (all stable CD)	29 trials involving 9,918 CD patients (mix of stable and unstable angina)
Key treatments of interest (n)	DES (sirolimus and polymeric paclitaxel, NR), BMS (NR)	BMS (NR), DES (NR)	PCI w/o stent (PTCA, NR); Coronary stenting (NR)
Treatments not included	N/A	N/A	N/A
Quality rating	Moderate	Moderate	Moderate
Examines Cost			
Currency, cost year	NR	Euro, 2012	NR
Cost follow-up time	NR	2 years	NR
Units	NR	Per patient	NR
Costs included	NR	Initial procedure, hospitalization, follow-up costs (including medical transport and medication) Initial diagnostic costs not included	NR
PCI (USD)	NR	DES: €9,303 ($12,149) BMS: €8,926 ($11,656)	NR
MT	NR	NR	NR
Examines Services			
Service follow-up time	6–12 months	NR	Range of 4–16 months
Units	%	NR	Frequency (unadjusted) OR of the rate of service in coronary stenting and PCI
CABG	NR	NR	Freq for PCI: 2.8% Freq for coronary stenting: 3.0% OR: 1.01 (not significant)
Repeat PCI	NR	NR	Freq for PCI: 847/5190 (*16.3%*) Freq for coronary stenting: 509/4728 (*10.8%*) OR: 0.59 (significant)
Any revascularization (PCI or CABG)	NR	NR	NR
Target lesion revascularization (repeat PCI or CABG)*	DES: 4.2% BMS: 13.2% OR: 0.26	NR	NR
Target vessel revascularization	NR	NR	NR
Coronary angiograph	NR	NR	NR
Hospitalizations	NR	NR	NR
Rehospitalization	NR	NR	
Outpatient visits	NR	NR	NR
Coronary angiograms	NR	NR	NR
Cardiac catheterization only	NR	NR	NR
Angioplasties	NR	NR	NR

(continued)

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease (continued)

	Brunner-La Rocca et al., 2007	Caruba et al., 2014	Caruba et al., 2015
Study design	Economic evaluation/evidence synthesis	Economic evaluation/evidence synthesis	Economic evaluation/evidence synthesis
Country	Switzerland	N/A	France
Key population of interest	PCI patients (mix of stable and unstable angina; BASKET trial)	15 RCTs (stable or stabilized CD; symptoms > 48 hours)	Virtual PCI patients (all stable CAD, 50–70 years)
Key treatments of interest (n)	DES (545), BMS (281)	PCI w/o stent (PTCA, NR), BMS (NR), DES (NR)	DES (NR); BMS (NR); MT (NR)
Treatments not included (n)	N/A	CABG (NR)	CABG (NR)
Quality rating	Moderate	High	High
Examines Cost			
Currency, cost year	Euro, 2004	USD, 2008	Euro, 2012
Cost follow-up time	18 months	1 year (n = 9565) and 3 years (n = 6443)	1 year
Units	Median cost per patient, bootstrapped mean cost per patient	Mean cost per patient	Mean cost per patient
Costs included	Initial procedure, hospitalization, stents, follow-up costs	Initial procedure, hospitalization, outpatient care, outpatient medication	Initial procedure, ambulatory care, hospitalization for complications, medical transport, medications
PCI	DES: €9,810, €11,808 ($15,355, $18,482) BMS: €8,200, €10,450 ($12,835, $16,356)	DES: 1 year: $23,973 ($30,065) 3 year: $20,536 ($25,754) BMS: 1 year: $15,228 ($19,097) 3 year: $25,513 ($31,996) PCI w/o stenting: 1 year: $12,483 ($15,655) 3 year: $14,277 ($17,842)	DES: €6,623 ($8,649) BMS: €5,908 ($7,715)
MT	NR	1 year: $3,069 ($3,849) 3 year: $13,864 ($17,387)	€1,567 ($2,046)
Examines Services			
Service follow-up time	NR	NR	NR
Units	NR	NR	NR
CABG	NR	NR	NR
Repeat PCI	NR	NR	NR
Any revascularization (PCI or CABG)	NR	NR	NR
Target lesion revascularization (repeat PCI or CABG)*	NR	NR	NR
Target vessel revascularization	NR	NR	NR
Coronary angiograph	NR	NR	NR
Hospitalizations	NR	NR	
Outpatient visits	NR	NR	NR
Coronary angiograms	NR	NR	NR
Cardiac catheterization only	NR	NR	NR
Angioplasties	NR	NR	NR

(continued)

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease (continued)

	Clavijo et al., 2016	Cohen et al., 2012	Denvir et al., 2007
Study design	RCT	RCT	Observational
Country	United States	United States	Scotland
Key population of interest	PCI patients (stable or low-risk coronary syndrome)	CD patients (likely mix of stable and unstable CD; SYNTAX trial)	PCI patients (likely mix of stable and unstable CD)
Key treatments of interest (n)	Same-day (50) vs. delayed (50) hospital discharge after PCI	DES (896)	BMS (2,393; 1,047 in 1998 and 1,346 in 2002)
Treatments not included (n)	N/A	CABG (854)	N/A
Quality rating	Moderate	Moderate	Moderate
Examines Cost			
Currency, cost year	NR	USD, 2007	NR
Cost follow-up time	NR	1 year	NR
Units	NR	Mean cost per patient	NR
Costs included	NR	Initial procedure, hospitalization, follow-up costs (including medication)	NR
PCI	NR	DES: $35,991; $8,426 for follow-up only ($46,170; $10,809)	NR
MT	NR	NR	NR
Examines Services			
Service follow-up time	30 days, 1 year	1 year	1 year
Units	Percentage by hospitalization type, unadjusted	Percentage, unadjusted	Percentage, unadjusted
CABG	NR	NR	1998: 3.9% 2002: 2.6%
Repeat PCI	1 year: ▪ Same day: 4% ▪ Delayed: 4%	14%	1998: 11.7% 2002: 9.2%
Any revascularization (PCI or CABG)	NR	NR	1998: 15.1% 2002: 11.3%
Target lesion revascularization (repeat PCI or CABG)*	NR	NR	NR
Target vessel revascularization	NR	NR	1998: 8.4% 2002: 5.1%
Coronary angiograph	NR	NR	NR
Hospitalization	30 day: ▪ Same day: 6% ▪ Delayed: 2% 1 year: ▪ Same day: 12% ▪ Delayed: 8%	NR	NR
Outpatient visits	NR	NR	NR
Coronary angiograms	NR	NR	NR
Cardiac catheterization only	NR	NR	NR
Angioplasties	NR	NR	NR

(continued)

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease (continued)

	Favarato et al., 2003	Fearon et al., 2018	Fearon et al., 2013
Study design	RCT	RCT	RCT
Country	Brazil	Europe and North America	Europe and North American
Key population of interest	CD patients (all stable; MASS II trial)	CD patients (all stable; FAME 2 trial)	CD patients (all stable; FAME 2 trial)
Key treatments of interest (n)	PCI w/o stenting (PTCA, 205); MT (203)	Fractional flow reserve PCI + MT (447); MT (441)	Fractional flow reserve PCI + MT (447); MT (441)
Treatments not included (n)	CABG (203)	N/A	N/A
Quality rating	High	High	High
Examines Cost			
Currency, cost year	USD, NR (used 2000)	USD, 2012	USD, 2012
Cost follow-up time	1 year	3 years	1 year
Units	Mean cost per patient (actual unitary, event-free patient year follow-up, event-free and angina-free patient-year	Mean cost per patient	Mean cost per patient
Costs included	Initial procedure, hospitalization, medication, coronary angiograms	Initial procedure, hospitalization, follow-up costs (including medication)	Initial procedure, hospitalization, follow-up costs (including medication)
PCI	Actual unitary: $8,675.85 ($13,040) Event-free patient-year: $10,348.93 ($15,556) Event-free and angina-free patient-year: $13,099.31 ($19,690)	$16,792 ($19,235)	$12,646 ($14,486)
MT	Actual unitary: $2,285.47 ($3,435) Event-free patient-year: $2,453.50 ($3,688) Event-free and angina-free patient-year: $5006.32 ($7,525)	$16,737 ($19,172) (difference between PCI and MT p=0.094)	$9,763 ($11,184) (difference between PCI and MT p<0.001)
Examines Services			
Service follow-up time	1 year	3 years	1 year
Units	Percentage, unadjusted	Percentage, unadjusted	Count of events (from 447 patients)
CABG	NR	NR	NR
Repeat PCI	NR	NR	NR
Any revascularization (PCI or CABG)	PCI: 12.2% MT: 10.8%	PCI: 10.3% MT: 44.2% (p<0.001)	NR
Target lesion revascularization (repeat PCI or CABG)*	NR	NR	NR
Target vessel revascularization	NR	NR	NR
Coronary angiograph	PCI: 8.3% MT: 2.5%	NR	NR
Hospitalizations	NR	NR	PCI: 88 (19.7%) MT: 144 (32.7%)
Outpatient visits	NR	NR	PCI: 249 (55.7%) MT: 251 (56.9%)
Coronary angiograms	NR	NR	PCI: 27 (6.0%) MT: 39 (8.8%)
Cardiac catheterization only	NR	NR	NR
Angioplasties	PCI: 8.3% MT: 3.5%	NR	NR

(continued)

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease (continued)

	Gada et al., 2012	Gaster et al., 2003	Hambrecht et al., 2004
Study design	Economic evaluation/evidence synthesis	RCT	RCT
Country	NR	Denmark	Germany
Key population of interest	60-year-old CD patients (all stable angina)	Male PCI patients with stable angina pectoris	Male CD patients, ≤ 70 years of age (all stable CD)
Key treatments of interest (n)	Chronic total occlusion PCI (NR); MT (NR)	Intravascular ultrasound guided (IVUS) PCI (54); coronary angiography guided (conventional) PCI (54)	PCI (51)
Treatments not included (n)	N/A	N/A	Exercise training (51)
Quality rating	Moderate	Moderate	High
Examines Cost			
Currency, cost year	USD, 2012	Euro, 1997	CAD, NR (used 2001)
Cost follow-up time	5 years	Up to 2.5 years (median)	1 year
Units	Mean cost per patient	Total cost across study population (mean per patient)	Mean cost per patient
Costs included	Initial procedure, hospitalization, stents, follow-up costs	Initial procedure, hospitalization, follow-up costs; indirect costs associated with medical activities (including depreciation of equipment, administration)	Initial procedure, hospitalization, follow-up costs
PCI	$31,512 ($36,097)	Conventional PCI: *€5,809 ($10,654)* IVUS PCI: *€3,031 ($5,559)*	6,086 CAD ($6,797)
MT	$27,805 ($31,851)	NR	NR
Examines Services			
Service follow-up time	NR	Up to 2.5 years (median)	1 year
Units	NR	Percentage, unadjusted	Number of patients (Percentage of patients with event among PCI group [n=50])
CABG	NR	Conventional: 17% IVUS: 11%	1 (*2%*)
Repeat PCI	NR	Conventional: 61% IVUS: 31%	NR
Any revascularization (PCI or CABG)	NR	NR	NR
Target lesion revascularization (repeat PCI or CABG)*	NR	NR	2 (*4%*)
Target vessel revascularization	NR	NR	NR
Coronary angiograph	NR	NR	NR
Hospitalizations	NR	NR	7 (*14%*)
Outpatient visits	NR	NR	NR
Coronary angiograms	NR	NR	NR
Cardiac catheterization only	NR	NR	NR
Angioplasties	NR	NR	NR

(continued)

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease (continued)

	Hlatky et al., 2009	Hung et al., 2011	Kuukasjärvi et al., 2007
Study design	RCT	Observational	Economic evaluation/evidence synthesis
Country	United States, Canada, Brazil, Mexico, the Czech Republic, and Austria	Taiwan	N/A
Key population of interest	CD patients with Type 2 diabetes (all stable CD; BARI 2D trial)	PCI patients (all stable CD)	13 studies (mix of stable and unstable)
Key treatments of interest (n)	PCI (NR); MT (NR) (total n = 2,368)	DES (186); BMS (194)	DES (NR); BMS (NR)
Treatments not included (n)	CABG (NR)	N/A	N/A
Quality rating	High	Low	Low
Examines Cost			
Currency, cost year	USD, 2007	Taiwan dollar (NT), NR (used 2005)	Euro, 2006
Cost follow-up time	4 years	2 years	2 years
Units	Mean cost per patient	Mean cost per patient	Mean cost per patient
Costs included	Initial procedure, hospitalization, follow-up costs (including medication)	Initial procedure, hospitalization, follow-up costs (including medication)	Initial procedure, hospitalization, follow-up costs
PCI	$73,400 ($94,159)	DES: 352,495 NT ($15,613) BMS: 298,947 NT ($13,242)	DES: €4,578.70 ($6,849) BMS: €4,003.30 ($5,989)
MT		$67,800 ($86,975) (difference between PCI and MT p=0.02)	NR
Examines Services			
Service follow-up time	4 years	2 years	NR
Units	Mean rate over 4 years	Percentage, unadjusted	NR
CABG	NR	NR	NR
Repeat PCI	NR	NR	NR
Any revascularization (PCI or CABG)	NR	NR	NR
Target lesion revascularization (repeat PCI or CABG)*	NR	DES: ▪ 1 year: 5% ▪ 2 year: 8% BMS: ▪ 1 year: 16% ▪ 2 year: 19%	NR
Target vessel revascularization	NR	DES: ▪ 1 year: 8% ▪ 2 year: 12% BMS: ▪ 1 year: 19% ▪ 2 year: 22%	NR
Coronary angiograph	NR	NR	NR
Hospitalizations	PCI: 1.83 MT: 1.4 (difference between PCI and MT p<0.001)	NR	NR
Outpatient visits	PCI: 112 MT: 109 (difference between PCI and MT p=0.47)	NR	NR
Coronary angiograms	NR	NR	NR
Cardiac catheterization only	NR	NR	NR
Angioplasties	NR	NR	NR

(continued)

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease (continued)

	Lee et al., 2014	Mark et al., 2009	Polanczyk et al., 2007
Study design	Observational	RCT	Economic evaluation/evidence synthesis
Country	South Korea	United States and Canada	Brazil
Key population of interest	PCI patients (likely mix of stable and unstable)	CD patients (all stable CD who had MI)	PCI patients (mix of stable and unstable CD)
Key treatments of interest (n)	DES (34229); BMS (9445)	PCI (232); MT (474)	DES (sirolimus; NR); BMS (NR)
Treatments not included	N/A	N/A	BMS followed by DES
Quality rating	Low	High	Low
Examines Cost			
Currency, cost year	Korean won, NR (used 2007)	USD, 2006	Brazilian reals, 2003
Cost follow-up time	6 months, 1 year, 2 years, 3 years, 4 years	2 years	1 year, lifetime
Units	Mean cost per patient	Mean cost per patient	Mean cost per patient (private; public)
Costs included	Initial procedure, hospitalization, follow-up costs	Initial procedure, hospitalization, physician fees, follow-up outpatient costs	Initial procedure, follow-up costs; medical fees in baseline excluded (costs for private payers and public institutions)
PCI	DES: ▪ 6 months: 8,174,000 ($9,332) ▪ 1 year: 9,592,000 ($10,951) ▪ 2 years: 11,726,000 ($13,388) ▪ 3 years: 13,220,000 ($15,093) ▪ 4 years: 13,635,000 ($15,567) BMS: ▪ 6 months: 7,480,000 ($8,540) ▪ 1 year: 8,820,000 ($10,070) ▪ 2 years: 10,755,000 ($12,279) ▪ 3 years: 12,330,000 ($14,077) ▪ 4 years: 12,960,000 ($14,797)	*$27,788 ($36,463)*	DES: ▪ 1 year: 17,840; 12,708 ($6,765; $4,819) ▪ Lifetime: 85,803; 53,565 ($32,536; $20,312) ▪ BMS: ▪ 1 year: 14,024; 5,788 ($5,318; $2,195) ▪ Lifetime: 86,218; 47643 ($32,693; $18,066)
MT	NR	*$20,699 ($27,161)*	NR
Examines Services			
Service follow-up time	NR	2 years	NR
Units	NR	Percentage, unadjusted	NR
CABG	NR	PCI: 4.3% MT: 3.6%	NR
Repeat PCI	NR	PCI: 7.8% MT: 11.5%	NR
Any revascularization (PCI or CABG)	NR	NR	NR
Target lesion revascularization (repeat PCI or CABG)*	NR	NR	NR
Target vessel revascularization	NR	NR	NR
Coronary angiograph	NR	NR	NR
Hospitalizations	NR	NR	NR
Outpatient visits	NR	NR	NR
Coronary angiograms	NR	NR	NR
Cardiac catheterization only	NR	NR	NR
Angioplasties	NR	NR	NR

(continued)

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease (continued)

	Saadi et al., 2011	Serruys et al., 2001	Shrive et al., 2005
Study design	Economic evaluation/evidence synthesis	RCT	Economic evaluation/evidence synthesis
Country	United States	Netherlands	Canada
Key population of interest	PCI patients with diabetes (likely mix of stable and unstable CD)	CD patients (mix of stable and unstable CD)	PCI patients (likely mix of stable and unstable CD; APPROACH trial)
Key treatments of interest (n)	4 DES (sirolimus, paclitaxel, everolimus, zotarolimus) (200,000)	PCI (600)	BMS (sirolimus, 1,812)
Treatments not included	N/A	CABG (605)	N/A
Quality rating	Low	Moderate	Moderate
Examines Cost			
Currency, cost year	USD, NR (used 2011)	USD, NR (used 1998)	CAD, 202
Cost follow-up time	1 year	1 year	4 years
Units	Mean cost per patient	Mean cost per patient	Mean cost per patient
Costs included	Initial procedure, hospitalization, follow-up costs	Initial procedure, hospitalization, follow-up costs (including medication)	Initial procedure, hospitalization, follow-up costs (including medication)
PCI	Range from $18,125 to $19,060 ($21,238 to $22,333)	$10,665 ($16,774)	Event-free: 12,533 CAD ($13,684) CABG: 39,347 CAD ($42,959) Repeat PCI: 22,907 CAD ($25,010) Repeat catheterization: 19,929 CAD ($21,759)
MT	NR	NR	NR
Examines Services			
Service follow-up time	1 year	1 year	NR
Units	1-year risk	Percentage in PCI group, unadjusted	NR
CABG	NR	7%	NR
Repeat PCI	NR	16%	NR
Any revascularization (PCI or CABG)	NR	21%	NR
Target lesion revascularization (repeat PCI or CABG)*	Range from 3.2% to 7.9%	NR	NR
Target vessel revascularization	NR	NR	NR
Coronary angiograph	NR	NR	NR
Hospitalizations	NR	NR	NR
Outpatient visits	NR	NR	NR
Coronary angiograms	NR	NR	NR
Cardiac catheterization only	NR	NR	NR
Angioplasties	NR	NR	NR

(continued)

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease (continued)

	SoS Investigators, 2002	van Hout et al., 2005
Study design	RCT	RCT
Country	Europe and Canada	Netherlands
Key population of interest	CD patients (likely mix of stable and unstable CD; SOS trial)	PCI patients (mix of stable and unstable CD; RAVEL trial)
Key treatments of interest (n)	PCI (488)	BMS (118); DES (sirolimus, 120)
Treatments not included (n)	CABG (500)	N/A
Quality rating	Moderate	Moderate
Examines Cost		
Currency, cost year	NR	Euro, NR (2005 or earlier)
Cost follow-up time	NR	1 year
Units	NR	Mean cost per patient (w/ angiographic follow-up; w/o angiographic follow-up)
Costs included	NR	Initial procedure, hospitalization, follow-up costs (including medication)
PCI	NR	DES: €9,969; €8,065 ($15,254; $12,341) BMS: €9,915; €7,899 ($15,172; $12,087)
MT	NR	NR
Examines Services		
Service follow-up time	Up to 3 years	1 year
Units	Percentage of PCI patients, unadjusted	Percentage
CABG	9%	DES: ▪ w/ angiographic follow-up: 0.8% ▪ w/o angiographic follow-up: 0.8% BMS: ▪ w/ angiographic follow-up: 0.8% ▪ w/o angiographic follow-up: 0.3%
Repeat PCI	13%	DES: ▪ w/ angiographic follow-up: 0% ▪ w/o angiographic follow-up: 0% BMS: ▪ w/ angiographic follow-up: 22.9% ▪ w/o angiographic follow-up: 11.5%
Any revascularization (PCI or CABG)	21%	NR
Target lesion revascularization (repeat PCI or CABG)*	NR	DES: ▪ w/ angiographic follow-up: 0.8% ▪ w/o angiographic follow-up: 0.8% BMS: ▪ w/ angiographic follow-up: 23.6% ▪ w/o angiographic follow-up: 11.8%
Target vessel revascularization	NR	NR
Coronary angiograph	NR	DES: ▪ w/ angiographic follow-up: 8.3% ▪ w/o angiographic follow-up: 10.3% BMS: ▪ w/ angiographic follow-up: 10.2% ▪ w/o angiographic follow-up: 14.1%
Hospitalizations	NR	NR
Outpatient visits	NR	NR
Coronary angiograms	NR	NR
Cardiac catheterization only	NR	NR
Angioplasties	NR	NR

(continued)

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease (continued)

	Varani et al., 2010	Weintraub et al., 2008
Study design	Observational	RCT
Country	Italy	United States and Canada
Key population of interest	PCI patients (mix of stable and unstable CD)	CD patients (all stable CD; stenosis > 70% with MI or >80% with angina symptoms; COURAGE trial)
Key treatments of interest (n)	BMS (1,315); DES (657)	PCI (1,149); MT (1,138)
Treatments not included (n)	Mix (uses both DES and BMS in same patient; 926)	N/A
Quality rating	Low	High
Examines Cost		
Currency, cost year	Euro, NR (used 2008)	USD, 2004
Cost follow-up time	1 year, 2 years	Trial period (4.6-year median), lifetime
Units	Mean cost per patient	Mean cost per patient
Costs included	Initial procedure, hospitalization, follow-up costs (including medication)	Initial procedure, hospitalization, follow-up costs (including medication)
PCI	DES: ▪ 1 year: €13,623 ($19,476) ▪ 2 years: €14,337 ($20,497) BMS: ▪ 1 year: €10,740 ($15,355) ▪ 2 years: €11,103 ($15,874)	Trial period: $34,843 ($47,839) Lifetime: $99,820 ($137,051)
MT	NR	Trial period: $24,718 ($33,937) Lifetime: $90,370 ($124,076) (Reported difference in PCI and MT lifetime costs was $9451 (CI: $6729-$12,173))
Examines Services		
Service follow-up time	1 year, 2 years	Trial period (4.6 year median), lifetime
Units	2-year rate	Counts (percentages calculated)
CABG	NR	NR
Repeat PCI	NR	PCI: 260 (22.6%) MT: 255 (22.4%)
Any revascularization (PCI or CABG)	NR	NR
Target lesion revascularization (repeat PCI or CABG)*	NR	NR
Target vessel revascularization	BMS: 15.3%–15.9% DES: 11.4%–11.8%	NR
Coronary angiograph	NR	NR
Hospitalizations	NR	NR
Outpatient visits	NR	NR
Coronary angiograms	NR	NR
Cardiac catheterization only	NR	NR
Angioplasties	NR	NR

(continued)

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease (continued)

	Weintraub et al., 2004	Wijeysundera et al., 2013	Zeymer et al., 2003
Study design	RCT	Economic evaluation/evidence synthesis	RCT
Country	Europe and Canada	Canada	Germany
Key population of interest	CD patients (likely mix of stable and unstable CD; SOS trial)	CD patients (all stable CD)	CD patients (all stable survivors of acute myocardial infarction)
Key treatments of interest (n)	PCI (488)	BMS (NR); DES (NR); MT (NR)	PCI w/o stenting (149); MT (151)
Treatments not included (n)	CABG (500)	N/A	N/A
Quality rating	Moderate	Low	High
Examines Cost			
Currency, cost year	UK pound, 2000	CAD, 2008	NR
Cost follow-up time	1 year	Lifetime	NR
Units	Mean cost per patient	Mean cost per patient	NR
Costs included	Initial procedure, hospitalization, follow-up costs	Initial procedure, hospitalization, follow-up costs (including medication for 65+ year only)	NR
PCI	£6,296 ($12,303)	DES: 25,536 CAD ($24,339) BMS: 25,081 CAD ($23,905)	NR
MT	NR	$22,952 ($21,876)	NR
Examines Services			
Service follow-up time	1 year	Lifetime	1 year
Units	Counts (percentages calculated)	NR	Percentage, unadjusted
CABG	32 (7%)	NR	PCI: 0.7% MT: 2.7% (p=0.37)
Repeat PCI	56 (11.5%)	NR	PCI: 5.4% MT: 13.2% (p=0.03)
Any revascularization (PCI or CABG)	NR	NR	NR
Target lesion revascularization (repeat PCI or CABG)*	NR	NR	NR
Target vessel revascularization	NR	NR	NR
Coronary angiograph	NR	NR	NR
Hospitalizations	NR	NR	
Outpatient visits	NR	NR	NR
Coronary angiograms	NR	NR	NR
Cardiac catheterization only	62 (12.7%)	NR	NR
Angioplasties	NR	NR	NR

(continued)

Table App 4.3-1. Evidence Table for PCI in Stable Coronary Disease (continued)

	Zhang et al., 2011	Zhang et al., 2015	Zhang et al., 2005
Study design	RCT	Economic evaluation/evidence synthesis	RCT
Country	United States and Canada	United States	Europe and Canada
Key population of interest	CD patients (all stable CD; stenosis >70% with MI or >80% with angina symptoms; COURAGE trial)	CD patients (mix of stable and unstable CD; ASCERT trial)	CD patients (likely mix of stable and unstable CD; SOS trial)
Key treatments of interest (n)	PCI (1149); MT (1138)	PCI (103,549)	PCI (488)
Treatments not included (n)	N/A	CABG (86,244)	CABG (500)
Quality rating	High	Low	Moderate
Examines Cost			
Currency, cost year	USD, 2004	USD, NR (used 2015)	UK pound, 2000
Cost follow-up time	3 years	Up to 4 years, lifetime	1 year
Units	Median cost per patient, cost depending on physical limitations (low vs. high), angina frequencies and quality of life within range	Propensity score bin bootstrapping adjusted mean cost per patient	Mean cost per patient
Costs included	Initial procedure, hospitalization, follow-up costs	Initial procedure, hospitalization, follow-up costs	Initial procedure, hospitalization, follow-up costs
PCI	Ranges from $30,004 to $43,232 ($41,194 to $59,357)	4 years: $55,640 ($59,551) Lifetime: $173,358 ($185,543)	ACS: £8014 ($15,660) Non-ACS: £5760 ($11,255)
MT	Ranges from $19,585 to $33,840 ($26,890 to $46,462)	NR	NR
Examines Services			
Service follow-up time	NR	NR	1 year
Units	NR	NR	Percentage, unadjusted
CABG	NR	NR	ACS: 5.2% Non-ACS: 7.0%
Repeat PCI	NR	NR	ACS: 10.3% Non-ACS: 11.0%
Any revascularization (PCI or CABG)	NR	NR	ACS: 15.5% Non-ACS: 18.0%
Target lesion revascularization (repeat PCI or CABG)*	NR	NR	NR
Target vessel revascularization	NR	NR	NR
Coronary angiograph	NR	NR	NR
Hospitalization	NR	NR	NR
Outpatient visits	NR	NR	NR
Coronary angiograms	NR	NR	NR
Cardiac catheterization only	NR	NR	NR
Angioplasties	NR	NR	NR

Note: Italicized estimates were calculated for the literature review.

ACS: acute coronary syndrome; BMS: bare metal stent; CABG: coronary artery bypass surgery; CAD: carotid artery disease; CD: coronary disease; DES: drug-eluting stent; MI: myocardial infarction; MT: medical therapy; N/A: not applicable; NR: not reported; OR: odds ratio; PCI: percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty; RCT: randomized controlled trial; USD: U.S. dollars

*Revascularization by repeat PCI or CABG of the index lesion, including for stent thrombosis.

Appendix 4.4: Evidence Table for Stress Testing for Stable Coronary Disease

Table App 4.4-1. Evidence Table for Stress Testing for Stable Coronary Disease

	Marwick et al., 2003	Thom et al., 2014
Study design	Observational	RCT
Country	United States	UK
Key population of interest	Patients with known or suspected CD	Patients with known or suspected CD
Key treatments of interest (n)	Exercise echo (3,860; 25% with known CD) Exercise ECG (3,796; 21% with known CD)	SPECT (224) Cardiac MRI (226) Echo (226)
Treatments not included	N/A	Coronary angiography
Quality rating	Moderate	Low
Examines Cost		
Currency	USD	UK pound
Cost year	2000	2005
Patients included	All patients by treatment group	All patients by treatment group
Cost follow-up time	3 years	3 years
Costs included	Initial service and follow-up costs (including societal economic costs); costs are risk-adjusted	Initial service and follow-up costs
Total observed, reported (2018 USD)	Echo: $17,419,657 ($26,184,050) ECG: $16,842,611 ($25,316,673)	NR
Total observed mean per patient, reported (2018 USD)	Echo: *$4,513 ($6,783)* ECG: *$4,437 ($6,669)*	SPECT: £4,644 ($8,103) Cardiac MRI: £4947 ($8,632) Echo: £5,530 ($9,649)
Lifetime, reported (2018 USD)	Echo: $373,477,439 ($561,386,012) ECG: $370,874,298 ($557,473,146)	NR
Lifetime mean per patient, reported (2018 USD)	Echo: *$96,756 ($145,437)* ECG: *$97,701 ($146,858)*	N/A
Examines Services		
Patients included	Patients with known CD by treatment group and post-test risk	Patients by treatment group
Service follow-up time	5 years	3 years
Units	Risk-adjusted rate*	Count *(frequency)*
Catherization	Echo: Low post-test risk: 7% Intermediate post-test risk: 17% High post-test risk: 45% ECG: Low post-test risk: 59% Intermediate post-test risk: 23% High post-test risk: 37%	NR
Revascularization	Echo: Low post-test risk: 12% Intermediate post-test risk: 25% High post-test risk: 41% ECG: Low post-test risk: 35% Intermediate post-test risk: 24% High post-test risk: 30%	NR

(continued)

Table App 4.4-1. Evidence Table for Stress Testing for Stable Coronary Disease (continued)

	Marwick et al., 2003	Thom et al., 2014
Percutaneous coronary intervention	Echo: Low post-test risk: 9% Intermediate post-test risk: 18% High post-test risk: 30% ECG: Low post-test risk: 31% Intermediate post-test risk: 18% High post-test risk: 18%	SPECT: 46 *(21%)* Cardiac MRI: 60 *(27%)* Echo: 62 *(27%)*
CABG	Echo: Low post-test risk: 3% Intermediate post-test risk: 7% High post-test risk: 11% ECG: Low post-test risk: 4% Intermediate post-test risk: 6% High post-test risk: 12%	SPECT: 33 *(15%)* Cardiac MRI: 28 *(12%)* Echo: 34 *(15%)*
Other hospital admission	NR	SPECT: 29 *(13%)* Cardiac MRI: 28 *(13%)* Echo: 53 *(23%)*
Angiography	NR	SPECT: 183 *(82%)* Cardiac MRI: 175 *(77%)* Echo: 181 *(80%)*
SPECT	NR	SPECT: 3 *(1%)* Cardiac MRI: 3 *(1%)* Echo: 6 *(3%)*
Cardiac MRI	NR	SPECT: 5 *(2%)* Cardiac MRI: 12 *(5%)* Echo: 5 *(2%)*
Echocardiography	NR	SPECT: 17 *(8%)* Cardiac MRI: 24 *(11%)* Echo: 18 *(8%)*
Positron emission tomography (PET) scan	NR	SPECT: 3 *(1%)* Cardiac MRI: 0 *(0%)* Echo: 1 *(0%)*
Preadmission clinic	NR	SPECT: 21 *(9%)* Cardiac MRI: 27 *(12%)* Echo: 24 *(11%)*
Follow-up clinic	NR	SPECT: 22 *(10%)* Cardiac MRI: 31 *(14%)* Echo: 21 *(9%)*
Outpatient visits	NR	SPECT: 270 *(121%)* Cardiac MRI: 300 *(133%)* Echo: 284 *(126%)*

Italicized estimates were calculated for the literature review.

CABG: coronary artery bypass surgery; CD: coronary disease; ECG: electrocardiogram; Echo: echocardiography; MRI: magnetic resonance imaging; N/A: not applicable; NR: not reported; RCT: randomized controlled trial; SPECT: single photon emission CT; USD: U.S. dollars

* The risk-adjusted model included cardiac risk factors, symptoms, prior myocardial infarction, and a propensity score

Appendix 4.5: Evidence Table for CEA in Asymptomatic Patients

Table App 4.5-1. Evidence Table for CEA in Asymptomatic Patients

	Henriksson et al., 2008	Kilaru et al., 2003
Study design	Economic Evaluation/Evidence Synthesis	Economic Evaluation/Evidence Synthesis
Country	Sweden	United States
Key population of interest	Patients with severe carotid stenosis (ACST trial; ≥60% carotid artery diameter reduction, all asymptomatic)	Patients with carotid stenoses greater than 70% (symptomatic) or 80% (asymptomatic)
Key treatments of interest (n)	CEA (NR)	CEA (447)
Treatments not included	N/A	N/A
Quality rating	Moderate	Low
Examines Cost		
Currency, cost year	Euro, 2006	USD, 1997
Patients included	Patients with CEA	Patients with CEA
Cost follow-up time	5 years	lifetime
Costs included	Initial service, costs with and without stroke	Initial service, costs of stroke and MI
Total mean per patient (2018 USD)	NR	NR
Total mean per patient, 60–69 years (2018 USD)	Men: €18,733 ($28,023) Women: €19,238 ($28,778)	NR
Total mean per patient, 70–79 years (2018 USD)	Men: €14,582 ($21,813) Women: €15,378 ($23,003)	$28,772 ($46,288)
Total mean per patient, 80 years (2018 USD)	NR	NR
Examines Services		
Patients included	NR	NR
Service follow-up time	NR	NR
Units	NR	NR
Rehospitalization	NR	NR
Reintervention	NR	NR

(continued)

Table App 4.5-1. Evidence Table for CEA in Asymptomatic Patients (continued)

	Pandya et al., 2015
Study design	Economic Evaluation/Evidence Synthesis
Country	United States
Key population of interest	Asymptomatic patients with carotid artery stenosis and 70–89% carotid artery luminal narrowing at clinical presentation
Key treatments of interest (n)	CEA (NR), MT (NR)
Treatments not included	Cerebrovascular reserved-based decision making
Quality rating	High
Examines Cost	
Currency, cost year	USD, 2011
Patients included	Patients with CEA, by percent stenosis
Cost follow-up time	Lifetime
Costs included	Initial service, costs of stroke, MI, doppler ultrasound
Total mean per patient (2018 USD)	NR
Total mean per patient, 60–69 years (2018 USD)	CEA 70–89% stenosis: $23,643 ($27,704) 50–69% stenosis: $23,643 ($27,704) MT 70–89% stenosis: $19,249 ($22,555) 50–69% stenosis: $15,734 ($18,436)
Total mean per patient, 70–79 years (2018 USD)	CEA 70–89% stenosis: $20,950 ($24,548) 50–69% stenosis: $20,950 ($24,548) MT 70–89% stenosis: $14,597 ($17,104) 50–69% stenosis: $11,688 ($13,695)
Total mean per patient, 80 years (2018 USD)	CEA 70–89% stenosis: $18,592 ($21,785) 50–69% stenosis: $18,592 ($21,785) MT 70–89% stenosis: $9,947 ($11,655) 50–69% stenosis: $7,798 ($9,137)
Examines Services	
Patients included	NR
Service follow-up time	NR
Units	NR
Rehospitalization	NR
Reintervention	NR

(continued)

Table App 4.5-1. Evidence Table for CEA in Asymptomatic Patients (continued)

	Thapar et al., 2013	Wallaert et al., 2016
Study design	Economic Evaluation/Evidence Synthesis	Observational
Country	UK	United States
Key population of interest	Patients with severe carotid stenosis (ACST trial; ≥60% carotid artery diameter reduction, all asymptomatic)	Asymptomatic CEA patients without prior stroke or transient ischemic attack (90% with <80% stenosis)
Key treatments of interest (n)	CEA (NR); MT (NR)	CEA (3,097)
Treatments not included	N/A	N/A
Quality rating	High	Moderate
Examines Cost		
Currency, cost year	UK pound, 2010	USD, 2011
Patients included	Patients with CEA	Patients with CEA, by risk of death at 2 years
Cost follow-up time	Lifetime	2 years
Costs included	Initial service, costs with and without stroke and social services	Initial service, readmission, reintervention, subsequent admission for stroke
Total mean per patient (2018 USD)	NR	Low risk of death: $8,801 ($10,313) Medium risk of death: $10,025 ($11,747) High risk of death: $17,815 ($20,875)
Total mean per patient, 60–69 years (2018 USD)	CEA: £8,496 ($10,183) MT: £7,855 ($9,415)	NR
Total mean per patient, 70–79 years (2018 USD)	NR	NR
Total mean per patient, 80 years (2018 USD)	NR	NR
Examines Services		
Patients included	NR	Patients with CEA
Service follow-up time	NR	2 years
Units	NR	Frequency by risk of death at 2 years
Rehospitalization	NR	Low risk of death: 10.2% Medium risk of death: 14.4% High risk of death: 12.8%
Reintervention	NR	Low risk of death: 5.8% Medium risk of death: 7.0% High risk of death: 7.7%

Italicized estimates were calculated for the literature review.

ACST: Asymptomatic Carotid Surgery Trial; CEA: carotid endarterectomy; MI: myocardial infarction; N/A: not applicable; NR: not reported; MT: medical therapy; USD: U.S. dollars