Research Prioritization Topic Briefs

PCORI Scientific Program Area:
Assessment of Prevention, Diagnosis and Treatment Options

The Johns Hopkins Evidence Based Practice Center

September 12, 2014

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Contents

Topic 1:

What is the comparative effectiveness of regional plus general anesthesia versus general anesthesia alone in orthopedic procedures in terms of short- and long-term patient-centered outcomes?

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION • This question is particularly relevant to orthopedic surgery. This is surgery on the musculoskeletal system, from minor outpatient procedures to complex operations such as spinal fusion and total knee or hip replacement. • Anesthetic techniques for orthopedic surgery include two major categories: general and regional anesthesia. **General anesthesia** refers to the administration of one or more general anesthetic agents through inhalation or intravenous injection to induce sleep (unconsciousness), amnesia (loss of memory), analgesia (loss of response to pain), relaxation of skeletal muscles, and loss of control of reflexes of the autonomic nervous system during the surgery. **Regional anesthesia** induces analgesia in parts of the body with use of anesthetics injected into the tissue itself, or into a nearby vein, or around a nerve that supplies sensation to the area. Regional anesthesia can be further divided into central and peripheral techniques: the central techniques include neuraxial blockade such as epidural anesthesia, or spinal anesthesia; the peripheral techniques include plexus blocks and single nerve blocks. Regional anesthesia can be performed as a single injection or with a catheter through which anesthetic is given over a prolonged period. • For this report, we focus on shoulder, hip, and knee surgeries in which both general and regional anesthesia are feasible intra-operatively.
Relevance to patient-centered outcomes	PATIENT-CENTERED OUTCOMES • Mortality • Cardiovascular complications • Deep venous thrombosis and pulmonary embolism • Intra-operative blood loss and need for transfusions • Duration of surgery • Block failure

	• Nerve damage • Anxiety • Pain (pre- intra-, and post-operative pain, both short- and long-term) • Nausea and vomiting • Pruritus • Urinary retention • Opioid and other pain medication use intra- and post-operatively • Postoperative cognitive function (e.g., delirium) • Functional status • Ability to participate in rehabilitation and time to start of rehabilitation • Length of hospital stay • Quality of life • Health services utilization • Other complications
Burden on Society	
Recent prevalence in populations and subpopulations	PREVALENCE Knee, hip, and shoulder surgeries are performed frequently in the U.S. • Of the 51.4 million inpatient procedures performed in the U.S in 2010, 719,000 were total knee replacements, 332,000 were total hip replacements.[1] There were 42,000 shoulder replacements performed in 2012.[2] More than half of the surgeries were performed in patients older than 55 years old.[3] • In addition to total knee, hip, and shoulder replacements, there were also 648,000 arthroscopies of the knee,[3] and 90,000 arthroscopies of the hip in 2010.[4] Over 600,000 surgeries are performed for rotator cuff injuries, which varies from arthroscopic repair (partial or complete) or reconstruction to arthroplasty.[5]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	The effects of regional and general anesthesia for any surgical procedures on patients' quality of life and other outcomes are summarized below. • An estimated 0.724 anesthesia complications occurred per 1,000 surgical discharges in the US in 2000.[6] • The expected mortality rate associated with general anesthesia is 1 in 300,000. Other severe complications include delirium, stroke, heart attack, and brain damage. Less severe complications include nausea and vomiting (up to 30% of patients), damage to teeth, sore throat and laryngeal damage, headache, dizziness, vision problems, and drowsiness.[7]

	• Regional anesthesia can be used alone or on conjunction with general anesthesia. When used alone, regional anesthesia avoids the need of intubation and airway management, and maybe an appropriate choice for some patients. Most complications of regional anesthesia are relatively minor such as headache, nausea, vomiting, hypotension, pruritus, and urinary retention. More severe complications include death, direct nerve damage, spinal hematoma, spinal infection, total spinal block, and technical failure.[6] • 40% to 70% of patients have severe postoperative pain. Postoperative pain negatively affects patients' quality of life, productivity, functional capacity,[8,9] lengthens hospital stay,[9] and increases use of health care services.[8] Readmissions due to pain after surgery are common. Regional anesthesia contributes to post-operative analgesia to provide pain control, minimize opioid use, reduce muscle spasm, and allow earlier mobilization, and co-operation with rehabilitation. • When regional anesthesia is used with general anesthesia, general anesthesia can often be lighter, lessening side effects from the anesthetics. [8,10] It may also reduce postoperative pain allowing faster discharges, fewer readmissions, and reduced use of opioids in the postoperative periods, particularly relevant for older patients.[11,12] The addition of regional blocks to general anesthesia has been accepted as practice in children and uncooperative patients.[11]
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• Knee, hip, and shoulder surgeries are among the most common orthopedic surgeries. With the aging population, the number of surgeries and anesthetic procedures performed is increasing accordingly.[13,14] • If there are proven differences in length of stay, operative time, readmissions, complications and need for more post-discharge care, the choice of anesthetic approach impacts society because of the high volume of these cases.[6,8]
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the	Several recent systematic reviews have examined the comparative effectiveness and safety of general, regional, or combined general and regional anesthesia for hip and knee surgeries. These systematic reviews reached inconsistent and sometimes conflicting conclusions. Discrepant findings may be attributable to different objectives and research questions, diverse patient populations and surgeries examined, variable inclusion criteria, and different search periods in identifying eligible studies. In addition,

available management options?	the trials included in these systematic reviews were generally small and of poor methodological quality. Consequently, no firm conclusions could be drawn about the relative benefits and harms of these management options. We provide a brief review of the findings from these systematic reviews below, by publication year. • Rodgers and colleagues examined neuraxial blockade for all types of surgeries in 2000. They found that neuraxial blockade reduced the odds of mortality, deep vein thrombosis, pulmonary embolism, transfusion requirements, pneumonia, and respiratory depression, compared to general anesthesia. The mortality benefit was consistent in the orthopedic subgroup. However, the comparison interventions they examined included a mix of procedures and postoperative analgesia, thus limiting the applicability of findings to our research question.[15] • Parker and colleagues compared regional and general anesthesia for hip fracture surgery in 2004. They concluded that overall there was insufficient evidence to rule out clinically important differences between regional and general anesthesia. Regional anesthesia may reduce acute postoperative confusion but no firm conclusion can be drawn for mortality or other outcomes. [16] • Mauermann and colleagues compared neuraxial block and general anesthesia for elective total hip replacement in 2006. They found that neuraxial block decreased the odds of deep venous thrombosis or pulmonary embolism, operating time, intraoperative blood loss, blood transfusion.[17] • Hu and colleagues compared regional and general anesthesia for total hip and knee replacement in 2009. They concluded that regional anesthesia reduces the operating time, the need for transfusion, deep-vein thrombosis, and pulmonary embolism.[18] • Macfarlane and colleagues compared regional anesthesia to general anesthesia for total hip and total knee arthroplasty in 2009. For both types of procedures, they found insufficient evidence from randomized controlled trials to know if anesthetic technique influenced mortality, cardiovascular morbidity, or the incidence of deep venous thrombosis or pulmonary embolism when using thromboprophylaxis. Regional anesthesia seemed to be associated with less blood loss for total hip arthroplasty but not for total knee arthroplasty. They did not find a difference in duration of surgery for total hip arthroplasty. For total knee arthroplasty, regional anesthesia and/or analgesia seemed to have better postoperative pain control, reduced morphine consumption and opioid-related adverse effects, reduced length of stay, and facilitated rehabilitation.[19,20]

	• Abou-Setta and colleagues compared spinal anesthesia to general anesthesia for hip fracture surgery in 2011. They identified a few small trials and concluded that there is insufficient evidence to suggest one approach is better than the other for acute pain management, mortality, or delirium; although the length of hospital stay seemed to be shorter for patients receiving general anesthesia. They did not find significant differences in the occurrence of hypotension, myocardial infarction, or ST segment depression.[21]
What could new research contribute to achieving better patient-centered outcomes?	New research could:[22-26] • Evaluate current anesthetic approaches on perioperative pain control and other patient-centered outcomes as described above. • Evaluate the combination of different modalities of anesthesia/analgesia (multimodal approach) to improve pain control; develop strategies to implement effective multimodal approaches in practice. • Examine the effectiveness of a perioperative home model for managing patients undergoing orthopedic surgeries. The perioperative home model aims to reduce variability in perioperative care through continuity of care rather than discrete preoperative, intraoperative, postoperative, and post-discharge episodes. One team, led by anesthesiologists, manages all aspects of care on this continuum. • Evaluate patient preferences regarding anesthesia techniques.
Have recent innovations made research on this topic especially compelling?	• Ongoing studies have focused on ○ the comparison of regional, general, or combined anesthesia for pain management and other outcomes such as delirium; ○ comparison of different anesthetic techniques, such as femoral and sciatic nerve blocks versus periarticular infusions, ultrasound guided blockade, different anesthetics and doses of anesthetics; ○ multimodal approach for perioperative pain management.
How widely does care now vary?	• There is no widely-accepted practice guideline for management of anesthesia for hip, knee, and shoulder surgeries. One practice guideline supports the use of neuraxial anesthesia to limit blood loss.[27] • Current practice varies widely. In a recent study of nearly 400,000 patients undergoing total hip or knee arthroplasty, using administrative data from approximately 400 U.S. hospitals, Memtsoudis and colleagues found that 11% of the procedures are performed under neuraxial anesthesia, 14% under combined neuraxial-general anesthesia, and 75% under general anesthesia.[22]

	• Practice variation is wider for knee surgery. A report by Pugely and colleagues, using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database found that 57% of primary total knee arthroplasties performed between 2005 and 2010 were done under general anesthesia, while 43% were done under spinal anesthesia,[28] while Stundner and colleagues found that 80% of bilateral total knee arthroplasties performed between 2006 and 2010 were done under general anesthesia, while 7% were done under neuraxial anesthesia and 13% used combined general-neuraxial anesthesia.[29] • Practice guidelines call for the use of general anesthesia for shoulder surgeries, however, a report by Memtsoudis and colleagues, using data from the National Survey of Ambulatory Surgery, found that from 1996 to 2006, the use of regional blocks for shoulder arthroplasties increased from 11.5% to 24%. [30]
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	• We searched *clinicaltrials.gov* on July 16, 2014 and identified 69 interventional studies examining regional or general anesthesia for hip, knee, and shoulder surgeries. • About half of the interventional studies (50%; 34/69) are registered as "completed", followed by 30% (21/69) records registered as "recruiting". • More than half of the interventional studies (54%; 37/69) examined "drug", followed by "procedure" (38%; 26/69), "device" (4%; 3/69), and "other" (4%; 3/69). • 17% (12/69) and 91% (63/69) of the interventional studies received funding from industry and "other", respectively (a study could receive funding from more than one sources). • 67% (46/69) and 12% (8/69) of the interventional studies included pain and quality of life as outcomes, respectively.
How likely it is that new CER on this topic would provide better information to guide clinical decision making?	Findings from ongoing studies will provide valuable information to guide clinical decision-making given the observed practice variation and the discrepant findings from existing research syntheses. New CER on this topic will provide better information to guide clinical decision-making given the observed practice variation and the discrepant findings from existing research syntheses.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that	FACILITATORS: • Involvement of guideline developers and other relevant stakeholders in preparing new CER can facilitate uptake.

would affect the implementation of new findings in practice?	• The need for fairly comparable operating room resources, despite the need for additional skills, will facilitate uptake • No universal guidelines presently support one over the other; this will be permissive and allow the incorporation of new CER into practice • A high percentage of the hip, knee and shoulder surgeries are performed in patients with degenerative diseases such as arthritis. As the population ages, the incidence of these surgeries will increase, with ever increasing interest in implementing the best and most efficient surgical and anesthetic techniques. • Knee and shoulder injuries are frequent in active individuals. The best pain control is demanded to allow a faster recovery, faster rehabilitation and reintegration to daily life (school, work and sports) BARRIERS: • Performing regional anesthesia in conjunction to general anesthesia requires additional skills and efforts both intra- and post-operatively. • The utilization of combined techniques may also be limited by physician and patient preference, level of expertise and institutional directives.
How likely is it that the results of new research on this topic would be implemented in practice right away?	• There may be training needs that would delay the implementation of results immediately. Sites where regional anesthesia is not the norm for orthopedic procedures may need time for establishing procedures and protocols, and training all involved staff. Patient teaching materials may need to be developed to assure that patients can make an informed decision about their anesthesia options.
Would new information from CER on this topic remain current for several years?	• New information from a CER is likely to remain current for several years given the observed lack of uniformity in the current practices in this field and the relevancy for patient centered outcomes. Pain management after orthopedic surgeries is and will remain fundamental for years to come. • Testing management options (anesthetic techniques alone or combined) with long-term outcomes and patient-centered outcomes can be challenging.

References for Topic 1; What is the comparative effectiveness of regional plus general anesthesia versus general anesthesia alone in orthopedic procedures in terms of short- and long-term patient-centered outcomes?

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Topic 2:

What is the comparative effectiveness of home exercise alone versus formal physical therapy alone versus combination of home exercise and formal physical therapy for tendinopathies and lateral ankle sprain in terms of short- and long-term patient-centered outcomes?

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION TENDINOPATHIES[1-4] Tendinopathy is a syndrome characterized by pain, focal tenderness and decreased strength within or around a tendon. Tendinopathy often results from overuse or overload of the tendon. Recent research has shown that the lesion is not caused by inflammation, as previously believed, but by degeneration and attempted regeneration resulting in neovascularization. Three out of four tendinopathies occur below the knee. The most common lesions seen are: • Patellar tendinopathy • Lateral and medial epicondylitis • Achilles tendon injuries • Rotator cuff tendinopathy ANKLE SPRAINS[5] Most ankle sprains result from damage to the lateral ligament structures (*i.e.,* anterior talofibular, calcaneofibular, and posterior talofibular ligaments) after a stressful event to the foot while landing from jumps, trauma on the heel while running or stress on the foot when placed in difficult positions (*i.e.,* inversion or supination). Severity of the ankle sprain ranges from mild to severe depending on the structural damage. Patients with a history of ankle sprain have a high risk of recurrence. In contrast with tendinopathies, the main cause of pain is inflammation and swelling. Common treatments for tendinopathies and ankle sprains include rest, medications for inflammation and pain, rehabilitation and when rehabilitation is not successful, surgery. Other treatments include cryotherapy, laser therapy, ultrasound therapy, extracorporeal shock-wave therapy, sound-assisted soft tissue massage, and augmented soft tissue mobilization. Combinations of therapies are also recommended.[1,2,6]

	Rehabilitation exercises may be prescribed for performance at home or in a formal physical therapy setting. Rehabilitation activities aim to restore activity and function. The comparative effectiveness of home exercise versus formal physical therapy is unknown.

Relevance to patient-centered outcomes	SYMPTOMS
	The symptoms of tendinopathies and ankle sprain include pain, discomfort and limited ability to use the affected site. Ankle sprains also result in swelling.
	
	PATIENT-CENTERED OUTCOMES[1-3]
	• Pain and pain management
	• Impact on activities of daily life
	• Time to return to exercise or sporting activities[7]
	• Inability to work
	• Recurrence of ankle sprain
	• Diminished quality of life from pain or limited mobility
	• Reduced physical activity levels across the lifespan
	• Propensity to develop chronic conditions: [5,8,9]
	  ○ Chronic ankle instability
	  ○ Increased risk for ankle osteoarthritis
	• Chronic pain

Burden on Society	
Recent prevalence in populations and subpopulations	PREVALENCE TENDINOPATHIES Overuse injuries are common among physically active individuals. Together they account for 7% of all physician visits in the U.S. • Patellar tendinopathy. This tendinopathy is frequent in runners. Up to 70% of runners will develop a lesion. Up to 15% of runners with a lesion will develop iliotibial syndrome (ITB) which is caused by the continued flexion of the knee. Individuals who perform jumping activities or activities that mimic the motion of jumping, like bending, are also at risk of this type of lesion (20% of lesions). • Lateral and medial epicondylitis is caused by the excessive use of the wrist and forearm, frequent in tennis players (up to 40% of players have it), golfers and throwers.[10] • Achilles tendon injuries are classified as insertional and non-insertional depending on anatomical location. This tendinopathy affects up to 9% of recreational runners

	and is a common reason why professional runners retire (up to 5% of professional runners end their career for this reason).[9,11] • Rotator cuff tendinopathies are common in throwing sports (like baseball and tennis) or people who perform overhead motions at work. Despite physical therapy options, surgery is common for this tendinopathy with 75,000 surgeries perform in the U.S. each year.[3,12] ANKLE SPRAINS Ankle injuries are the most common injuries among athletes making up to 45% of all sports-related injuries. There are an estimated of 28,000 cases of ankle sprain each day in the United States including both athletes and individuals who sprain their ankles performing routine activities.[5] [13] AT-RISK SUBPOPULATIONS Tendinopathies and ankle sprains are common in active individuals. The risk of having a tendinopathy increases with age. There is limited high quality data on tendinopathies by race and sex but there do not appear to have major differences by these factors.[14] Whites and blacks are more likely to have ankle sprains than Hispanics. Young men are the demographic group most likely to have an ankle sprain.[13]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• Pain[8] • Activity limitation in sports participation, daily life and work [2] • Time off from work to attend formal physical therapy sessions
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• The current prevalence of tendinopathies and ankle sprains combined with the increased number of individuals engaging in physical activity make research on treatments for tendinopathies and ankle sprains a high priority topic.

Options for Addressing the Issue	

Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	There was one AHRQ report, one Cochrane review and one Cochrane protocol were relevant to physical therapy for tendinopathies or ankle sprains.
	
	• Patellar tendinopathy
	  ○ No relevant systematic reviews.
	• Lateral and medial epicondylitis
	  ○ No relevant systematic reviews.
	• Achilles tendon injuries
	  ○ The 2001 review *Interventions for treating acute and chronic Achilles tendinitis* included physical therapy as an intervention option but no physical therapy interventions were described.[15] This review was withdrawn in 2011 because it was considered out of date.
	  ○ One Cochrane protocol published in December 2013.[16] The protocol aims to assess the benefits and harms of exercise, orthoses and splinting for treating Achilles tendinopathy. Each intervention will be compared with each other intervention and no intervention, placebo or rest. Intervention delivery mode and method will also be examined.
	• Rotator cuff
	  ○ The 2010 AHRQ report *Comparative Effectiveness of Nonoperative and Operative Treatments for Rotator Cuff Tears* was assessed in November 2012 and considered current. The majority of the Key Questions focused on operative techniques and outcomes. Two studies involved home exercise after operation (1. Individualized physical therapy program with home exercise vs. home exercise, 2. Videotape vs. home exercise instruction) and the authors concluded that the evidence was too limited to make a conclusion. No studies were identified that examined home exercise versus physical therapy prior to surgery.
	• Ankle sprain
	  ○ No relevant systematic reviews.

What could new research contribute to achieving better patient-centered outcomes?	There is very little existing evidence or ongoing research comparing physical therapy with home-based therapy for these conditions. The majority of the literature is focused on physical therapy techniques, medical and surgical treatments. If research supports that home therapy is equivalent or superior to physical therapy, and acceptable to patients, it is expected that rehabilitation, pain relief, return to work and sports might happen more expediently.

Have recent innovations made research on this topic especially compelling?	Besides exercise based treatment (mainly eccentric therapy) there are several other therapies that undergo continued research and improvement; • Cryotherapy • Laser therapy • Ultrasound therapy • Extracorporeal shock-wave therapy (ESWT) • Sound-assisted soft tissue massage (SASTM) or augmented soft tissue mobilization (ASTM) To date rehabilitation protocols are based on exercise combined with these therapies, leaving surgical interventions as a last choice. Since tendinopathies are the result of a degenerative process, the latest research has focused on the use of biologicals and stem cells.
How widely does care now vary?	Variation in care is unknown. Variation in care may depend upon where the patient is seen for the injury. An emergency room or primary care practitioner may be more likely to recommend at home exercise first. Specialists may be more likely to recommend formal physical therapy or medical or surgical treatments or a combination of home exercise and other options, although this is largely unknown.
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	There are 94 studies registered in ClinicalTrials.gov associated with tendinopathy. No trial compares at-home exercise to formal physical therapy. Trials that involve exercise include: • **Not yet recruiting** ○ Eccentric Exercise (application of load and muscle exertion while the muscle is elongated to reduce oxygen consumption and energy expenditure) for Chronic Mid-portion Achilles Tendinopathy ○ The Influence of Eccentric Training on the Volume and Vascularization of the Rotator Cuff in Patients With Rotator Cuff Tendinopathy and Healthy Subjects ○ Eccentric Training With or Without Elbow Brace for Epicondylitis ○ VIBration Training in Epicondylitis • **Recruiting** ○ Eccentric Exercises for Rotator Cuff Tendinopathy ○ Eccentric Exercise Versus Eccentric Exercise and Astym®(Assisted Soft Tissue Mobilization: a massage tool to soften scar tissue and regenerate soft tissue) for Insertional Achilles Tendinopathy ○ Rotator Cuff Tendinopathy Exercise Trial ○ Plasma Injections Plus Exercise for Patellar Tendinopathy ○ High Volume Saline Injections for Achilles Tendinopathy

	○ Astym® Compared Eccentric Exercise for Chronic Mid-substance Achilles Tendinopathy ○ Autologous Tenocyte Implantation in Patients With Chronic Achilles Tendinopathy ○ Exercise and Shoe Orthoses in Treatment of Posterior Tibial Tendon Dysfunction ○ Percutaneous Needle Tenotomy (PNT) Versus Platelet Rich Plasma (PRP) With PNT in the Treatment of Chronic Tendinosis – No exercise involved ○ Radial Extracorporeal Shock Wave Therapy (rESWT) Treatment of Subacromial Shoulder Pain combined with supervised exercise ○ Resistance Training as Treatment of Achilles Tendinopathy • **Completed** ○ With results: Bracing and Strengthening for Posterior Tibial Tendon Dysfunction. For the primary outcomes no statistical tests were provided, but the brace + exercise group had higher values than the brace group on the Foot Function Index at 12 weeks. It was unclear if higher values are better or worse. ○ Without results: ▪ The Value of Platelet-Rich Plasma in Chronic Midportion Achilles Tendinopathy: a Double-blind Randomized Clinical Trial with eccentric exercise ▪ The Efficacy of Polidocanol Injections as a Treatment of Chronic Achilles Tendinopathy for patients who failed exercise ▪ Effect Study of an Eccentric Training Program and Stretching for Patients With Chronical Rotator Cuff Tendinopathy • **Terminated**: Study of the Effect of Neck Treatment on Shoulder Impingement. Expected enrollment 30, unknown how many enrolled. There are 86 studies registered in ClinicalTrials.gov associated with ankle sprains. One trial compared at-home exercise to formal physical therapy but did not post the results. Trials that involve exercise include: • Not yet recruiting ○ Rehabilitation Study Comparing Two Exercise Programs for Ankle Sprains • Recruiting ○ Jumping Exercises Approach in Individuals With Chronic Ankle Instability ○ Effects of Talocrural Joint Mobilizations in the Treatment of Subacute Lateral Ankle Sprains ○ Ankle Sprain Rehabilitation With the Wii Balance Board (for rehabilitation after

	surgery) ○ Effect of Kinesiotaping on Ankle Stability ○ Balance Training vs. Balance Training w/ STARS • Completed, None posted study results ○ Manual Therapy and Exercise Versus Home Exercises in the Management of Patients Status Post Ankle Sprain ▪ This study is relevant to the topic. The study was last updated in July 2013 in ClinicalTrials.gov. • Purpose: *To compare the effectiveness of a physical therapy management approach consisting of manual therapy and exercise to a home program of exercise only. The investigators hypothesize that the group receiving manual therapy and exercise will have better outcomes.* ○ Influence of Sensorimotor Treatment in the Balance of Soccer ○ Effects Of High Voltage Pulsed Current On Post-Traumatic Injuries ○ Effect of Neuromuscular Warm-up on Injuries in Female Athletes ○ Short Term Bed Rest Study: Evaluation of the Use of Artificial Gravity, Induced by Short-arm Centrifugation No relevant studies on tendinopathies or ankle sprains were identified in NIH Reporter.
How likely it is that new CER on this topic would provide better information to guide clinical decision making?	Very little evidence exists on in which situations home versus formal physical therapy interventions should be recommended. At present, a health care provider has very little evidence available to make an evidence-based recommendation for at home versus formal physical therapy for tendinopathies and ankle sprains. New CER will provide better information.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS These interventions are currently available. Many primary care, urgent care and emergency medicine health care practitioners are currently prescribing at-home exercises. There are trained physical therapists to provide care for those that are referred to them. BARRIERS: • New interventions are in development and the majority of existing research aims to

	examine their efficacy and safety relative to physical therapy. Because there is little evidence base for at-home exercise and formal physical therapy, if these new interventions are effective they may be preferred to physical therapy because the evidence base is stronger. • Adherence and compliance is a common concern with exercise and physical therapy because they may require more time commitment than medical or surgical therapies. Understanding the barriers to adherence with different physical therapy approaches is needed. • There may be time or co-payment barriers for formal physical therapy for some patients. • Not all clinicians are comfortable with providing instruction in home exercises. • Physical therapists may find recommendations for home therapy to be threatening to their livelihood.
How likely is it that the results of new research on this topic would be implemented in practice right away?	Many first-line providers in primary care, urgent care and emergency department settings are currently recommending at-home exercise. Effective at-home exercise therapies can be implemented right away, if the evidence is appropriately disseminated to clinicians. If formal physical therapy is better for a subset of patients, this information also needs to be disseminated to assure that the right treatments are getting to the right patients.
Would new information from CER on this topic remain current for several years?	At-home exercise and physical therapy will likely remain the first line treatments for many cases of tendinopathies and ankle sprains even if new medical, shock wave therapy and surgical options are identified. New information will likely remain current for several years.

References for topic 2: What is the comparative effectiveness of home exercise alone versus formal physical therapy alone versus combination of home exercise and formal physical therapy for tendinopathies and lateral ankle sprain in terms of short- and long-term patient-centered outcomes?

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Topic 3: What is the comparative effectiveness of the use of inferior vena cava (IVC) filters compared with use of anticoagulants in the management of patients with acute venous thromboembolism in terms of patient-centered outcomes and the prevention of morbidity and mortality from recurrent acute venous thromboembolism?

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION[1,2] • Venous thromboembolism (VTE) includes the conditions of deep venous thrombosis (DVT) and pulmonary embolism (PE). A DVT occurs when a blood clot forms in a deep vein of the body, often a leg vein. A PE may occur if the blood clot detaches from the vein and travels in the blood stream to lodge in the vessels of the lung. • When a patient presents with an episode of VTE, treatment needs to be started rapidly to prevent complications, including death. DESCRIPTION OF TREATMENT OPTIONS • Anticoagulants, including warfarin and heparin, have been available for decades. Patients on anticoagulation need frequent monitoring with blood draws and often dietary adjustments to avoid bleeding or clotting complications.[3-7] Newer anticoagulants have been developed which require less monitoring and may cause less bleeding.[8] However, the newer agents are not easily reversed which can be harmful for critically ill patients or patients in need of emergency surgery. • Inferior vena cava (IVC) filters, which are umbrella-like devices placed in the large vein below the heart, are typically used to prevent PE in patients with a contraindication to anticoagulation.[9,10] Patients with a temporary contraindication to anticoagulation (i.e., need for emergency surgery) are often recommended to begin anticoagulants after the temporary contraindication has passed because the IVC filter itself increases the risk of DVT, while reducing the risk of PE. Retrievable IVC filters are now available for patients with temporary indications, although some patients who receive retrievable filters never return to have the filter removed.[11] This topic asks whether IVC filters may be effectively used, with or without anticoagulation, at the time of an acute DVT to prevent PE.

Relevance to patient-centered outcomes	• Anticoagulation is associated with bleeding, including life-threatening gastrointestinal and intracerebral bleeding. • IVC filters effectively prevent PE but contribute to DVTs. • Many patients with temporary contraindications to anticoagulation and who receive a filter must later take anticoagulation. • Patients who receive retrievable filters need to return for a subsequent hospital encounter to have their IVC filter removed. • Often the patient is not involved in the decision-making process to select anticoagulation or IVC filter placement because the standard of care is anticoagulation unless there is a contraindication. • Patients may value having options for PE prevention if presented with relevant information.
Burden on Society	
Recent prevalence in populations and subpopulations	PREVALENCE • Calculating the prevalence of VTE is more difficult due to the overlap of diagnoses (PE and DVT may be present at the same time), the presence of unreported cases and the presence of recurrent cases counted more than once. Many VTE are now treated as outpatients and will not be known from studies of inpatients. These factors result in wide variation in the prevalence estimates: ○ Based on a query of the 2012 Nationwide Inpatient sample, there were 322,720 discharges in the US associated with an ICD-9-CM code for VTE, with low mortality (less than 2% of these patients died in-hospital).[12] ○ According to the Surgeon General projections, more than 350,000 Americans are affected by VTE each year.[1] ○ According to the CDC, there are 547,596 hospitalizations with VTE each year in the US. [13] ○ A report based on autopsies of nursing home residents suggests that the prevalence of VTE may be two times greater than the published estimates based on diagnosed VTE.[13] • The prevalence of VTE is similar in men and women.[12,13] • Risk of VTE increases with age ○ 83% of cases in 2012 were in patients older than 45 years old. ○ 50% of the cases were older than 65 years. [12] • Risk of VTE varies by race ○ African Americans have a 30 percent higher risk of VTE than whites. ○ Asians and Native Americans have a 70 percent lower risk of VTE than whites.[1]

Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• PEs are frequently lethal. VTE (DVT and PE) is the cause of 100,000 deaths each year. This number may be as high as 180,000 when VTE is the indirect cause of death.[1,13]
	  ○ 20% of patients with a PE die before diagnosis or the day after diagnosis.
	  ○ 10% to 30% of patients will die within one month of diagnosis.[14]
	• DVT are associated with lasting complications.[1]
	  ○ Up to 50% of patients will have post-thrombotic syndrome which is characterized by swelling, pain and scaling in the affected limb.
	  ○ Up to 30% will have a recurrent VTE within 10 years.
	• All patients need treatment for some period of time and face potential adverse events including bleeding (from anticoagulants) and DVT (from IVC filters).
	• VTE often occur in a hospital or long-term care facility setting. Patients with VTE often have a longer length of stay than patients without VTE.[15]
	• Patients who receive a retrievable IVC filter must return to have the filter removed resulting in an additional health care encounter.

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• Although primary prevention of VTE is important, new CER on the prevention of fatal PE after DVT is also a high priority given the high prevalence and lethality of this condition.
	  ○ DVT is a highly prevalent condition.
	  ○ More people die from VTE annually than HIV, breast cancer and motor vehicle accidents combined.
	  ○ AHRQ identifies preventing VTE and its sequelae in its list of *10 Patient Safety Tips for Hospitals*, in recognition of its consequences.[16]

Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	• There are no head to head trials that have compared IVC filters with anticoagulation for *treatment* of DVT. • A 2013 AHRQ report related to IVC filters was identified entitled *Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations*. This review described the evidence for drugs and devices that were either FDA approved for VTE prophylaxis or are used off label by clinicians for this indication at the time of the review. The studies were generally studies of primary prevention. All study designs were included for IVC filter comparisons. ○ One key question directly addressed IVC filters: *What are the comparative effectiveness and safety of IVC filters to prevent PE in hospitalized patients with trauma?* Fifty-eight studies were identified (0 low risk of bias, 5 moderate risk of

	bias and 53 high risk of bias). The following findings were made: ○ Low strength of evidence: ▪ IVC filter placement is associated with a lower incidence of PE compared with no IVC filter placement. ▪ IVC filter placement is associated with a lower incidence of fatal PE compared with no IVC filter placement. • A 2010 Cochrane review was identified related to IVC filters.[17] The goal of the review was to examine evidence for the efficacy of IVC filters to prevent PE with secondary outcomes of mortality, thrombosis distal to the filter, and filter-related complications. Two trials that included 529 participants, presumably without DVT at baseline, were identified. A quasi-randomized study of 129 participants with traumatic hip fractures showed a reduction in PE but not mortality. An unblinded, randomized trial of 400 participants with VTE tested permanent IVC filters with concurrent anticoagulation versus anticoagulation alone found that permanent IVC filters prevented PE but increased DVT at eight years and found no difference in mortality. The authors concluded that there is insufficient evidence to make recommendations; there is a lack of evidence on outcomes when used for approved indications and that further trials are needed to assess IVC filter efficacy and safety.
What could new research contribute to achieving better patient-centered outcomes?	Patients are rarely asked for their preferences regarding anticoagulation versus permanent filter placement versus retrievable filter placement. Data on patient preferences is needed. Evidence regarding whether clinicians would use patient input on this topic is also needed. If new research demonstrates the superiority of one approach, a reduction in PE-related deaths could be achieved.
Have recent innovations made research on this topic especially compelling?	• Retrievable filters continue to come to market with theorized, although untested, advances over earlier models. • A large trial underway, called ATTRACT, is testing another treatment option which would further set the stage for patient involvement in the decision-making process. This trial tests catheter-directed thrombolysis to dissolve DVTs compared to standard anticoagulation. [18]

How widely does care now vary?	• Despite the strong recommendations of guidelines for *primary prevention* of VTE, there is variation in care including the absence of anticoagulation in high risk patients.[19,20] There is little data on variation in the use of IVC filters after DVT for prevention of PE, but it is expected to be great.
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	A research agenda for IVC filters was developed by a multidisciplinary research consensus panel and published in 2009.[21] ClinicalTrials.gov was searched to identify relevant studies. No ongoing research is directly addressing the question of filter vs anticoagulants among individuals without a contraindication to anticoagulation. There were 29 relevant studies (4 randomized trials) based on a search for "inferior vena cava filter" on June 17, 2014. • **Not yet recruiting, not randomized:** ○ Using a Novel Algorithm to Improve the Retrieval Rate of Inferior Vena Cava Filters (iRetrieve Study) ○ The SENTRY Clinical Study • **Recruiting:** ○ Randomized, patients and caregivers aware of treatment group: Prevention of Recurrence After Thrombolysis in Acute Iliofemoral Venous Thrombosis (PRAIS) Study ○ Not randomized: ▪ VERITAS: An Evaluation of the Veniti Vidi Retrievable Inferior Vena Cava Filter System in Patients at Risk for Pulmonary Embolism ▪ VenaTech Convertible Vena Cava Filter U.S. Multi-Center Clinical Trial ▪ Cook IVC Filter Study ▪ Angela Catheter Early Feasibility Clinical Study ▪ FILTER - Filter Initial & Long Term Evaluation After Placement and Retrieval (Including Laser-Assisted Retrieval) Registry ▪ VTEval Project - A Prospective Cohort Study to Evaluate Diagnosis, Management and Outcome in Individuals With Venous Thromboembolism ▪ Evaluation of the Influence of Body Position on the Inferior Vena Cava (IVC) Diameter ▪ Failed Retrieval of Inferior Vena Cava (IVC) Filters: Long-Term Outcomes • **Active, not recruiting, not randomized:** ○ A Prospective, Multi-Center Study of the Bard® Denali™ Retrievable Inferior Vena Cava Filter System

	• **Completed with results, not randomized:**
	  ○ Celect Vena Cava Filter Clinical Trial
	  ○ RexMedical- Option* Vena Cava Filter IDE Study
	  ○ Prospective, Multi-center, Single-arm Study to Assess the Safety of Retrieval of the Recovery G2 Filter.
	  ○ Safety Study of the Angela Catheter in Subjects With Risk of Pulmonary Embolism
	  ○ The Use of Fondaparinux in Preventing Thromboembolism in High Risk Trauma Patients
	• **Completed without results:**
	  ○ <u>Randomized</u>
	  ▪ Patients and caregivers not aware of treatment group (double blind): Introducer Curving Technique for Tilt of Transfemoral Gunther Tulip Inferior Vena Cava Filter. Participants randomized to different filter tips (curved vs straight)
	  ▪ Patients and caregivers aware of treatment group: PREPIC 2 : Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption
	  ○ <u>Not randomized:</u>
	  ▪ Crux Biomedical Evaluation of the Crux Inferior Vena Cava Filter 4
	  ▪ Crux Biomedical Evaluation of the Crux Inferior Vena Cava Filter System 3 (RETRIEVE 3)
	  ▪ Crux Biomedical Vena Cava Filter Study - United States
	  ▪ Crux Biomedical IVC Filter - Evaluation of the Crux Inferior Vena Cava Filter System (Retrieve)
	  ▪ Study of IVC Filter Retrieval With the Gunther Tulip Vena Cava Filter
	  ▪ A Pivotal Study to Evaluate the Safety and Effectiveness of RMT Medical Technology's SafeFlo® Vena Cava Filter
	  ▪ Protection From Pulmonary Embolism With the Permanent OptEase® Filter (PROOF)
	• **Terminated, no results:**
	  ○ <u>Randomized</u>, patients and caregivers aware of treatment group: Anticoagulation and Inferior Vena Cava Filters in Cancer Patients With a Venous Thromboembolism, 64 enrolled.
	  ○ <u>Not randomized</u>: National Inferior Vena Cava (IVC) Filter Registry, 20,000 enrolled

	• **Withdrawn no results**, not randomized: PENELOPE Observational Study, 0 enrolled NIH Reporter search for "inferior vena cava filter" on June 18, 2014 resulted in one relevant study. Risk Factors For Venous Thromboembolism In The Community (5R01HL066216-12) has the following specific aims: ○ **Aim 1**: Determine "why VTE remains such a persistent problem" by updating the Olmsted County, MN VTE inception cohort to include the 45-year period, 1966-2010 1a) test whether recently implemented CMS performance measures have affected secular trends in VTE incidence and prophylaxis- related complications 1b) quantify changes over time in the population-attributable risk of major VTE risk factors 1c) determine whether changes in the prevalence of major VTE risk factors can account for trends in the observed incidence of VTE ○ **Aim 2**: To determine "when genetic testing is appropriate" by 2a) testing Factor V Leiden, Prothrombin G20210A, and novel ABO SNPs as risk factors for VTE after hospitalization for major surgery and acute medical illness 2b) developing 2c) validating VTE risk assessment tools for these two high-risk populations ○ **Aim 3**: To "conduct research into how [arm] DVT should best be managed" by identifying all Olmsted County residents with incident arm cerebral, hepatic, portal, splenic, mesenteric and renal vein thrombosis 3a) estimate the incidence of thrombosis in these "other" venous circulations 3b) quantify outcomes (survival and VTE recurrence) 3c) test other venous circulation thrombosis as potential predictors of survival and VTE recurrence ○ **Aim 4**: To "investigate the roles of IVC filters" by identifying all Olmsted County residents with IVC filter placement over the 45-year period, 1966-2010 4a) estimate the incidence of IVC interruption or filter placement 4b) determine outcomes (survival, complications and VTE incidence and recurrence) 4c) test IVC filter placement as a risk factor for incident VTE, or as predictors of survival and recurrent VTE.

How likely it is that new CER on this topic would provide better information to guide clinical decision making?	Understanding the role that patients can play in the decision-making process, how clinicians can incorporate patient input into the process and which method of preventing PE is best (anticoagulation versus filter) are all needed.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • Treatments exist and are in use. • Filters are easy to place and most centers have personnel who can place the filters, such as interventional cardiologists and interventional radiologists. BARRIERS • Not everyone who has a VTE will necessarily be able to play a role in decision-making either due to their level of consciousness when the decision must be made (i.e., trauma patients) or due to contraindications to anticoagulation. Individuals with a contraindication to anticoagulation may still play a role in the decision to receive a permanent versus retrievable filter. • Health care providers may not be ready to involve patients in the decision-making process, especially since the guidelines provide such strong endorsement of IVC filters only when anticoagulants are contraindicated. • Filter placement and retrieval is likely to be more expensive than use of anticoagulants • The risk – benefit balance may be weighed very differently by different patients.
How likely is it that the results of new research on this topic would be implemented in practice right away?	Current practice guidelines strongly recommend the use of anticoagulants over filters in primary prevention, except for specific contraindications. Treatment guidelines do not address use of filters for PE prevention following DVT. New research findings could be easily incorporated into practice, particularly if a major society includes the evidence in a guideline update.
Would new information from CER on this topic remain current for several years?	The ATTRACT trial is a large ongoing trial that aims to use thrombolytic therapy to remove DVTs.[18] This trial will not render any planned CER on this topic obsolete but new CER might need to incorporate thrombolysis as an additional trial arm if the trial suggests superiority of this approach.

References for topic 3: What is the comparative effectiveness of the use of inferior vena cava (IVC) filters compared with use of anticoagulants in the management of patients with acute venous thromboembolism in terms of patient-centered outcomes and the prevention of morbidity and mortality from recurrent acute venous thromboembolism?

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Topic 4:

Under what circumstances/conditions/procedures are the use of an implantable cardioverter-defibrillator (ICD) indicated? What is the comparative effectiveness of ICD versus the alternative treatments in terms of short- and long-term patient-centered outcomes?

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION An implantable cardioverter-defibrillator (ICD) is a battery-powered device consisting of a generator and one or more leads capable of sensing a ventricular arrhythmia. When a potentially life-threatening arrhythmia is detected, the ICD delivers an electric shock to terminate the arrhythmia, preventing sudden cardiac death (SCD).[1] SCD is conventionally defined as a cardiac death that occurs within 1 hour of cardiac symptom onset and without another probable cause of death.[2] About three quarters of SCDs are caused by ventricular tachyarrhythmias, in which ICDs could play an important role.[3] ICD technology has improved over time: the size of the generator has become smaller; and the ICD leads can be placed endocardially via a transvenous approach, obviating the need for opening the chest for surgical implantation in most cases. A related device-based therapy, cardiac resynchronization therapy (CRT), can be delivered alone or in conjunction with ICD (i.e., CRT-D). While ICDs aim to restore normal sinus rhythm in the presence of life-threatening arrhythmias, CRT has the potential to improve functional status and symptoms of heart failure through monitoring and detecting irregularities of the heart's electrical system, and restoring normal, coordinated pumping action of the ventricles.[1,4] <u>ICD use for secondary prevention of SCD:</u> ICD therapy was initially tested on and indicated for patients who were survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable sustained ventricular tachyarrhythmia following exclusion of completely reversible causes.[5] <u>ICD use for primary prevention of SCD:</u> ICDs are also used as primary prevention of SCD in patients with myocardial infarction (MI), since patients with reduced left ventricular ejection fraction (LVEF) are at increased risk of SCD. Specifically, the indications are 1)

	LVEF ≤35 percent due to prior MI, at least 40 days post-MI, and in New York Heart Association Class II or III; 2) nonischemic dilated cardiomyopathy with LVEF ≤35 percent and in New York Heart Association Class II or III; 3) left ventricular dysfunction due to prior MI, at least 40 days post-MI, and LVEF ≤30 percent, and in New York Heart Association Class I.[1] These clinical indications correlate with the expanded coverage criteria of the Centers for Medicare and Medicaid Services (CMS), and significantly broaden the candidate pool for ICD.
Relevance to patient-centered outcomes	SCD and all-cause mortality have been the most important outcomes traditionally; however, there is increasing recognition of the importance of shared decision-making regarding ICD therapy, and the impact of ICDs on quality of life, especially near the end of life as many older adults may value quality over quantity. Efficacy outcomes[6] • Sudden cardiac death • All-cause mortality • Atrial fibrillation end points • Heart failure end points • Stroke or thromboembolism end points • New York Heart Association functional classification • Subjective and objective symptom improvement • Quality of life • Functional status • Exercise capacity Harms[7-9] • Inappropriate ICD detections and shocks • End-of-life shocks • Anxiety • Hospitalization • Short-term adverse events secondary to implantation of the device such as bleeding, damage to the vessel at the catheter insertion site, infection, cardiac tamponade, pneumothorax, lead dislodgement • Long-term adverse events such as lead or generator malfunction, thrombosis, infection.

Burden on Society	
Recent prevalence in populations and subpopulations	PREVALENCE • SCD accounts for approximately 300,000 deaths (ranges from 200,000 to 450,000) annually in the U.S.[1] SCD is responsible for half of all heart disease deaths and a quarter of all deaths in the U.S.[10] About 90% of SCDs are arrhythmic with 75% of caused by ventricular tachyarrhythmias.[1] • Over 500,000 Medicare beneficiaries are eligible for ICD therapy and over 140,000 ICDs are implanted annually in the U.S.[11,12] Analysis of the National Cardiovascular Data Registry – ICD Registry suggests that about 22% of patients with ICD implants did not meet evidence-based criteria for implantation.[13] • The rate of ICD implantation in the U.S. is five times as high as the rate in other Western countries.[14]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• The beneficial effect of ICDs in reducing all-cause mortality and SCD is well established.[1] The outcomes in older adults with multiple comorbidities are less clear because these patients were underrepresented in clinical trials. • ICDs do not improve functional status. • The electrical shock itself is painful. Inappropriate shocks may occur due to arrhythmia from another origin or electromagnetic interference, producing fear and anxiety, limiting daily activities, and interfering with daily life. Inappropriate ICD therapy, including inappropriate shocks, occurs in 20 to 24% of patients. Recent research has shown that inappropriate shocks could be reduced by better ICD programming.[15-18] • CRT-D has shown positive effects in improving patients' functional capacity and quality of life.[19] • Cumulative medical costs are substantially higher among patients receiving an ICD. ICDs have a large upfront cost and considerable additional costs. Nearly 1 in 8 shock events is followed by hospitalization; and the shock related expenditures are similar between ICD and CRT-D patients.[20] • The estimated initial implantation costs for an ICD implant were between $36,000 to $54,000 in 2006 and have declined to nearly $30,000 currently. The annual ICD costs after implantation were between $10,000 to $17,000 in the 1990s, and have fallen to less than $7,000 currently, with some out-of-pocket costs to patients.[21-25] • The battery life for ICD is between 4 and 6 years; 40% of ICD patients will need at least one generator replacement.[26] Generator replacement requires a surgical procedure, which is not risk free. The infection rate is between 2.6% to 7% and is higher than the de novo implant.[27-30] The incidence of major complications is between 4 and 15% with ICD generator replacement.[31] The cost of treating an infection complication sometimes exceeds the cost of the initial ICD implant.[32]

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• Cardiac arrest due to ventricular fibrillation and MI are highly prevalent conditions among older Americans. • The expanded indications and CMS coverage criteria significantly broadened the candidate pool for ICD. • ICDs are costly to the health system. • The societal burden suggests that CER on ICD related topics should be given high priority.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	Available management options include antiarrhythmic drugs, ICD, and CRT-D. Benefits: • Antiarrhythmic drugs were developed to suppress abnormal electrical cardiac impulse in patients with ventricular tachycardia and ventricular fibrillation. However, antiarrhythmic drugs do not provide survival benefit and some drugs can even increase the risk of death.[33] Antiarrhythmic drugs are now used primarily for atrial fibrillation and other less severe rhythm disturbances. • When used for secondary prevention of SCD, ICDs are more effective than antiarrhythmic drugs in reducing the hazard of death based on a meta-analysis of three randomized controlled trials (hazard ratio = 0.72; 95% confidence interval: 0.60 to 0.87.[34] • When used for primary prevention of SCD, high quality evidence suggests that ICDs reduce the hazard for all-cause mortality (hazard ratio = 0.69; 95% confidence interval: 0.60 to 0.79)[1,35] and the hazard for SCD (hazard ratio = 0.37; 95% confidence interval: 0.26 to 0.52).[1] Analyses failed to show differential effects across subgroups by age, sex, and other patient characteristics, presumably due to small sample size and low power. • There is inconsistent evidence on whether CRT-D is superior to ICDs alone in reducing all-cause mortality.[1] CRT-D seems to produce better quality of life outcomes than ICD alone, particularly in patients with moderate to severe heart failure.[19] Harms: • In-hospital adverse events from ICD are infrequent (1-3%).[1] • Up to 21% of patients receive inappropriate shocks. Inappropriate shocks decrease quality of life.[1,15,16] • ICD therapy carries psychological consequences, such as behavioral disorders,

	anxiety, or social withdrawal, especially among patients who have experienced shocks.[6] • ICDs and CRT-Ds are not infallible; electronics, batteries, and leads fail. Complications related to replacement of ICD generators include infection, the need for reoperation, and death.[6] • Conventional ICD therapy in any form may be associated with worsening heart failure, particularly in patients with poor cardiac ventricular systolic function.[36] • CRT-D implantation has a higher risk of device- or implantation-related complications at 30 days after implantation compared with ICD alone.[1]
What could new research contribute to achieving better patient-centered outcomes?	New research could: • Identify patient subgroups more likely to derive net benefit from ICD and explore treatment heterogeneity in patients with different baseline risk for SCD.[1,36] • Establish the comparative effectiveness of ICDs versus other treatment modalities in older patients (≥65 years) and in patients with multiple comorbidities. Because the elderly are underrepresented in clinical trials, much of the rationale for implanting devices in these patients rests on weak evidence derived from *post-hoc* subgroup analyses.[1,36] • Seek to understand the frequency and causes of inappropriate shocks and devise management strategies to mitigate both inappropriate therapies and their psychological and quality of life consequences.[16] • Incorporate patient preferences in the decision to place ICD. • Evaluate end of life considerations in patients with ICDs (e.g., when to deactivate ICDs) to avoid painful shocks at the end of life. Cardiologists who implant devices do not commonly have discussions with patients about end-of-life issues and device deactivation. There is also limited published experience with deactivation of devices.[9,37]
Have recent innovations made research on this topic especially compelling?	Our analysis of clinicaltrials.gov found that ongoing trials have focused on: 1) decision aids, knowledge enhancement, education, behavior interventions, psychological support, exercise, post-ICD monitoring and follow-up, and organizational models to maximize the benefits of ICDs; 2) ICD placement for patients with co-morbidities, for children and the elderly; and identification of patients most likely to benefit through risk stratification; 3) reduction of inappropriate ICD shocks; 4) ICD deactivation strategies; 5) ICD technology development; 6) ICD implantation in recipients who also need other procedures (e.g., heart surgery, MRI).

How widely does care now vary?	• ICD implantation rates vary widely among hospitals, ranging from 1% to 35%. Hospitals with high ICD placement volume also have better and faster adoption of other evidence-based heart failure therapies.[38] • Performance measures about ICD use exist, encouraging evidence-based care.[39] • However, existing practice guidelines tend to focus on evidence of device effectiveness. Insufficient consideration has been given to involving patients in decision-making.[40]
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	Research on ICD use is active. We searched *clinicaltrials.gov* using the term "implantable cardioverter defibrillator" on June 25, 2014. • Of the 415 records identified, 254 are registered as "interventional studies". • About half of the interventional studies (46%; 117/254) are registered as "completed", followed by 22% (56/254) records registered as "recruiting". • Half of the interventional studies (50%; 127/254) examined "device", followed by "drug" (19%; 49/254), "procedure" (11%; 28/254), "behavioral" (9%; 23/254), "other" (9%; 24/254), "diet" (0.8%; 2/254), and "radiation" (0.4%, 1/254). • 64% (162/254) and 7% (18/254) of the interventional studies received funding from industry and government, respectively. • 20% (50/254) of the interventional studies included quality of life as an outcome measure.
How likely it is that new CER on this topic would provide better information to guide clinical decision making?	It is very likely that completion of the ongoing studies and new CER addressing the evidence gaps identified above will provide better information to guide clinical decision-making given the expanded ICD indications and coverage criteria, aging population and increasing disease burden, along with the paucity of research evaluating patient experience and patient centered outcomes.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS: • There are well-established practice guidelines about use of ICDs. • Performance measures about ICD use encourage evidence-based practice. • A large number of patients are eligible for ICD placement. • ICDs are covered by medical insurance in most cases. BARRIERS: • There are financial incentives to performing more procedures. • The benefits and risks are complicated to explain to patients, and must include detailed discussion of the impact on quality of life.

How likely is it that the results of new research on this topic would be implemented in practice right away?	• Approaches to improving appropriate use of ICDs are likely to be implemented in practice right away due to increasing emphasis on performance measures. • New practices, such as incorporating patient preference in the decision to place an ICD and those practices that aim to improve patient-centered outcomes, are likely to be implemented quickly in practice in hospitals that value patient-centeredness. • New evidence on the comparative effectiveness of ICDs in the elderly and in those with multiple comorbidities is likely to be incorporated right away because of the weak evidence base that currently exists. • New treatment modalities other than ICDs will not come quickly into practice given the need to establish efficacy and safety.
Would new information from CER on this topic remain current for several years?	• Preventing SCD will remain pressing for years to come, given the aging population and the disease burden overall. • ICD use has been established as an effective treatment to prevent SCD. Its effect size is large and would be difficult to surpass with any new treatment modalities. • The focus of future CER will likely need to be on strategies to maximize the benefit of ICDs, enhance the patient experience and decision making, and improve patient centered outcomes.

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Topic 5: Imaging Tests for the Evaluation of Cognitive Decline

Comparison of functional imaging tests for the evaluation of neurocognitive decline.

Criteria	Brief Description
Introduction	
Overview/ definition of topic	DESCRIPTION OF NEUROCOGNITIVE DECLINE • Broad category of brain diseases that cause long-term memory loss, inability to perform daily functions, and behavior changes.[1] • Provisional diagnosis can be made clinically but only post-mortem examinations can confirm presence/absence of disease.[1] • Only ~10 percent of neurocognitive decline cases are treatable and <1% are partially or fully reversible.[1] CAUSES • Alzheimer's disease (accounts for 60 to 70 percent of neurocognitive decline cases in the United States)[2] ○ Characterized by difficulty learning new information and progresses to disorientation, mood and behavior changes, confusion, memory loss, and difficulty speaking, swallowing, and walking.[3] ○ Patients with Alzheimer's disease can also suffer from Lewy body dementia and/or vascular dementia.[4] • Lewy body dementia (~25% of U.S. neurocognitive decline cases)[2] ○ Characterized by presence of Lewy bodies (abnormal aggregates of protein in nerve cells in regions of the brain that involve thinking, memory, and motor control) and progressive neurocognitive decline, including deficits in attention and executive function.[5] ○ Functional imaging of patients with Lewy body dementia shows low dopamine transporter uptake.[6] • Vascular dementia (~20% of U.S. neurocognitive decline cases)[2] ○ Caused by impaired blood supply to the brain, often caused by stroke.[7] • Frontotemporal lobar degeneration (<1% of U.S. neurocognitive decline cases)[8] ○ Spectrum of heterogeneous disorders of unknown etiology characterized by progressive changes in behavior, dysfunction, and language impairment.[9] DEFINITION AND TYPES OF FUNCTIONAL IMAGING TESTS USED TO ASSESS COGNITIVE DECLINE[10] • Unlike structural imaging, which examines anatomical features, functional imaging measures changes in blood flow, metabolism, and receptor binding in order to identify abnormalities in brain tissue and diagnose and assess the extent of neurocognitive decline.[10] • Main types of functional imaging scans include: ○ Positron emission tomography (PET)

	▪ Usually involves use of radio-labeled analog of glucose, ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG), which indicates regions of reduced glucose uptake that may be indicative of cerebral atrophy.[1] ▪ In patients with Alzheimer's disease, ^{18}F-FDG-PET usually shows reduced glucose metabolism in certain brain regions.[2] • These changes may appear early (even before clinical symptoms) in the course of disease.[2] ▪ ^{18}F-FDG-PET can also detect changes in dopamine metabolism and brain receptor binding.[11] ▪ ^{18}F-FDG-PET has been reimbursed by Centers for Medicare and Medicaid Services (CMS) since 2004 for patients who meet the diagnostic criteria for both Alzheimer's disease and frontotemporal dementia.[12] ▪ CMS reimburses ~$1,000 for each scan.[13] ○ Single photon emission computed tomography (SPECT) ▪ Nuclear imaging that involves injection of a radionuclide (often Technetium (Tc)-00m hexamethylpropyleneamine-oxime [HMPAO] or ^{123}I-ioflupane) that binds to brain tissue and allows assessment of regional brain metabolism.[2] ▪ CMS reimburses ~$600 per scan.[14] ○ Functional magnetic resonance imaging (fMRI) ▪ Identifies areas of the brain responsible for language, sensory, and motor functions.[10] ▪ fMRI provides information about the functional integrity of brain networks that support cognitive functioning.[15] • fMRI studies have found decreased hippocampal activity when encoding new information in patients with Alzheimer's disease compared with healthy older adults.[15] ▪ fMRI for the purposes of diagnosing or assessing the extent of neurocognitive decline is considered experimental and is not reimbursed by CMS.[16] ▪ Each scan costs ~$1,000.[17] ○ ^{1}H Magnetic resonance spectroscopy (^{1}H MRS) ▪ Uses ^{1}H signals to determine concentrations of brain metabolites.[4] ▪ Can detect elevated myoinositol and decreased N-acetylaspartate levels, which are characteristics of neurodegenerative dementia.[4] ▪ Early studies have shown that ^{1}H MRS is sensitive to detection of pathophysiologic processes associated with risk of dementia.[4] ▪ Used only for research, not clinically, due to lack of standardization across study sites and insufficient understanding of basis of ^{1}H MRS metabolite changes.[4] ▪ Considered experimental and not reimbursed by CMS.[18]
Relevance to patient-centered outcomes	• Use of functional imaging has the potential to assist with the accurate diagnosis and characterization of extent of cognitive decline.

	• Although there are no known curative treatments for dementia, the ability to correctly diagnose cognitive decline helps identify patients who are candidates for supportive treatments and may alleviate patient and family anxiety due to uncertainty. • Correct diagnosis of cognitive decline also allows patients and their families to understand and prepare for future medical needs.
Burden on Society	

Recent incidence and prevalence in populations and sub-populations	PREVALENCE AND SUB-POPULATIONS
	• Alzheimer's Disease
	  ○ Incidence: 148 cases/100,000 in the United States[19]
	  ○ Prevalence: >5 million in U.S.[19]
	  ○ Two-thirds of Americans with Alzheimer's disease are women.[19]
	  ○ Number of Americans with Alzheimer's disease is climbing dramatically as U.S. population ages.[20]
	• Lewy body dementia
	  ○ Incidence: 3.5 cases/100,000[21]
	  ▪ However, this is almost certainly low since Lewy body dementia is very difficult to diagnose.[21]
	  ○ Prevalence: 1.3 million Americans.[21]
	  ○ Typically begins after age 50 and increases exponentially with age.[21]
	  ○ Patients typically die within 5-7 years after diagnosis.[5]
	• Vascular dementia
	  ○ Incidence: 6000-12,000/100,000 in people over age 70[22]
	  ○ Prevalence: 500,000-1.8 million[22]
	  ▪ Diagnosis is difficult and numbers likely reflect underestimates of disease.[22]
	  ○ Typically appears between 60-75 years.[7]
	  ○ Disproportionately affects African-Americans.[7]
	• Frontotemporal lobar degeneration
	  ○ Incidence: 2.7-4.1/100,000 person-years.[8]
	  ○ Prevalence: 20,000 to 30,000 in U.S.[8]
	  ○ Most cases present in patients between 45-64 years.[9]

Effects on patients' quality of life, productivity, functional capacity, mortality, and use of health services	QUALITY OF LIFE/FUNCTIONAL CAPACITY/MORTALITY • Alzheimer's disease is the sixth leading cause of death in the United States[19] • Neuropsychiatric symptoms in patients with Alzheimer's disease, including agitation, aggression, delusions, depression, hallucinations, sleep disturbances, and wandering, seriously impact quality of life for patients and loved ones.[23] • Visual hallucinations are also common early in Lewy body dementia.[23] • Symptoms often lead to placement in nursing homes.[23] • Caring for patients with neurocognitive decline is a large burden on caregivers.[19] ○ Agitation and aggression in patients with neurocognitive decline often result in abusive behavior toward their caregivers.[23] USE OF HEALTH SERVICES/PRODUCTIVITY • In 2013, caregivers provided 17.7 billion hours of unpaid care for Alzheimer's disease patients.[19]

	• The annual cost of informal caregiving for dementia in the United States is estimated at $18 billion[24] and may be as high as $80 billion.[25] • Direct costs (nursing homes, Medicare, out-of-pocket expenses) of dementia in 2010 were $109 billion.[25]
How strongly does the overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	FACTORS IN FAVOR • Disease has huge resource use and cost burden. • Patients and caregivers experience high anxiety and psychological burden upon diagnosis of these diseases. • Early identification of neurocognitive diseases might benefit current patients by allowing receipt of available treatment or entry into clinical trials. FACTORS AGAINST • Only modest benefits from treatments that have been approved by the U. S. Food and Drug Administration (FDA) to treat dementia.[26] • Identifying which patients will benefit from functional imaging remains challenging.[1]
Options for Addressing the Issue	

Based on recent systematic reviews, what is known about the relative benefits and harms of available management options?	• Although ^{18}F-FDG-PET has better sensitivity and specificity than SPECT in diagnosing Alzheimer's disease compared with healthy controls and patients with other forms of neurocognitive decline,[27] SPECT is more widely used than ^{18}F-FDG-PET because it is less expensive. (The most commonly used SPECT radioisotope has a much longer half-life than ^{18}F-FDG, which makes it less expensive to use since it can be manufactured further from the imaging facility.[2])
	• Equipment to perform SPECT is less expensive than ^{18}F-FDG-PET machines.[2]
	• ^{18}F-FDG-PET had 90 percent sensitivity and 80 percent specificity in differentiating Alzheimer's disease from dementia with Lewy bodies, confirmed on autopsy.[27]
	  ○ ^{18}F-FDG-PET performed better than clinical diagnostic criteria and SPECT.[27]
	• Sensitivity of SPECT in identifying dementia compared to healthy controls (confirmed at autopsy) ranges from 63 percent to 78 percent; specificity ranges from 71 percent to 93 percent.[28]
	• At present, ^{1}H MRS and fMRI are experimental and do not have a role in clinical diagnosis or assessment of neurocognitive decline.[27]
	  ○ We could not identify studies comparing the relatively novel imaging techniques of ^{1}H MRS and fMRI with the more widely used techniques (^{18}F-FDG-PET or SPECT).
	• Although fMRI is not often used, its use has potential to increase because it is less invasive than ^{18}F-FDG-PET or SPECT and can be used at the same time structural MRI images are being obtained.[15]
	• The quality of evidence regarding use of imaging for diagnosis of neurocognitive decline is generally limited.[1]
	• Because treatment effectiveness for most neurocognitive decline is limited, a potential harm of use of functional imaging for diagnosis and assessment of these diseases is psychological trauma for patients and caregivers, particularly if diagnoses are inaccurate.[29]
	  ○ However, most patients with and without cognitive impairment have indicated that they would prefer to be informed about a diagnosis of neurocognitive decline.[29]

What could new research contribute to achieving better patient-centered outcomes?	• New research could provide comparative data on the long-term effects of functional imaging technologies on patient quality of life, health care utilization, and costs in patients with neurocognitive decline. • New research could compare different functional imaging technologies in terms of their impact on patient and clinician decision making (e.g., long term medical planning, coping strategies, and planning for the future) in patients with neurocognitive decline. • New research could identify and quantify patient preferences for the receipt and use of different functional imaging tests.
Have recent innovations made research on this topic especially compelling?	• Use of functional imaging to identify and monitor progress in patients with neurocognitive decline is an active field of research. • Many experimental therapies that attempt to slow or halt progression of neurocognitive diseases are being researched, making early identification more valuable. • The annual incidence of Alzheimer's disease and other dementias is projected to double in the United States by 2050.[20]
How widely does care now vary?	• Primary care physicians (usually the first point-of-contact when neurocognitive decline is suspected) show wide variability in ability to diagnose and manage patients with dementia.[30] ○ Patients in rural areas in particular have difficulty accessing specialists in caring for patients with neurocognitive decline.[30] • Patients in rural areas likely have less access to facilities with capacity to perform functional imaging.
What is the pace of other research on this topic as indicated by recent publications and ongoing trials?	• **Clinicaltrials.gov**: Search: "dementia and functional imaging" ○ Total ongoing trials: 84 (majority involve fMRI and ^{18}F-FDG-PET imaging) ○ Total completed trials: 83 • **NIH Reporter** (search: "dementia and functional imaging") ○ Projects: 0 ○ Publications: 0
How likely is it that new CER on this topic would provide better information to guide clinical decision making?	• Research that resulted in more accurate diagnosis of neurocognitive decline could enhance clinicians' and patients' abilities to make plans to address issues that result from these diseases; however, basic science studies might be more appropriate than comparative effectiveness research at this time.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • Functional imaging technologies are being used for indications besides neurocognitive decline, so they are widely used in academic medical and research facilities. • Many biopharmaceutical companies are pursuing treatments for dementia. BARRIERS • Diagnosis of neurocognitive decline remains difficult (e.g., gold standard is post-mortem evaluation), making these diseases hard to characterize and study.

	• Without existing proven treatments for these diseases, use of functional imaging to identify disease might not result in better disease management or patient outcomes.
How likely is it that the results of new research on this topic would be implemented right away?	• Aging population and exponential increase in neurocognitive decline cases in the near future translates to increased interest from patients, caregivers, and payers in implementing new findings.
Would new information from CER on this topic remain current for several years or would it be rendered obsolete quickly by subsequent studies?	• While the technical specifications of the imaging modalities and radionuclides used with them are changing rapidly, the base technologies for these imaging modalities are likely stable and CER will remain current for several years.

^{1}H MRS = ^{1}H magnetic resonance spectroscopy; ^{18}F-FDG = ^{18}Fluorine-fluorodeoxyglucose; CMS = Centers for Medicare and Medicaid Services; fMRI = functional magnetic resonance imaging; PET = positron emission tomography;

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Topic 6: "Statin Therapy in Patients Age 70 and Older"

Comparative Effectiveness of Statin Therapy for the Primary Prevention of Atherosclerotic Disease in Patients Age 70 and Older

Criteria	Brief Description
Introduction	

Overview/Definition of Topic	• Atherosclerosis is a disease in which plaque builds up inside the arteries, leading to serious problems including cardiovascular disease (CVD), heart attack, stroke, or even death.[1,2]
	• Cholesterol, atherosclerosis, and statins
	  ○ Evidence indicates that statins substantially reduce cardiovascular events and all-cause mortality.[3-5]
	  ○ The use of statins has resulted in a substantial reduction in the incidence of ischemic stroke.[6]
	  ○ Intensive low-density lipoprotein (LDL) cholesterol lowering with statins is recommended for patients with established atherosclerotic CVD and for primary prevention in individuals with CVD risk factors such as diabetes and hypercholesterolemia by U.S. and European guidelines.[2,7,8]
	• Atherosclerosis in the elderly (persons over 70)
	  ○ Because of population aging, prevention of CVD in the elderly will assume increasing relevance in the future.[5]
	  ○ A large and increasing number of cardiovascular events (more than two-thirds) occur in elderly subjects.[8]
	  ○ Elderly individuals without established CVD outnumber those with established CVD, thus the majority of cardiovascular events occur in these patients, despite their relatively lower risk.[5]
	  ○ Analysis of data from the Cardiovascular Health Study (National Heart, Lung, and Blood Institute)[9] among elderly participants at entry into the study showed that subclinical CVD is prevalent among older individuals, is independently associated with risk of coronary heart disease (CHD), and substantially increases the risk of CHD among participants with hypertension.[10]
	  ○ The elderly are more frequently affected by comorbidities, including diabetes mellitus, peripheral arterial diseases, hypertension, hyperlipidemia, and renal dysfunction, compared with younger people.[4,5]
	  ○ Guidelines recommend that elderly patients initiating statin therapy for primary CVD prevention should be treated with moderate intensity, rather than high intensity, statin regimens.[2]
	• Statins for primary prevention of atherosclerosis in the elderly
	  ○ Primary prevention refers to treatment or lifestyle measures aimed at preventing disease from occurring.
	  ○ A 39 mg/dL lower total cholesterol has been associated with a one-sixth reduction (hazard ratio: 0·83 [95% CI 0·81 to 0·85]) of cardiovascular mortality in the elderly.[11]

	○ In elderly patients with previous cardiovascular events, the use of statins is recommended by guidelines.[2,7] ○ There are currently no definitive guideline indications for statin treatment in elderly subjects with risk factors but without established CVD. ▪ No randomized controlled trials (RCT) specific to this age group have assessed the risk-benefit profile of statin use; however, RCT subgroup analyses are available.[3] ▪ RCT evidence does support the continuation of statins for elderly individuals who are already taking and tolerating these drugs.[2] ▪ Initiation of statins for primary prevention of atherosclerotic CVD in elderly individuals requires consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care.[2]
Relevance to patient-centered outcomes	• Greater utilization of statins by elderly individuals without previous history of CVD has the potential to prevent cardiovascular and cerebrovascular (stroke) events, thus improving elderly individuals' life expectancy, quality of life, and other important outcomes. However, there is the potential for negative impacts on quality of life and other patient-related outcomes related to side effects and the need to be on preventive treatment.
Burden on Society	
Recent Incidence and prevalence in populations and subpopulations	• Approximately 20 million Americans were elderly in 2010, representing approximately 6 percent of the population, and the number is expected to double by 2050.[12] • For elderly individuals, the remaining lifetime risks for developing:[4,13-16] ○ Any CVD: ▪ 1 in 2 women ▪ 1 in 2 men ○ Coronary heart disease: ▪ 1 in 4 women ▪ 1 in 3 men ○ Atrial fibrillation: ▪ 1 in 4 women ▪ 1 in 4 men ○ Congestive heart failure: ▪ 1 in 5 women ▪ 1 in 5 men ○ Stroke: ▪ 1 in 5 women ▪ 1 in 6 men • 67 percent of the over 800,000 cardiovascular deaths per year in the United States occur in elderly individuals.[4] • Over 16 million Americans have coronary heart disease, and more than half of them were elderly individuals.[4] • 7 million have had a stroke, the incidence of which approximately doubles with successive age decades after 45 to 54 years old.[4] • 8 to 10 million Americans have peripheral artery disease, the majority of whom are elderly individuals.[4]

Effects on patients' quality of life, productivity, functional capacity, mortality, and use of health services	• QUALITY OF LIFE, FUNCTIONAL CAPACITY ○ Atherosclerotic CVD undermines functional capacity and independence.[12] ○ Patients with CVD present with a continuum of events that includes the presence of risk factors, angina, myocardial infarction, and ischemic heart failure, often with marked health-status deficits, including poor health-related quality of life.[17] ○ Productivity is not widely studied in this age group, perhaps because most elderly individuals are assumed to have left the workforce. • MORTALITY ○ Approximately 80 percent of people who die of CHD are elderly.[4] ○ CHD causes approximately 1 of every 6 deaths in the United States.[18] ○ 50 percent of men and 64 percent of women who die suddenly of CHD have no previous symptoms of this disease. Between 70 and 89 percent of sudden cardiac deaths occur in men, and the annual incidence is 3 to 4 times higher in men than in women; however, this disparity decreases with advancing age.[4] • USE OF HEALTH SERVICES ○ CVD greatly increases reliance on long-term care, resulting in increased health care costs.[12] ○ The annual direct and indirect cost of CVD and stroke in the United States is an estimated $297.7 billion.[4] ○ Nearly three-fourths of the total expenditures for circulatory diseases are for elderly individuals.[19]
How strongly does the overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• FACTORS IN FAVOR ○ Given the magnitude of the disease burden, there is a high potential for positive impact on a large and growing population of elderly individuals with atherosclerosis. ○ Alternative methods for the primary prevention of CVD resulting from atherosclerosis could result in significant individual and societal health care cost-savings, and improvement in elderly individuals' quality of life. • FACTORS AGAINST ○ Primary prevention through alternative approaches such as diet modification, physical activity, and smoking cessation have had limited population-level effects compared to statin therapy.[20] Future CER studies on alternative primary prevention approaches may similarly fail to identify a superior comparator to statins.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of available management options?	• BENEFITS ○ Two recent meta-analyses have studied statins for the primary prevention of cardiovascular events in elderly individuals without previous CVD. ▪ Saravese et al. (2013)[5] • 8 trials enrolling 24,674 elderly subjects (42.7% female; mean age 73.0 +/- 2.9 years). Mean follow-up was 3.5 years. • Statins, compared with placebo, significantly reduced the risk of MI by 39.4 percent (relative risk [RR] 0.61, 95% CI 0.43 to 0.85) and the risk of stroke by 23.8 percent (RR: 0.76, 95% CI 0.63 to 0.93).

	○ 24 elderly subjects without established cardiovascular disease would need to be treated with statins for 1 year to prevent one MI, and 42 would need to be treated with statins for 1 year to prevent one stroke. • Risks of all-cause death (RR: 0.94, 95% CI 0.86 to 1.04) and cardiovascular death (RR: 0.91, 95% CI 0.67 to 1.20) were favorably but not significantly reduced. This may be due to the short mean follow-up time of 3.5 years. ▪ Brugts et al. (2009)[3] • 10 trials enrolling a total of 70,388 total subjects (34% female; 23% had diabetes mellitus). Mean follow-up was 4.1 years. • Treatment with statins significantly reduced the risk of all-cause mortality (odds ratio [OR] 0.88, 95% CI 0.81 to 0.96), major coronary events (OR 0.70, 95% CI 0.61 to 0.81), and major cerebrovascular events (OR 0.81, 95% CI 0.71 to 0.93) in the overall population. • Subgroup analyses of elderly patients (age >65) showed favorable but insignificant benefits of statins in preventing all-cause mortality (OR 0.95, 95% CI 0.80 to 1.12), major coronary events (OR 0.86, 95% CI 0.67 to 1.09), and major cerebrovascular events (OR 0.79, 95% CI 0.53 to 1.18) compared with placebo. This may be due to the short follow-up time of 4.1 years. • HARMS ○ Increased cost and statin side effects exposure. ○ Statins are associated with a small increase in the risk of incident type 2 diabetes (hazard ratio [HR] 1.09, 95% CI 1.02 to 1.17).[21-24] ▪ Intensive-dose statin therapy is associated with higher risk than is lower-dose therapy (HR 1.12, 95% CI 1.04 to 1.22). ○ Statin-related myopathy is a clinically important cause of statin intolerance and discontinuation,[25-28] and may be especially disabling or dangerous in elderly patients, who are already at greater risk for falling injuries.[29] ○ Some patients also report nausea and diarrhea.[26] ○ Although statins have been linked with increased risk for cancer in observational studies,[30] subsequent studies have shown no difference in cancer risk for statin users.[6,30] ○ Caution should be exercised for elderly individuals who are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens.[2]
What could new research contribute to achieving better patient-centered outcomes?	• The current evidence base for statin use in the elderly is limited to subgroup analyses from more broadly focused RCTs, and meta-analyses of this subgroup data. • A targeted RCT studying statin-mediated primary prevention of atherosclerotic disease, specifically focusing on the elderly, could provide definitive evidence for or against the initiation of statin therapy in this age group. • Additional analyses of important subgroups of elderly individuals could provide further insight. In particular, obtaining the risk-benefit profile for individuals without a known CVD risk factor, versus those with a single CVD risk factor such as diabetes or

	hypercholesterolemia, versus those with multiple CVD risk factors, would be informative.[5] • Patient preference studies examining the quality of life of elderly patients taking statins. • Research into the impacts of polypharmacy (multiple concomitant medications).
Have recent innovations made research on this topic especially compelling?	• No recent major innovations have made new research especially compelling. • Many generic statins have recently entered the market. • There is also a long-term clinical and societal trend favoring the increased use of statins because of their highly favorable risk-benefit profile, and an increasing focus on patient subgroups such as the elderly.[2,5] • Statin therapy is one of the most heavily studied topics in cardiovascular health, and elderly health care is also a topic of high interest.
How widely does care vary?	• Guidelines support the continued use of statins for primary prevention in elderly individuals who began taking them before they became elderly.[2] • Guidelines are reluctant to recommend initiation of statins for elderly individuals with no previous history of use.[2]
What is the pace of other research on this topic as indicated by recent publications and ongoing trials?	• **Clincialtrials.gov** ○ Search: statins elderly primary prevention ▪ 16 results from search, 1 RCT of note: • A Clinical Trial of STAtin Therapy for Reducing Events in the Elderly (STAREE) • Australian study, not yet recruiting • The STAREE study will examine whether treatment with statin (atorvastatin 40mg) compared with placebo will prolong overall survival or disability-free survival among healthy elderly people (≥70 years). ○ Search: statins primary prevention ▪ Total ongoing trials: 84 ▪ Total completed trials: 97 ▪ Most concerned with differing statin drugs and/or dosage. • **NIH RePORTER** ○ Search: statins AND elderly AND "primary prevention" ▪ Three projects, all completed, same research team. ▪ All three concerned CVD risk scores for elderly individuals, not statins in particular. ○ Search: statins AND "primary prevention" ▪ 51 projects, 5 clinical trial studies, 1 active
How likely is it that new CER on this topic would provide better information to guide clinical decision making?	• An RCT for this patient population would very likely impact clinical decision making. As previously stated, guidelines are hesitant to recommend initiating statin treatment in elderly individuals who have not had previous CVD. Other than meta-analysis results, which are somewhat uncertain, there is no clear evidence to support decision making on whether or not to recommend statin therapy for the primary prevention of atherosclerotic disease in patients age 70 and older.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and	• FACILITATORS

barriers that would affect the implementation of new findings in practice?	○ Statin therapy is a well-established approach for preventing atherosclerotic CVD in younger patients and for secondary prevention.[2,4,6,7,11] ▪ Knowledge of statins' risk-benefit profile is well documented in these groups. ○ Well-studied drug ○ Generic version available • BARRIERS ○ Unclear risk-benefit profile. ○ The reduced benefit of treatment associated with aging due to the increased incidence of competing non-CVD clinical events partially offsets the life expectancy gain provided by treatment.[31] ○ Medical and social factors specific to elderly individuals and impacting on adherence to treatment must also be taken into account when considering drug prescription in this age group.[2,7,8,11]
How likely is it that the results of new research on this topic would be implemented right away?	• With sufficient evidence of favorable risk-benefit profile and cost-effectiveness, it is likely that guidelines would swiftly move to include placing elderly individuals without previous CVD history on statin therapy. Without new CER evidence, the status quo is likely to remain in place.
Would new information from CER on this topic remain current for several years or would it be rendered obsolete quickly by subsequent studies?	• New CER information would likely last for several years, as statins are a well-established therapy with proven benefits and low risk.

CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk

References for Topic 6: Comparative Effectiveness of Statin Therapy for the Primary Prevention of Atherosclerotic Disease in Patients Age 70 and Older

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TOPIC 7: What is the comparative effectiveness of genetic testing among children in whom a rare disease is suspected? Outcomes of interest include benefits/harms of genetic testing; treatment decisions; clinical outcomes; impact on patient/caregiver decision making (e.g., prognosis, testing in family members, reproductive choice); and other patient-centered outcomes"

Criteria	Brief Description
Introduction	

Overview/definition of topic	DESCRIPTION OF CONDITION[1-4]
	• As our understanding of the human genome and the genetic basis for many diseases increases, evaluation for gene alterations associated with clinical syndromes or increased risk for disease conditions is increasingly common.
	  o Such testing can be used for many purposes, including screening, diagnosis, risk stratification, and therapeutic management.
	  o Many tests are available to evaluate for the presence of genetic diseases, and this number is increasing rapidly.[3]
	  o Appropriate use of available tests, particularly newer tests, is often uncertain; genetic tests for many diseases are developed on the basis of limited data related to the condition and may not yet provide valid or useful results to individuals who are tested.[4]
	• Genetic testing and screening of minors is particularly common.
	  o "Genetic screening" refers to testing on a population basis to identify at-risk individuals – includes fetal/infant screening tests for rare metabolic, hematologic, neurologic, or endocrine system abnormalities.
	  o "Genetic testing" refers to tests seeking to confirm a particular diagnosis – these tests are performed when there is a suspicion for a genetic disorder based on screening results, family history, ethnicity, physical findings, etc.
	• This brief will focus on *genetic testing* for diagnostic purposes rather than genetic screening.

Relevance to patient-centered outcomes	SYMPTOMS[1,2]
	• Genetic diseases can have a wide spectrum of symptoms, which vary widely in severity from mild to life-threatening or life-limiting.
	  o In some cases early detection of diseases through genetic testing can impact symptoms via earlier initiation of preventive/therapeutic interventions.
	
	OUTCOMES[1,2]
	• Outcomes also vary widely in different genetic diseases.
	  o Genetic testing may impact outcomes by triggering closer surveillance and recurrence risks.

Burden on Society	

Recent incidence and prevalence in populations and subpopulations	INCIDENCE/PREVALENCE (NEW CASES vs. PROPORTION OF POPULATION LIVING WITH THE CONDITION)
	• Genetic diseases vary widely in their incidence and prevalence – they are generally relatively rare, but run in families due to their inherited nature, so individual risk depends on one's family history and ethnicity.
	• Assessment of the incidence and prevalence of some genetic diseases may be complicated by two issues:[5]
	  o Incomplete penetrance – Patients may not develop the symptoms of a genetic disease even with inheritance of a disease-causing mutation.
	  o Variable expressivity – A genetic disease may manifest with different symptoms in different patients.

Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE[2,5,6]
	• Quality of life varies with the given genetic disease in question, along with the degree to which the disease is penetrant and how it is expressed.
	• Impact on quality of life can be severe for many genetic conditions.
	• In cases where an individual is at risk for development of a genetic disease, quality of life may also be affected by uncertainty regarding his/her disease status (i.e., whether the individual actually inherited the disease-causing mutation).
	  o In such cases, genetic testing can affect quality life by reassuring the patient that they do not have the disease-causing mutation.
	  o Genetic testing may also confirm that the patient does have the disease-causing mutation, which can facilitate earlier treatment, but may also lead to worry, anger, depression, stigmatization, and discrimination.
	
	PRODUCTIVITY/FUNCTIONAL CAPACITY
	• Productivity and functional capacity vary with the genetic disease in question, along with the degree to which the disease is penetrant and how it is expressed in a given individual; in some cases productivity and functionality may be severely affected.
	
	MORTALITY
	• Mortality varies with the genetic disease in question, along with the degree to which the disease is penetrant and how it is expressed in a given individual.
	• Life expectancy is dramatically reduced for many patients with genetic diseases.
	• In many cases, genetic testing may direct patients toward available prevention, monitoring, and treatment options that can affect their prognosis.[5]

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• Although most genetic diseases are relatively rare, the cumulative impact of the many known and recently discovered genetic diseases is significant. • Genetic diseases tend to have a dramatic impact on patients' quality of life and life expectancy. • In light of the growing numbers of available genetic tests, the potential impact of genetic testing on disease outcomes and patient quality of life, and uncertainty in when and how to use genetic testing,[3] this is a potentially valuable area for comparative effectiveness research (CER). • Over $5 billion was spent on genetic testing in 2010 in the U.S., and it is estimated that this figure will reach between $15 billion and $25 billion by 2021.[7] • Of note, genetic testing was not listed by the Institute of Medicine (IOM) as a priority area in their 2009 list of 100 priorities for CER.[8]
Options for Addressing the Issue	

Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	SCREENING/EARLY DIAGNOSIS[2]
	• Genetic testing can identify individuals at risk for genetic diseases long before the onset of signs or symptoms.
	
	TREATMENT[1,2,4-6]
	• Once a genetic disease has been diagnosed, treatment options vary widely depending on the disease.
	• Early diagnosis of a genetic disease may direct a person toward available prevention, monitoring, and treatment options that can alter their disease course and prognosis.
	  o In some cases, knowledge of one's genetic disease status may help patients make decisions about having children.
	• There are also controversies regarding utilization of genetic testing in many cases:
	  o Because the genetic component of many diseases has not been fully elucidated, many genetic tests are developed on the basis of limited data so may not always provide helpful results.

	○ There are potential emotional and social consequences associated with genetic testing; people may feel anxious, depressed, or guilty about their results, and stigmatization or discrimination regarding employment or insurance can occur. ○ Because of incomplete penetrance and variable expressivity, genetic testing may be unable to determine if a person will show symptoms of a disorder, or the ultimate prognosis. ○ Many genetic diseases lack treatment options once they are diagnosed, limiting the utility of genetic testing. ○ Testing children for adult-onset disorders is controversial; professional societies recommend testing children only when they will immediately benefit from the results (e.g., clarify the etiology of current symptoms or inform treatment decisions).[2] ○ Another source of controversy in genetic testing is direct-to-consumer (DTC) advertising; while DTC genetic testing increases consumer autonomy, it increases potential for incorrect/inappropriate test utilization, misinterpretation of results, and lack of appropriate follow-up. ○ Though the prevalence of DTC genetic testing among children is unclear, professional societies strongly recommend against using DTC genetic testing for children.[1] • Anyone considering genetic testing should make an effort to understand all relevant issues prior to pursuing testing; genetics professionals can explain the benefits, risks, and limitations of a given test and empower patients in their decision-making.
What could new research contribute to achieving better patient-centered outcomes?	New research could contribute to achieving better patient-centered outcomes by: • Clarifying the relative benefits and risks/harms associated with genetic testing in particular scenarios • Informing patient and stakeholder decision-making with regard to pursuit of genetic testing • Defining important patient-centered outcomes relating to genetic testing • Clarifying situations where genetic testing can be particularly helpful (particular disease states, implications for family members, reproductive decision-making) • Identifying situations and particular tests for which genetic testing is not helpful or not cost-effective • Clarifying the impact and appropriateness of DTC genetic testing
Have recent innovations made research on this topic especially compelling?	Recent innovations:[3,4] • Genetic tests have been developed for thousands of diseases, most of which evaluate single genes and are used to diagnose rare genetic disorders (e.g., Fragile X Syndrome, Duchenne Muscular Dystrophy). • Other genetic tests look at inherited mutations in genes that protect from cancer (such as *BRCA* for breast and ovarian cancer); others are being developed to evaluate groups of genes that affect risk of common diseases like diabetes; and still others can be used to identify genetic variations affecting individuals' response to medicines. • Whole exome sequencing is now available and the cost is falling dramatically • Over 1000 genetic tests are currently in use, with many more in development.[3]
How widely does care now vary?	VARIABILITY IN CARE[9,10] • In part due to lack of knowledge regarding available tests and lack of comfort with appropriate indications, genetic testing utilization varies widely between clinicians. • Adoption of genetic testing policies and availability of genetic counseling varies between health systems.
What is the pace of other research on this topic (as	RECENT PUBLICATIONS • Performing a search of Medline for 8/2009-2014, there were 833 publications

indicated by recent publications and ongoing trials)?	possible relevant to diagnostic testing with genetic tests for rare diseases. Only 2 of these were categorized as RCTs. Twenty-five were listed as systematic reviews. ONGOING TRIALS • A search of clinicaltrials.gov for open studies focusing on genetic testing for diagnosis found 44 studies which addressed a broad range of clinical conditions including diaphragmatic hernia, pheochromocytoma, autism, cardiac myopathy, diabetes, obesity. Almost all studies were observational studies without an active comparator.
How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • Ratio of benefits vs. risks/harms associated with genetic testing in different clinical scenarios • In light of the high cost of genetic testing nationwide, the cost-effectiveness of genetic testing in different clinical scenarios is unclear. • The most important patient-centered outcomes relating to genetic testing • The clinical utility and ethics of DTC genetic testing in different clinical scenarios LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES • It is likely that appropriately designed CER comparing different strategies for genetic testing could effectively address these and other areas of uncertainty.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • There is significant public interest in genetic testing. • Wide availability of genetic testing for many disease states BARRIERS • The scientific basis for many genetic conditions is incompletely understood, making the value of some genetic tests uncertain. • Some forms of genetic testing are costly. • The likely continued availability of patient-directed DTC genetic testing may mitigate the impact of CER in some areas.
How likely is it that the results of new research on this topic would be implemented in practice right away?	EVIDENCE OF BENEFIT • Findings would be likely to be implemented widely if there is evidence for better patient-centered outcomes. EVIDENCE OF NO BENEFIT OR HARM • It is likely that research demonstrating no evidence for benefit would also impact practice by supporting current approaches.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	Though genetic testing options continue to evolve, well-designed CER addressing questions and controversies relating to genetic testing would likely have relevance for years to come.

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TOPIC 8: What is the comparative effectiveness of available treatments for Sjogren's Syndrome?

Outcomes of interest include: symptom relief; complications like rate of cancer and infection; side effects from treatments; pregnancy outcomes (e.g., rates of lupus and congenital heart block in newborns); and other patient-centered outcomes.

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION • Sjögren's Syndrome is a chronic autoimmune disease in which people's white blood cells attack their moisture-producing glands. Onset of the disease usually begins when people are in their 40s or 50s. • Sjögren's Syndrome is a systemic disease, affecting the entire body. It can present as a disease by itself (primary Sjögren's Syndrome) or in conjunction with other autoimmune conditions (secondary Sjögren's Syndrome). • Severe dry month (xerostomia) and dry eye (keratoconjunctivitis sicca) are considered the hallmark symptoms of Sjögren's; however, this syndrome may also cause dysfunction of other organs such as the kidneys, gastrointestinal system, blood vessels, lungs, liver, pancreas, and the central nervous system. • Women with Sjögren's antibodies pass these to their fetus during pregnancy and put the fetus at risk for neonatal lupus. • Sjögren's Syndrome symptoms can present like those of other conditions, thus, this disease is commonly overlooked or misdiagnosed for several years. • There is no cure for this disease and it can be very resistant to treatment. Current treatment is limited to ease symptoms.
Relevance to patient-centered outcomes	SYMPTOMS • Severe dry eyes (eyes that feel dry or burn, eyes that feel sandy or gritty, red eyes, blurry vision) • Severe dry mouth (need to drink liquids to swallow foods, difficulty talking due to dry mouth, can lead to dental problems like cavities) • Dry, itchy skin • Vaginal dryness • Joint or muscle pain • Fatigue • Unspecific neurological complaints OUTCOMES • Sjögren's Syndrome has an impact on many aspects of patients' lives including: o Impaired quality of life o Decreased daily functioning o Impaired mental health (including depressive symptoms) o Fatigue with diffuse pain o Limitations with work o Poor quality of sleep (waking frequently to take sips of water) • Other conditions more common in patients with Sjögren's Syndrome include:[1,2] • Non-Hodgkin B-cell lymphoma (RR=13.76; 95% CI 8.53 to 18.99.)[3] • Overall risk of malignancies (RR=1.54; 95% CI 1.17 to 1.88)[3] • Thyroid cancer (RR=2.58; 95% CI 1.14 to 4.03)[3] • Pulmonary fibrosis • Renal tubular acidosis • Arthritis

	• Raynaud's phenomenon • Skin vasculitis • Lymphadenopathy • Neonatal lupus in offspring of woman with Sjögren's antibodies.
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	INCIDENCE (NEW CASES) & PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION) Variability in presentation of Sjögren's Syndrome has led to variability in classification criteria for Sjögren's Syndrome. Incidence and prevalence differ depending on criteria used (e.g., Copenhagen criteria, European classification criteria, Sjögren's International Collaborative Clinical Alliances Cohort).[2] • For an autoimmune disease, Sjögren's is relatively common in adults. (Sjögren's Syndrome is very rare in children.) o A US study estimated 3.9 people per 100,000 get primary Sjögren's Syndrome per year (95% CI 2.8 to 4.9 people a year).[4] • Prevalence varies based on criteria used. o One recent systematic review reported a range of 0.21% to 2.7% for primary Sjögren's Syndrome.[2] o Prevalence of secondary Sjögren's Syndrome varies by disease:[2] • Systemic lupus erythematous (Range: 6.5% to 19%) • Rheumatoid arthritis (Range: 4% to 31%) • Systemic sclerosis (14% to 20.5%) • An estimated 10% of infants born to mother with Sjögren's (or Sjögren's antibodies) will develop a rash in the neonatal period that will resolve as the maternal Sjögren's antibodies disappear over the first 6 months of life. An estimated 2% of fetuses will develop complete heart block, with irreversible damage to their heart. This results in about 10% neonatal death. Of those children who survive, half require a pacemaker soon after birth, and a small percentage will develop heart failure and require a heart transplant as a child.[5] • Key risk subgroups: o Like many autoimmune disorders, women are at greater risk than men (Range: 9:1 to 20:1).[6,7] o Caucasians are at an elevated risk compared to other racial and ethnic groups. o Risk of Sjögren's Syndrome increases with age. For example, one study reported that people in their 70s had an 8 times high prevalence than people in their 40s.[8] o Greater risk in offspring of women with Sjögren's (or Sjögren's antibodies) [5]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE o Sjögren's Syndrome leads to functional limitations, depression, dryness, pain, disability, and is associated with other comorbid conditions, all of which can significantly affect quality of life. o Fatigue is a common, debilitating, and difficult to treat symptom that frequently impacts the quality of life. PRODUCTIVITY o Many patients with primary Sjögren's Syndrome have a chronic pain syndrome similar to fibromyalgia which can limit their ability to work. o Nearly 70% of primary Sjögren's Syndrome patients suffer from *disabling* fatigue.[9] o Patients with Sjögren's Syndrome also experience significant daytime sleepiness which likely affects productivity.[10] FUNCTIONAL CAPACITY[10]

	o Patients with primary Sjögren's Syndrome experience clinically and statistically significant functional disability compared to persons without Sjögren's Syndrome. o Patients with this disease experience more physical fatigue, pain, depression, and anxiety. MORTALITY[11] o Compared to the general population, patients with primary Sjögren's Syndrome have an increase in all-cause mortality but the comparison is not statistically significant (standardized mortality ratios = 1.17; 95% CI 0.81 to 1.63).
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• Given the significant impact on functional status, productivity, and quality of life, high priority should be given for optimizing treatments that improve patient-centered outcomes like pain, dryness, and fatigue. • Moreover, there are fetal complications of this disease that carry a heavy society burden. Congenital heart block from neonatal lupus is a costly complication that requires life-long management of pacemakers in most affected offspring.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	Evidence from recent systematic reviews exploring management of Sjögren's Syndrome:[14-16] • Sjögren's Syndrome is relatively resistant to treatment. Treatment is mainly focused on symptom relief. • There is limited comparative evidence on the relative benefits and harms of different treatments to manage the symptoms of Sjögren's Syndrome. SCREENING/EARLY DIAGNOSIS • Diagnosing Sjögren's Syndrome can be complex as many of the symptoms of this disease mimic those of other illnesses. Consequently, many patients experience significant delays in a diagnosis. • The Sjögren's Syndrome Foundation conducted a survey of patients that estimated an average time to diagnosis of 4.7 years from the onset of symptoms.[12] • Sjögren's Syndrome is diagnosed by a mix of objective and subjective test of glandular (cells that secrete bodily products) function or attaining some minimum criteria of symptoms.[13] MANAGEMENT OPTIONS[16] • Overall Approach: o Avoid drying environments (air-conditioning, wind, excessive heat). o Avoid medications that increase drying, including antidepressants, antihistamines, beta-blockers, anticholinergics, diuretics, neuroleptic medications. • Treatment of xerostomia (dry mouth): o Patient self-care though such activities as good dental hygiene, regular hydration, avoidance of overly air-conditioned or heated environments. o Sugar-free gum or candies. o Cevimeline – FDA approved for Sjögren's and is the main drug used for symptoms of dry mouth. o Three placebo-controlled trials support the use of pilocarpine for dry mouth. o One placebo-controlled trial supports use of topical cyclosporine.[17] o Emerging but poor quality evidence supports the use of herbal Chinese medicine to relieve symptoms of dry eyes and mouth.[14] o There is very little evidence to support non-pharmacological approaches to dry

	mouth. A recent Cochrane review only identified 9 RCTs that assessed the use of acupuncture, electrostimulation devices or electric toothbrushes for dry mouth. None of these studies included Sjögren's Syndrome patients. Low quality evidence supports the use of acupuncture to improve whole saliva secretion (MD 0.19 ml/minute, 95% CI 0.07 to 0.31).[15] • Treatment of dry eyes: o Artificial tears o Ocular lubricant (at night) o Punctal plugs – small plastic plugs inserted into the naso-lacrimal duct to keep tears in the eye o Ciclosporin (prescription eye drops that increase tear production) • Systemic and extraglandular symptoms (e.g., respiratory, kidney, liver, neurologic, and vascular involvement) o Treatment is tailored to the organ involved and severity of inflammation and damage in the organ. o Immunosuppressant medications (corticosteroids, hydroxychloroquine, methotrexate, azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil) • Neonatal lupus: o Studies suggest that maternal treatment with hydroxychloroquine during pregnancy for women with Sjögren's Syndrome antibodies may decrease the risk for complete heart block.[5,18] o There is no clearly defined screening protocol for fetal echocardiogram to identify early heart block changes and insufficient study of whether treatment of early heart block may prevent complete heart block.
What could new research contribute to achieving better patient-centered outcomes?	• There is little evidence that compares the benefits and harms of different types of treatments, or combinations of treatments, to manage the symptoms or fetal complications of Sjögren's Syndrome. • New research could significantly contribute to better patient-centered outcomes that target: o treatment resistant symptoms such as fatigue and chronic pain o use of therapies during pregnancy to reduce fetal complications.
Have recent innovations made research on this topic especially compelling?	There is a compelling argument for fostering comparative effectiveness research in this area, given the following: • for an autoimmune disorder, there is a high burden of disease • large burden on patient-centered outcomes (pain, functional ability) • existence of effective strategies to improve symptoms (dry mouth and dry eyes) • new biologic therapies being tested with patients that may significantly improve patient-centered outcomes • dearth of comparative effectiveness research on treatments for symptoms of Sjögren's Syndrome • emerging evidence on therapies to prevent complications in offspring.
How widely does care now vary?	VARIABILITY IN CARE • There is likely high variably in care due to the complexities in diagnosing and treating Sjögren's Syndrome. • Many patients are not offered effective prescription medications to relieve symptoms until they are seen in tertiary care settings.
What is the pace of other research	RECENT PUBLICATIONS • MEDLINE search from 1/1/2009 – 8/19/2014: total 3,322 citations

on this topic (as indicated by recent publications and ongoing trials)?	o 99 labeled as randomized controlled trials/therapy o 121 labeled as meta-analyses or systematic reviews ONGOING TRIALS • There are at least 26 ongoing studies listed in 'clinicalTrials.gov' of which, 5 appear to be studies of biologics (one new agent and 4 marketed). o
How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • What are the most important patient-centered outcomes? • What are the comparative benefits and harms of non-pharmacological approaches (electrostimulation devices, acupuncture, self-care behaviors) to managing sicca symptoms of Sjögren's Syndrome? • What are the comparative benefits and harms of pharmacological approaches to managing sicca symptoms of Sjögren's Syndrome? • What management strategy or combination of management strategies works best to manage important patient-centered outcomes (e.g., pain, fatigue)? • What are the comparative benefits and harms of different management strategies? • Are there differences in treatment effects by subgroups of patients? • What are effective strategies to foster long-term adherence to management strategies? • What are the best methods for identifying and engaging Sjögren's Syndrome patients early in the disease? • For pregnant women with Sjögren's Syndrome (or Sjögren's Syndrome antibodies), how should neonatal lupus and complete heart block be monitored during pregnancy? • For pregnant women with Sjögren's Syndrome (or Sjögren's Syndrome antibodies), what treatments reduce the risk of fetal complications? What are the comparative impact of these treatments for maternal and child outcomes? LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES • There is a high likelihood that appropriately designed comparative effectiveness studies would be able to effectively address these and other areas of uncertainty. • Understanding the best interventions in this area could improve patient-centered outcomes and standardize care for patients with Sjögren's Syndrome.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • Sjögren's Syndrome can have a profound impact on patient quality of life. Thus, patients are often motivated to engage in treatments that may improve their symptoms. • Safe, effective therapies for fatigue and chronic pain will be quickly adopted by patients and physicians. • Pregnant women with Sjögren's Syndrome are concerned about neonatal lupus and want effective approaches to prevent it. BARRIERS • Diagnosing Sjögren's Syndrome is complex and many patients experience significant delays in a diagnosis. • Many of the currently available therapies for fatigue and chronic pain lead to mouth and eye dryness, making it less likely that an effective therapies for dry mouth and dry eyes will be identified that can be used by most people with Sjögren's Syndrome. • The expense of new biologic therapies for Sjögren's Syndrome may be prohibitive for some people.
How likely is it that	• It is very likely that new guidance on the most effective treatment options to manage

the results of new research on this topic would be implemented in practice right away?	Sjögren's Syndrome symptoms and fetal complications would be implemented rapidly.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	• There are few randomized controlled trials of promising treatments for patients with Sjögren's Syndrome. It is highly likely that new information on the management of Sjögren's Syndrome will be current for several years.

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of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. Circulation. 2012; 126(1):76-82.

TOPIC 9: What is the comparative effectiveness of alternative screening options (no screening, screening) for glaucoma? Do these findings differ depending on the chosen screening test, frequency of screening, specific patient characteristics?	
Criteria	**Brief Description**
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION • Glaucoma is a leading cause of blindness[1]; it is not curable and vision, once lost, cannot be regained. • Glaucoma is characterized by damage to the optic nerve. There are two main forms of glaucoma: o Open-angle glaucoma is the most common form and characterized by progressive peripheral visual field loss (tunnel vision) and usually, though not always, is associated with elevated pressure in the eye (intraocular pressure). o Angle-closure glaucoma is less common (10% of glaucoma cases) and occurs in eyes with a certain shape. Angle-closure glaucoma may present as a painful red eye and must be treated promptly to prevent permanent blindness. • The biological basis of glaucoma and the factors that lead to its progression are poorly understood. • Certain treatments (medications, eye surgeries) can reduce risk of optic nerve damage and visual field loss compared to no treatment. Direct benefit of treatments on specific visual impairments are less clear.
Relevance to patient-centered outcomes	SYMPTOMS • Open-angle glaucoma starts with virtually no symptoms. Patients slowly loose vision over time and may not have noticeable sight loss for many years. • Angle-closure glaucoma is usually accompanied by symptoms such as decreased vision, halos around lights, headache, severe eye pain, nausea and vomiting. OUTCOMES • Glaucoma has an impact on many aspects of patients' lives including: o Impaired vision which can lead to blindness o Reduction in quality of life o Loss of independence (e.g., ability to drive a car) o Reductions in daily functioning o Increased risk of falls and fear of falling o Increased risk of motor vehicle accidents o Impacts on mental health (social isolation and depression due to blindness) o Limitations with or inability to work o Decreased ability to engage in other health behaviors (like physical activity)
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	INCIDENCE (NEW CASES) & PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION) • In the US, 2.8 million people are living with open-angle glaucoma and that the number will increase to 3.4 million by 2020.[1,2] It is estimated that 1/2 to 2/3 of people living with glaucoma do not know they have glaucoma.[3,4] • Prevalence of open angle glaucoma among Americans aged 40 and over is about 1.86%.[2] • Risk of glaucoma increases with age and approaches 4% by age 80.[2] Key risk subgroups: o African Americans are at elevated risk and have almost 3 times the age-adjusted prevalence of glaucoma than whites.[2] Compared to whites, African Americans are 6.6 times more likely to go blind from glaucoma.[5] o Hispanic populations are also at an increased risk compared to whites.[4] o Persons with a family history of glaucoma[6]

	o Patients with increased intraocular pressure o Older Americans
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE • Glaucoma causes vision loss and leads to functional limitations, disability, and lost earnings, all of which can affect quality of life.[7] • Glaucoma patients with greater visual field loss are more likely to be home-bound.[8] • Quality of life of caregivers is also impacted. As vision decreases, caregiver burden increases. PRODUCTIVITY • Glaucoma is the second leading cause of blindness in the U.S. Blindness can cause decreased workforce participation and reduced wages. FUNCTIONAL CAPACITY • Most common functional limitations include reduced vision and blindness. • Persons with glaucoma are at higher risk of falls due to impaired vision.[9] • Reduced visual field, common in glaucoma, is associated with reduced walking and physical activity.[10] MORTALITY • Studies assessing whether an increased risk of mortality is associated with glaucoma have mixed results; some studies showing an increased risk for certain groups with glaucoma (diabetics, hypertensives) and other studies finding no increased risk of death.[11] • Glaucoma may be an important contributor[12,13] to mortality due to consequences of visual impairment (i.e., traumatic injury, falls, accidents, social isolation, poor self-management of co-morbid illness).
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	While the current prevalence of glaucoma is low, the impact on functional status, productivity, and quality of life for those affected is tremendous. Also, demographic shifts towards an aging population will increase the prevalence of glaucoma over time. As glaucoma is progressive and vision impairment is irreversible, priority should be given to optimizing screening approaches that have the ability to identify patient early in the disease process so that effective interventions can be applied to slow the progression of the disease.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?[14]	Based on two systematic reviews on open angle glaucoma from AHRQ[15] and the UK Health Technology Assessment[16], we found: • Insufficient to limited evidence on the relative benefits and harms of screening for primary open-angle glaucoma in adults. • Screening methods assessed included: direct and indirect ophthalmoscopy; fundus photography or computerized imaging of the posterior pole, optic disc, or retinal nerve; pachymetry (corneal thickness measurement); perimetry; tonometry. SCREENING/EARLY DIAGNOSIS • There are several screening tools for glaucoma used either individually or in combination. Screening for glaucoma involves assessment of 1) the structure of the optic nerve, 2) functional vision loss, and 3) level of intraocular pressure. • Many patients with open angle glaucoma do not have increased IOP and not all persons with increased IOP have or will develop glaucoma. While elevated intraocular pressure is a consistent risk factor for the presence of glaucoma, several studies found intraocular pressure was lower than 22mmHg in 25% to 50% of patients with glaucoma.[16]

	• Most screening tools have a specificity of 85% or higher and no test demonstrates clear superiority.[16] • No RCTs, quasi-randomized controlled trial, cohort, or case control studies of screening have been identified in systematic reviews that assessed if screening compared to no screening or other screening improves key patient-centered outcomes like less visual impairment.[15] • While there are no direct harms of screening for glaucoma beyond local discomfort to the eyes, risks of overtreatment and overdiagnosis exist but have not been quantified. TREATMENT[17] • Treatments for glaucoma focus on decreasing intraocular pressure. • Medical therapies, laser and incisional surgical treatments decrease intraocular pressure, and reduce the risk for optic nerve damage and visual field loss compared with no treatment. • There is no clear evidence about what treatments are best for improving patient-reported vision function and blindness. • Harms of most medical treatments are minimal, but surgical treatments may have more serious complications such as vision-threatening bleeding or infection.
What could new research contribute to achieving better patient-centered outcomes?	• There are currently no RCTs comparing open angle glaucoma screening to no screening or to other glaucoma screening strategies. • Existing evidence does not allow for conclusions about the comparative effectiveness of open angle glaucoma screening tools on key patient-reported outcomes. • New research could provide evidence to support the following: o The role of early detection of glaucoma on patient-reported vision issue o Screening tool that optimizes patient-reported vision issues o How the effects of screening differ by key subgroups o Optimal sequencing of screening tools o How and where screening should be conducted o Best provider to conduct screening test o If screening is found to be effective, methods for identifying and engaging patients early in the glaucoma disease process
Have recent innovations made research on this topic especially compelling?	• Spectral domain optical coherence tomography, a common clinical tool, may perform well as an open angle glaucoma screening tool but it has not been well-tested for this purpose. This instrument is portable and non-contact and could potentially detect other eye diseases like diabetic retinopathy and macular degeneration. • There is a compelling argument for fostering comparative effectiveness research in this area, given the following: o Large burden on patient-centered outcomes (quality of life, functional ability) o Lack of high quality comparative effectiveness research on screening modalities o High quality evidence that certain treatments reduce damage to optic nerve and reduce visual impairment compared to no treatment
How widely does care now vary?	VARIABILITY IN CARE • Lack of consensus or clear evidence to support any one screening modality contributes to significant variability in care. • While the American Academy of Ophthalmology recommends regular eye exams to screen for glaucoma, only 53% of whites, 47% of African Americans, and 37% for Hispanics with self-reported vision issues report seeking an annual eye exam.[18]
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS • MEDLINE search from 1/2009 – 8/2014 targeting screening and glaucoma found 140 citations o None were randomized controlled trials addressing screening for open angle glaucoma. o One study was a systematic reviews addressing screening.[15]

	ONGOING TRIALS • There are no current studies listed in 'clinicalTrials.gov' focused on screening for open angle glaucoma
How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • What are the most important outcomes of screening for patients? • Are there stages of disease at which screening is more appropriate? • Does early detection lead to better short-term (reduced visual field, falls) and long-term (blindness, social isolation) patient-centered outcomes? • What are the comparative benefits and harms of different screening strategies? • What screening tools, combination of screening tools, and sequence of screening tools works best for identifying early glaucoma? • At what frequency should screening be offered? • What screening tools or combination of screening tools optimizes patient-reported vision issues and reduce vision impairment? • Should screening be targeted to key subgroups of patients? If so, what are these subgroups? • Do the benefits and harms of screening differ by subgroups of patients? • What are effective strategies to foster long-term adherence to effective screening modalities? • Where should screening be conducted to optimize early detection and adherence? • Who is the best provider to initiate screening tests? • Can screening for glaucoma be effectively combined with screening for other chronic eye diseases such as diabetic retinopathy and macular degeneration? • What is the best method to ensure that people who screen positive receive appropriate and ongoing care? • If screening is found to be effective, what are effective methods for identifying and engaging patients early in the glaucoma disease process? • Will screening lead to meaningful reductions in key patient-centered outcomes like impaired vision or blindness? • Should screening be conducted at a population-level or targeted based on such factors as age, family history, intraocular pressure, or race? • What screening tools optimize early detection while minimizing patient barriers to adherence? • What screening tools optimize early detection while minimizing health care systems barriers to implementation? LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES • Well-conducted CER could reduce these, and other, clinical uncertainly tremendously.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • Glaucoma is a leading cause of blindness and, thus, has a wide impact on patient quality of life, functioning, and productivity. • Patients may be motivated to engage in early detection if it reduces the likelihood of blindness. • Spectral domain optical coherence tomography screening is a recent innovation that could prove to be a better screening tool with advantages over current tools (e.g., non-contact, portable). • Medical and surgical treatments that impact intermediate outcomes exist and are well-tolerated by patients. BARRIERS • The disease is asymptomatic until the late stages.

	• There is no stand-alone test with excellent sensitivity and specificity for glaucoma diagnosis; currently multiple tests need to be performed to triangulate disease. • Screening for glaucoma is primarily conducted by eye care specialists, thus, potentially limiting access. • Certain treatments (medications, eye surgeries) can reduce risk of optic nerve damage and visual field loss compared to no treatment. Direct benefits of treatments on specific visual impairments are less clear. This uncertainty may diminish patient and non-eye care specialist enthusiasm for, and adherence to, screening.
How likely is it that the results of new research on this topic would be implemented in practice right away?	• Screening modalities are more likely to be implemented right away if they are easy to implement for both the provider and the patient. • Many payers already cover glaucoma screening as a benefit. For example, Medicare pays for glaucoma screening for high risk groups as defined as patients with diabetes, a family history of glaucoma, who are African American and 50 or older, or are Hispanic American and 65 or older.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	• CER priority areas that seek to identify best strategies for early detection of glaucoma that optimizes reductions in vision impairment are needed. • These types of findings are not likely to become obsolete quickly.

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TOPIC 10: What is the comparative effectiveness of antiviral treatments for Hepatitis C on short- and long-term outcomes? Outcomes of interest include the rate of sustained virologic response (SVR), fibrosis, cirrhosis, hepatocellular carcinoma, and other patient-centered outcomes (e.g., quality of life, functional outcomes, anxiety). Do these findings differ depending on specific patient subgroups such as patients with no/early/advanced liver disease or in specific genomic subgroups? (Note a specific interest in exploring the role of Solvadi® (sofosbuvir) as compared to other new antivirals vs older drugs.)

Criteria	Brief Description
Introduction	

Overview/definition of topic	DESCRIPTION OF CONDITION[1-3]
	• Hepatitis C virus (HCV) is a small, enveloped, single-stranded RNA virus
	• HCV is transmitted primarily through exposure to infected blood via:
	  o Injection drug use (most common means of transmission in the United States)
	  o Receipt of donated blood, blood products, and organs
	  o Needlestick injuries in health care settings
	  o Birth to an HCV-infected mother (4% of pregnancies)
	  o Less commonly, transmission can occur through sex with an infected person
	• Infection with HCV can cause both acute and chronic hepatitis (liver inflammation):
	  o Acute infection is generally asymptomatic or causes nonspecific symptoms
	  o Approximately 80% of patients with acute HCV infection develop chronic infection (as indicated by persistent HCV RNA in the blood and/or elevated liver enzyme tests reflecting ongoing inflammation in the liver)
	• Of the 6 known genotypes of HCV, genotypes 1, 2, and 3 are the most common in the United States, causing 97% of all infections
	  o Genotypes 4-6 are more common in other parts of the world (e.g., >90% of cases in Egypt are genotype 4 and genotype 5 is most common in South Africa)
	• Chronic HCV is the most common cause of cirrhosis and the most common indication for liver transplantation in the United States

Relevance to patient-centered outcomes	SYMPTOMS[1,2]
	• Acute infection with HCV is often asymptomatic
	• Among individuals with chronic infection, approximately 20-30% develop cirrhosis over a 20- to 30-year period
	• Cirrhosis means the patient has developed advanced scarring or fibrosis in the liver, and this scarring develops in response to chronic inflammation; as it progresses, cirrhosis can lead to decompensated liver disease, the symptoms of which include:
	  o Fatigue, weakness, poor appetite
	  o Ascites (large volume fluid collection in the abdomen)
	  o Esophageal varices (dilated blood vessels in the esophagus), which can lead to severe bleeding
	  o Encephalopathy (confusion caused by ammonia and other toxins in the blood)
	  o Jaundice (yellowing of the skin due to buildup of bilirubin)
	  o Gynecomastia (tender enlargement of the breast tissue)
	  o Splenomegaly (spleen enlargement)
	  o Anemia (low red blood cells), thrombocytopenia (low platelets)
	
	OUTCOMES[3-5]
	• Among the 20-30% of patients with chronic HCV developing cirrhosis, several important outcomes occur at higher rates:
	  o Decompensated liver disease: for patients with HCV cirrhosis, the 5-year probability for liver decompensation is 22.2%, with a yearly incidence of 4.4%
	  o Hepatocellular carcinoma (HCC): the 5-year probability of developing HCC is 10.1% among patients with HCV cirrhosis, with a yearly incidence of 2.0% - most cases occur in patients with advanced cirrhosis

	o Rare immune system-related complications: cryoglobulinemia, lymphoma o Mortality: the CDC estimates that 15,106 deaths were caused by HCV in 2007, and HCV-related deaths increased significantly between 1999 and 2007 as the population of patients with HCV has aged ▪ Per another report, among 200 patients with compensated cirrhosis at baseline, the probability of survival after diagnosis of decompensated HCV-related liver disease was 51% percent at 5 years
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	INCIDENCE (NEW CASES)[3] • The incidence of HCV infection is difficult to estimate because acute infection is typically asymptomatic and therefore seldom detected or reported • Per adjusted CDC estimates, ~17,000 new HCV infections occurred in 2007 PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION)[1,3] • It is estimated that 185 million individuals worldwide are infected with HCV • Approximately 3-4 million individuals in the United States have chronic HCV infection, with higher rates among men and African-Americans • The prevalence of HCV is particularly high among: o Patients born between 1945-1965 o Current or former injection drug users o Incarcerated people o Homeless people o Veterans o Recipients of blood transfusions or organ transplants before July 1992 (before testing became more rigorous) o Chronic hemodialysis patients o Patients with human immunodeficiency virus (HIV)—1/3 of HIV patients also have HCV
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE[1,6] • The sequelae of decompensated liver disease (fatigue, ascites, hepatic encephalopathy, variceal bleeding,) have a profound impact on patient quality of life • The extent to which earlier HCV infection stages may affect quality of life is debated o For example, there may be a causative link between HCV infection and depression relating to infection of brain cells • Treatments for HCV, particularly interferon (IFN) have a profound negative impact on quality of life due to both physical (constitutional symptoms, anemia, autoimmune disease) and psychological (severe depression) side effects PRODUCTIVITY[7] • Regardless of whether patients are undergoing active treatment, evidence exists that chronic HCV infection is associated with decreased work productivity and increased absenteeism; this is also the case for liver transplant recipients FUNCTIONAL CAPACITY[8] • Non-cirrhotic patients with chronic hepatitis C have lower performance on 6-minute walk testing compared to healthy controls o The explanation for this is not clear, but may relate to the symptoms (e.g., depression) patients with earlier stages of infection can experience • Patients with cirrhosis have worse 6-minute walk performance than non-cirrhotic HCV patients, and 6-minute walk in this population correlates with clinical parameters (albumin, anemia) and survival MORTALITY • If decompensated liver disease develops, mortality is dramatically increased (see

	"Outcomes" above)

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• For 2013, the total yearly cost of HCV is estimated at $6.5 ($4.3-$8.4) billion[9,10]
	  o It is predicted that this cost will peak in 2024 at $9.1 ($6.4-$13.3) billion
	  o The lifetime cost of an individual infected with HCV in 2011 was estimated at $64,490 in 2011 dollars; the lifetime cost increased to $205,760 when adjusted for medical inflation. It is significantly higher among individuals with a longer life expectancy
	• Given the costs of HCV, along with its impact on mortality, quality of life, and other important parameters, HCV treatment should be considered a high-priority target for comparative effectiveness research (CER) evaluating the impact of available treatments on patient-centered outcomes
	• Its substantial public health impact led the Institute of Medicine (IOM) to designate comparison of treatments for HCV as a priority area for CER[11]

Options for Addressing the Issue	

Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	SCREENING/EARLY DIAGNOSIS[12,13]
	• Screening and early diagnosis utilize HCV antibody tests
	• The CDC and USPSTF recommend screening the following populations for HCV:
	  o Born in the United States between 1945 and 1965
	  o History of injecting illegal drugs
	  o Received clotting factors made before 1987
	  o Received blood/organs before July 1992
	  o History of chronic hemodialysis
	  o Have evidence of liver disease (abnormal liver blood tests)
	  o HIV-infected patients
	
	TREATMENT[1,2,14]
	• The decision of when/how to treat HCV is complicated and should consider the current stage of liver disease, HCV genotype, extra-hepatic manifestations, anticipated adverse effects, patient preferences, and previous treatments attempted
	• Cure with HCV treatment is defined as a "sustained virologic response" (SVR), which is defined by undetectable levels of HCV RNA 12-24 weeks after therapy completion
	  o Data regarding the comparative effectiveness of different regimens on longer term outcomes is limited, but SVR is known to lead to reduced rates of liver-related mortality, hepatic decompensation, and the development of HCC[15]
	• Rapid changes are occurring in HCV treatment. One of the first direct-acting antivirals (DAAs), telaprevir, was recently withdrawn from the market due to advances with other medications. Agents currently available for HCV treatment include:
	  o IFN (pegylated interferon alfa-2a or -2b)—stimulate immune response to HCV
	  o Ribavirin—oral antiviral nucleoside analog
	  o Simeprevir/boceprevir (DAAs)—selective HCV protease inhibitors for genotype 1
	  o Sofosbuvir (DAA)—nucleotide polymerase inhibitor (brand name Solvaldi®) for genotypes 1-6
	  o Several more DAAs are currently in development, with the following agents expected to receive U.S. Food and Drug Administration (FDA) approval in 2014
	  ▪ Ledipasvir (NS5A inhibitor) in combination with sofosbuvir for genotype 1 infection[16,17]
	  ▪ ABT-450 (protease inhibitor boosted by ritonavir), ombitasvir (NS5A inhibitor), dasabuvir (non-nucleoside polymerase inhibitor) for genotype 1 infection[18]
	  ▪ Daclatasvir (NS5A inhibitor) and asunaprevir (protease inhibitor) for genotype 1b infection[19]

	• Recent systematic reviews have evaluated treatment options for achieving SVR with HCV, and there is mounting evidence that regimens including DAAs (particularly the newer agents, sofosbuvir and simeprevir), with or without IFN, are more effective and better tolerated than traditional IFN/ribavirin-based regimens. For example: o There is strong evidence for sofosbuvir + IFN + ribavirin for treatment-naïve patients with HCV genotype 1, and there is evidence supporting this regimen for treatment-experienced patients. o There is strong evidence for sofosbuvir + ribavirin alone for treatment-naïve or treatment-experienced patients with HCV genotypes 2 and 3 (but not genotype 1). o There is strong evidence for simeprevir + IFN + ribavirin for treatment-naïve or treatment-experienced patients with HCV genotype 1. o Though evidence is limited and the combination is not approved by the FDA, the combination of sofosbuvir + simeprevir holds promise for treatment of patients with HCV genotype 1 due to its apparent effectiveness and tolerability. o There is strong evidence for boceprevir or telaprevir in combination with IFN + ribavirin for genotype 1 patients, but these older DAAs are less well-tolerated and have more drug interactions than sofosbuvir/simeprevir. • The new DAAs currently in development are looking to be very effective and may potentially replace the above treatments. • Liver transplant is an option for patients with advanced HCV liver disease, but re-infection occurs in all patients without treatment.
What could new research contribute to achieving better patient-centered outcomes?	New research could contribute to achieving better patient-centered outcomes: • Newer regimens (e.g., sofosbuvir + simeprevir) are much better tolerated than traditional IFN-based regimens, so if confirmed in real-world practice, could have a dramatic impact on patient-centered outcomes (e.g., quality of life, productivity) • Cost-effectiveness research is needed—the cost of treatment for a patient with HCV genotype 1 may be as high as $150,000, which may impact use of newer agents[1] • CER further exploring longer term patient-centered outcomes (e.g., mortality, liver failure, HCC, hospitalization) is needed
Have recent innovations made research on this topic especially compelling?	Recent innovations: • The emergence of sofosbuvir and simeprevir, along with other DAAs in development, have dramatically changed HCV treatment • The potential replacement of even some of these new DAAs with additional agents currently in development/under FDA review • These new treatment options strongly warrant further study both in real world practice and in comparison to each other.
How widely does care now vary?	VARIABILITY IN CARE[1,20] • HCV infection is more common in African-Americans than in Caucasians • African Americans appear to have lower rates of SVR with IFN-based therapy vs. Caucasians o Preliminary evidence suggests that this difference may be reduced with sofosbuvir treatment • Limited data have been published regarding treatment of African American and Hispanic patients using regimens that include sofosbuvir or simeprevir. The scarcity of data is mostly driven by low enrollment of these groups in existing trials.
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS • A MEDLINE search from 8/13/2009 through 8/13/2014 yielded a total of 7,207 citations potentially relevant to the effectiveness of HCV treatment options. o 383 were labeled as randomized controlled trials/therapy o 325 were labeled as meta-analyses or systematic reviews o 12 were labeled as observational studies

	ONGOING TRIALS
	• A search of www.clinicaltrials.gov for open studies using the terms "hepatitis C" and "treatment" yielded 125 studies. Of those:
	  o 116 focused exclusively on HCV
	  o 19 listed sofosbuvir as the drug/intervention
	  o 3 focusing on ledipasvir in combination with sofosbuvir (planned completion late 2015) for patients with genotype 1 infection
	  o 3 targeting daclatasvir or asunaprevir for patients with genotype 1b infection (planned completion in 2015)
	  o 1 studying ombitasvir/ABT-450/ritonavir and dasabuvir in patients with genotype 1 infection (planned completion Spring 2015)
	• HCV Target (Hepatitis C Therapeutic Registry and Research Network) is a research consortium (led by University of Florida and University of North Carolina at Chapel Hill) and includes 103 academic and community sites. Investigators have established a common research database and are conducting a longitudinal observational study to answer important questions about HCV therapy with DAAs. More information is available at: http://www.hcvtarget.org/.

How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • Impact of newer HCV regimens in racially and economically diverse populations • Cost-effectiveness of newer HCV regimens • Impact of newer HCV regimens on longer term patient-centered outcomes • Comparative effectiveness of the new regimens against each other • Whether ribavirin is needed • Duration needed for hard-to-treat patients (e.g., genotype 1a with cirrhosis patients)—do they need 24 weeks? • How short can we make treatment for some patients (i.e., can it be reduced to 8 weeks? 6 weeks?) • Is HIV-HCV really different from HCV mono-infections? • Can we predict which patients with HCV will develop cirrhosis? LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES • There is a high likelihood that appropriately designed comparative effectiveness studies would be able to effectively address these and other areas of uncertainty, although longer term outcomes may be challenging to evaluate in randomized trials
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • HCV has a reasonably high prevalence (which is increasing), causes substantial morbidity and mortality, and is already considered a high-priority condition • Many treatment options exist for HCV, all of which may affect quality of life and other patient-centered outcomes in different ways • Racial disparities exist in rates of HCV, and likely in response to treatment, but there are gaps in our knowledge about the latter • Given the wide range of available treatment options and remaining areas of clinical uncertainty, CER on treatment for HCV is likely to have an important impact BARRIERS • Cost of newer agents • Difficulty of conducting trials examining longer term patient-centered outcomes
How likely is it that the results of new research on this topic would be implemented	EVIDENCE OF BENEFIT • Findings would be likely to be implemented widely if there is evidence for better patient-centered outcomes. EVIDENCE OF NO BENEFIT OR HARM

in practice right away?	• It is likely that research demonstrating no evidence for benefit would also impact practice by supporting current practice.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	Although treatment options continue to evolve, it is likely that new information regarding antiviral treatment and effects on patient-centered outcomes in different populations would remain relevant for years

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