Research Prioritization Topic Briefs

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

The Johns Hopkins Evidence Based Practice Center

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Topic 6:

Comparative effectiveness of stem cell transplantation versus immunosuppressive therapy for acquired severe aplastic anemia among children and young adults

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION[1-3] • Aplastic anemia is a clinical syndrome where the stem cells in the bone marrow fail to produce new blood. This causes a deficiency of all three blood cell types (pancytopenia): red blood cells (anemia), white blood cells (leukopenia), and platelets (thrombocytopenia). • Aplastic anemia has different severity levels defined by laboratory results. Severe aplastic anemia is defined as:[1] o Bone marrow cellularity less than 25%, or marrow cellularity less than 50% but with less than 30% residual hematopoietic cells. o Two out of three of the following in peripheral blood: neutrophils less than 0.5 $x10^9$/L, platelets less than 20 $x10^9$/L, or absolute reticulocyte count less than 20 $x10^9$/L. • Aplastic anemia can be inherited or acquired. Acquired aplastic anemia is considered an immune-mediated disease.[4] In acquired aplastic anemia, cytotoxic T cells, which have an important role in the immune system's response to infections, attack the bone marrow even though no infection is present. No one knows exactly what causes acquired aplastic anemia, and in most cases the cause is unknown. Acquired aplastic anemia is associated with exposure to infectious agents *(e.g.,* cytomegalovirus, parvovirus), nutritional deficiencies (*e.g.,* copper), drugs (*e.g.,* sulfonamides) and toxins (*e.g.,* benzene).[4] • Treatments for aplastic anemia include:[2,4] o Blood transfusions to reduce anemia, fatigue, weakness and bleeding risk. o Growth factors to stimulate the bone marrow. o Stem cell transplantation to restore the stem cells (progenitor blood cells) from the bone marrow. Stem cell transplantation can be autologous (with cells from the patient) or allogeneic (with cells from a donor). The *human leukocyte antigen (HLA)* system is used to match the donor's and recipient's system to avoid rejection. Family donors have a higher chance to match, but with the use of the bone marrow bank there is an increased chance of finding an unrelated

	match. Unmatched donors are also increasingly being used as an allogeneic source as transplantation science has improved. o Immunosuppressive treatment (IST) to control immune system activity. In aplastic anemia, the most commonly used treatments are horse anti-thymoglobulin (ATG) and cyclosporine. Less frequently used are methotrexate and steroids. • The Third Consensus Conference on the Treatment of Aplastic Anemia (2011) recommended stem cell transplantation from a matched donor (HLA-matched donor) as the standard of care for young (age < 40 years) patients. However, only 20-25% of patients will have a HLA-matched sibling. For those patients without a matched donor, or those who are not good candidates for transplant due to comorbidities or non-severe aplastic anemia, immunosuppressive therapy is recommended as the treatment of choice.[5] • The Consensus statement recommends stem cell transplantation from unrelated donors when a course of immunotherapy has not worked (*e.g.,* in the relapsed or refractory setting) and those who have other higher risk features or experience clonal evolution to myelodysplastic syndrome or paroxysmal nocturnal hemoglobinuria.[5] • With advances in transplant therapy, there is increasing interest in unmatched donors (unrelated donor peripheral blood stem cells or UD-PBSCs) and cord blood transplants (umbilical cord mesenchymal/stroma stem cells or UC-MSCs) for early treatment. • The outcomes of using unmatched donors as an early treatment was published as an abstract in 2014. The study reported on 29 patients with unrelated donor transplantation without prior immunosuppressive therapy and compared each patient with 3 matched controls undergoing HLA-matched transplantation. Outcomes at a mean of 1.6 years follow-up were not statistically significantly different, particularly for event-free survival. Patient-reported outcomes were not included in the abstract.[6] • Clinical challenges in unmatched donor transplantation include graft versus host disease (GVHD) and failure to engraft.

Relevance to patient-centered outcomes	SYMPTOMS[3]
	Symptoms depend on the type of blood cells that are affected.
	• When red cells are affected, symptoms include:
	  o Rapid heart rate
	  o Shortness of breath with exertion
	  o Weakness
	• When white cells are affected, symptoms include:
	  o Fever
	  o Higher risk of infections
	• When platelets are affected, symptoms include:
	  o Easy unexplained bruising
	  o Nosebleeds and bleeding gums
	  o Prolonged bleeding from cuts
	
	PATIENT-CENTERED OUTCOMES [9]
	• School attendance
	• Work absences
	• Hospital visits
	• Burden of time for appointments
	• Opportunistic infections
	• Caregiver burden.
	• Worries about bleeding and infection
	• Stress from dependence on blood and platelet transfusion
	• Social burden of needing to avoid crowds and other people due to infection risk
	• Burden of travel, since patients often need to be treated at large centers and the burden of travel is significant.
	• Burden to the entire family because the illness often affects the young.
	• Disparities in care since minorities are less represented in donor registries and more likely to have blended families with a higher prevalence of unmatched donors
	• Disparities for families with fewer financial resources with the expensive and burdensome caregiving and health care needs

Burden on Society	
Recent prevalence in populations and subpopulations	INCIDENCE AND PREVALENCE[3] • Acquired aplastic anemia in children and young adults is rare. Only 2 of every 1 million children aged 15 and younger are diagnosed each year. About 500 children in the United States are diagnosed annually.[10] • Boys and girls are equally affected. • There is no data on the prevalence of acquired aplastic anemia in different races, but studies have shown that African-Americans have lower survival rates after transplantation as well as higher incidence of GVHD. This may be explained by a lower availability of donors within the family and the low numbers of minority donors in the bone marrow bank.[11]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• Children with aplastic anemia are presumed to have a lower quality of life compared with children without aplastic anemia, although there are no studies addressing this issue. • Given patients' young age, caregiver burden and lost work productivity are significant. • Treatment is time-consuming and stressful. Time burden and quality of life issues are different for the two treatment modalities. Successful transplantation without complications results in a short-term burden on quality of life. Immunosuppressive therapy that does not completely resolve the symptoms results in a burden on the quality of life for the duration of treatment. • Symptomatic and curative treatments are expensive and burdensome in health care services. In 2012 there were 1,850 children admitted to hospitals with diagnosis of aplastic anemia in the U.S. with an average hospital stay of 9 days. The inpatient care cost was 67 million dollars (about $36,000 per child).[12] There is no economic data on the cost burden for outpatient care. • Transfusions are a significant societal burden on the blood supply, especially platelets, which are a limited resource. • Adolescent patients often need to transition from pediatrics to adult medicine, which can be burdensome and challenging for patients and families. • If untreated, severe aplastic anemia can be fatal. Mortality rates depend on treatment response and complications (*e.g.,* graft versus host disease, infections).

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• Even though aplastic anemia is a rare condition, it has severe complications, can be deadly and has significant quality of life consequences. • Young patients often have a lifetime of frequent and burdensome complications and treatments such as transfusions. • Research findings may be applicable to other bone marrow failure syndromes, such as those that are inherited or in the elderly.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	• A 2012 review from the Evidence-based Practice Center Program addressed the effectiveness of stem cell transplantation in the pediatric population, but did not focus on aplastic anemia and did not systematically review this literature.[13] • Stem cell transplantation of matched sibling donors compared with immunosuppressive therapy (cyclosporine and/or antithymocyte or antilymphocyte globulin) for acquired severe aplastic anemia was addressed in a 2013 Cochrane systematic review.[10] Randomized controlled trials (RCTs) and non-randomized studies were eligible if allocation of patients to treatment groups was consistent with Mendelian randomization (the view that nature itself has already 'randomized' the paternal and maternal part of a gene given that donor and recipient are siblings). No RCTs were identified. Only 3 non-randomized studies met the inclusion criteria, and all studies had significant limitations. The pooled hazard ratio for overall mortality for transplantation compared to immunosuppressive therapy was 0.95 (95% confidence interval 0.43 to 2.12). All data were collected more than 10 years ago, and treatment-related mortality was very high for transplantation (20-42%). No studies reported quality of life. The review concluded that the data was insufficient to support any conclusions about the comparative effectiveness of the interventions. • A systematic review included 26 non-randomized studies of matched transplantation compared to immunotherapy. In a meta-analysis of the 19 studies reporting on overall survival, the study reported too much heterogeneity to conduct a pooled analysis. Effect estimates ranged from 0.19 to 2.89. Recent year of treatment and young age were associated with better survival in the transplantation group.[14] • No reviews have addressed unmatched donor transplantation.

What could new research contribute to achieving better patient-centered outcomes?	• High-quality comparative effectiveness research involving multiple centers to create sufficiently large studies will be important as more unmatched donor transplantations are conducted and interventions and outcomes for unmatched donor transplantation continue to improve. • There is a need for research in minorities and mixed races and the impact of the availability/unavailability of donors for these patients within their families or bone marrow donors. • Examining patient-reported outcomes in addition to mortality is needed.
Have recent innovations made research on this topic especially compelling?	• The continued improvements in supportive care for transplantation as well as graft-versus-host disease prophylaxis allow unmatched donor sources to be used with less morbidity and may make unmatched donor transplantation an increasingly viable option for these patients. In the recently published comparison of matched compared to unmatched donor transplantation, outcomes at a mean of 1.6 years follow-up were not statistically significantly different between groups, particularly event-free survival.[6] • Some new research addresses better treatments for refractory aplastic anemia, but studies are small and advances modest.[7] • Researchers have recently developed a disease-specific quality of life questionnaire for aplastic anemia and/or paroxysmal nocturnal hemoglobinuria through a rigorous process. This will be evaluated as part of an ongoing prospective study.[8]
How widely does care now vary?	• Matched donor transplantation is the standard of care for patients where this option is available. The prevalence of different treatment options is not known.
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	We did not identify any relevant studies in NIH reporter. We identified no trials in Clinicaltrials.gov comparing transplantation to immunosuppressive therapy. We identified several relevant ongoing studies of transplantation in Clinicaltrials.gov: • NCT01364363 is a non-randomized open-label efficacy study of unrelated donor transplantation for multiple disorders, including aplastic anemia, which started in 2005 with an estimated completion year of 2023 and anticipated enrollment of 50. • NCTT02224872 is a Phase II trial of non-myeloablative conditioning and transplantation of partially HLA-mismatched/haploidentical related or matched unrelated bone marrow for patients with refractory severe aplastic anemia and

	other bone marrow failure syndromes. The primary outcome is whether this type of transplantation is feasible and safe (survival one year after transplant). Patient-reported outcomes are not included. The estimated enrollment was 20 and the trial will be completed in 2019. • A new trial is being developed of haploidentical versus cord donor transplant in patients with refractory aplastic anemia, who have very high mortality; this will not open for another year.
How likely it is that new CER on this topic would provide better information to guide clinical decision making?	• Additional studies in other populations evaluating outcomes of unmatched donor transplantation would help to guide decision-making and when transplantation is appropriate. • How best to treat patients with refractory disease is a key unresolved issue that could be addressed by comparative effectiveness research. If patients fail immunosuppressive therapy, the next best option is transplantation. Those patients who are unable to move forward for transplantation and meet criteria for severe aplastic anemia have high mortality, most often due to infection.
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: • Treatment is conducted by a small number of clinicians at select institutions, so diffusion would not be an issue as long as the clinical community has a stake in the research process. BARRIERS: • Transplantation is expensive and may be challenging for some patients.
How likely is it that the results of new research on this topic would be implemented in practice right away?	• Treatment is already standardized for treatment-naïve patients with matched donors. • Practice is already changing towards increased use of unmatched donors.
Would new information from CER on this topic remain current for several years?	• At this point, stem cell transplantation is likely to be the standard treatment for patients with matched donors for many years.

References for topic 6: Comparative effectiveness of stem cell transplantation versus immunosuppressive therapy for acquired severe aplastic anemia among children and young adults

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Topic 7:
Comparative effectiveness of early therapy versus observation for monoclonal gammopathy of undermined significance in the prevention of multiple myeloma

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION[1-3] • Multiple myeloma (MM) is a malignant proliferation of a single clone of plasma cells that results in the monoclonal production of immunoglobulin (cytogenetically heterogeneous clonal plasma cell proliferative disorder). • MM is classified as asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ or tissue dysfunction. Target organs and typical dysfunctions are extensive skeletal destruction, infections, anemia, hypercalcemia, and renal failure. Hypercalcemia, renal failure, anemia and bone lesions are referred to as CRAB features. • Research suggests possible associations with immunosuppression, certain occupations, exposure to certain chemicals, and exposure to radiation and some genetic factors. However, there are no strong connections. • MM is almost always preceded by an asymptomatic premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS). MGUS is defined by the presence of a serum monoclonal protein (M-protein), at a concentration less than 3 g/dL, bone marrow with less than 10% monoclonal plasma cells (if done), and no end organ damage (although osteoporosis may be present and in some cases neuropathy). The rate of progression of MGUS to MM is 0·5–1% per year. • Smoldering multiple myeloma is an intermediate clinical stage between MGUS and MM – defined as having more than 10% plasma cells without evidence of bone disease - in which the risk of progression to malignant disease in the first 5 years after diagnosis is much higher, at about 10% per year; there are defined risk criteria for progression. • MGUS is present in 3–4% of the population over the age of 50 years. • The diagnosis of MGUS requires the absence of CRAB features that can be attributed to the underlying plasma cell disorder (all features must be absent). • About 80% of MM originates from MGUS involving immunoglobulins other than immunoglobulin M (non-IgM MGUS), and 20% from light-chain immunoglobulin MGUS (LC-MGUS). In the event of progression, IgM immunoglobulin MGUS (IgM

	MGUS) usually evolves into Waldenström macroglobulinaemia, but in rare instances IgM MGUS can progress to MM (IgM myeloma). • The precise risk of progression is affected by the concentration of the monoclonal protein, type of monoclonal protein, serum free light chain ratio, bone marrow plasmacytosis, proportion of phenotypically clonal plasma cells, and presence of immunoparesis (the decreased levels of immunoglobulins in the blood). • In recent years, the introduction of autologous stem-cell transplantation and the availability of multiple new effective agents such as thalidomide, lenalidomide, and bortezomib have changed the management of myeloma and extended overall survival. • Current guidelines recommend immediate treatment of symptomatic (active) disease and clinical observation for smoldering myeloma and MGUS. However, recent research suggests that immunomodulatory drugs may delay the progression to symptomatic myeloma in high-risk smoldering myeloma. A recent trial of lenalidomide plus dexamethasone [4] showed potential benefit, although this was a small study with a number of flaws, and even high-risk smoldering myeloma is not generally being treated in clinical practice. • The treatment strategy is mainly related to age. It has been shown that treatment in early phases is more effective since clones are more sensitive, remissions are more frequent and long-lasting, and patients are less susceptible to adverse events.[5]
Relevance to patient-centered outcomes	SYMPTOMS of multiple myeloma[6] • Bone pain or bone fractures • Peripheral neuropathy • Fatigue • Increased vulnerability to infections • Increased or decreased urination • Restlessness – eventually followed by extreme weakness and fatigue • Confusion • Increased thirst • Nausea and vomiting • Loss of appetite and weight loss • Impaired kidney function • Dehydration

	PATIENT-CENTERED OUTCOMES • Pain (from bone compromise) • Impaired functional status and quality of life • Adverse effects of treatment, such as neuropathy, fatigue, cytopenias, deep vein thrombosis, and gastrointestinal toxicity • Need for supportive care
Burden on Society	
Recent prevalence in populations and subpopulations	INCIDENCE AND PREVALENCE[2,7] • MM accounts for nearly 1% of all cancers and for approximately 13% of all hematologic malignancies. • The annual incidence in the U.S. ranges from 4 to 6 cases per 100,000 persons. • The incidence increases with age; the median age of diagnosis is 66 years old and it is very rare in individuals under the age of 40 years. • In 2012, there were 18,435 hospitalizations in the U.S due to MM; 45% of these patients were between 45 and 65 years old, 50% were older than 65 years, and 55% were male.[8] • Incidence in African–Americans is 2–3 times that in Caucasians. • Significant disparities in access to care and use of stem cell transplantation exist dependent on demographic, social, and geographic factors. • After transplantation, all races have similar outcomes.[9]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• Even with treatment (including transplantation), the MM often causes significant quality of life issues due to fractures and other complications. • Many patients are older when they develop MM and may not be eligible for transplantation. • Treatments for MM are expensive and use large amounts of health care services.
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	Although MM is rare (only 1% of all cancers), MGUS is common affecting 3-4% of the population over the age of 50. Even if progression from MGUS to MM is rare, at 1% a year, MGUS affects a significant proportion of the population; therefore, there is a need to identify patients at higher risk and evaluate alternative approaches to prevent progression.

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 systematic reviews addressing treatment to prevent progression of MGUS to MM. • The National Comprehensive Cancer Network (NCCN) guidelines do not address progression from MGUS and do not recommend treatment to prevent progression in Smoldering MM – although enrollment for SMM in clinical trials is strongly recommended and multiple clinical trials are available or in development.[10] • The updated guidelines cite one study that evaluated reducing progression in smoldering myeloma.[7] This was a Phase III randomized trial of lenalidomide plus dexamethasone in 119 patients with high risk SMM that showed significant prolongation of time to progression, and improved 3-year survival (94% vs 80%, p=0.03); toxic effects were mainly grade II (moderate severity).[4] However, this study had a number of limitations, including issues with the diagnostic criteria (some patients in this study actually had myeloma), concerns about assessment of study outcomes, and use of diagnostic testing for high-risk myeloma that is not generally available. In addition, treatment had side-effects (such as blood clots) and was not curative. • There is one randomized trial of curcumin (from turmeric). This study had 36 patients, of which 19 had MGUS (others had smoldering multiple myeloma).[11,12]However, the curcumin potential benefit was likely too small to justify further clinical trials, and the outcome was response measured in paraprotein levels, not survival.
What could new research contribute to achieving better patient-centered outcomes?	• Even in patients with high-risk MGUS, studies of alternative management strategies will need long-term follow-up and large numbers of patients to demonstrate a meaningful difference in survival and quality of life. • Studies of alternative management strategies would ideally focus on high-risk (smoldering myeloma) as the risk of progression in low-risk MGUS is low and would need a very large sample size to show a difference between management options. • Since there are not yet studies showing evidence of efficacy for treatment in smoldering myeloma, it is harder to justify studies of treatment for MGUS, especially since MGUS is mostly asymptomatic and new treatments are likely to be very expensive or have significant adverse effects. • Patient-reported outcomes have not previously been well-integrated into the evaluation of treatment alternatives, including concerns about progression and side-effects of treatment.

Have recent innovations made research on this topic especially compelling?	• There are no innovations in treatment that specifically target MGUS. However, as multiple new agents are being developed for myeloma, it is possible that some will have potential for treatment of MGUS in the next few years, although, as described above, the risk of progression is low and treatments are very expensive and have side-effects.
How widely does care now vary?	• Currently there is little variation in treatment. Guidelines recommend against treatment unless symptomatic (active) disease and clinical observation for smoldering myeloma and MGUS. • Guidelines recommend that all patients with MGUS should be risk-stratified, and that patients with low-risk MGUS can be monitored symptomatically or with blood testing. The monitoring of MGUS patients is therefore likely quite variable.[13]
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	There is a small to moderate amount of ongoing research on treatments for MM and smoldering MM, but no ongoing research on MGUS Our search on Clinicaltrials.gov retrieved the following studies: <u>Actively recruiting:</u> • More than 400 studies are actively recruiting for MM with different types of interventions (e.g. steroids, immunotherapy, transplantation), different phases of the disease, and different designs (RCTs, observational studies, databases). • There are 10 studies for smoldering myeloma with similar interventions, but none for MGUS. <u>Not actively recruiting</u> • NCT00099047 - Celecoxib in Preventing MM in Patients With Monoclonal Gammopathy or Smoldering Myeloma; Phase II; secondary outcomes (serum levels) (Started 2004) • NCT00942422 - Green Tea Extract in Treating Patients With Monoclonal Gammopathy of Undetermined Significance and/or Smoldering Multiple Myeloma, Phase II, serum levels (Started 2009) <u>Terminated:</u> • NCT00899353 - Prevention of Disease Progression in Early Stage Indolent B Cell Malignancies, Omega 3 fatty acids <u>Completed (no results):</u> • NCT00006219: A Phase II Clinical Trial of Dehydroepiandrosterone and Biaxin in Monoclonal Gammopathy of Undetermined and Borderline Significance. Most patients had smoldering myeloma in this uncontrolled study.[14] Our search on NIH reporter retrieved no clinical trials for treatment of MGUS.

How likely it is that new CER on this topic would provide better information to guide clinical decision making?	• CER is unlikely to lead to new information on treatment of MGUS at this time. • If ongoing research identifies biomarkers that identify patients at high risk of progression to myeloma, reevaluation of CER on monitoring or potential treatment might be indicated.
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: • MM is a serious illness that many would want to prevent. • Patients are concerned about MGUS, but they usually accept that it is unlikely to lead to cancer once appropriate education is provided. BARRIERS: • Patients with MGUS are asymptomatic, and are likely to be reluctant to take treatments that have known adverse effects. • MGUS is often undetected, given that guidelines do not call for routine screening for MGUS in the absence of symptoms or signs suggestive of myeloma. • MGUS often is followed by primary care providers without a referral to a specialist. • Treatments for myeloma are very expensive and have significant adverse effects – so it would be difficult to justify using them for long-term treatment of MGUS.
How likely is it that the results of new research on this topic would be implemented in practice right away?	It is unlikely that new research will show a benefit of treating MGUS, but if new research showed a benefit of a specific approach to monitoring of MGUS, clinicians could adopt a new approach without too much difficulty.
Would new information from CER on this topic remain current for several years?	If new CER is done, new information is likely to remain current for several years given the modest amount of research being done on management of MGUS.

References for topic 7: Comparative effectiveness of early therapy versus observation for monoclonal gammopathy of undermined significance in the prevention of multiple myeloma

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Topic 8:

Comparative effectiveness of second-line drug therapies after failed metformin use (sulfonylureas, meglitinides, thiazolidinediones, acarbose, incretin agents, etc.) in type 2 diabetes treatment

Suggested/Modified Topic 8: Comparative effectiveness of second-line drug therapies after metformin use for the treatment of type 2 diabetes

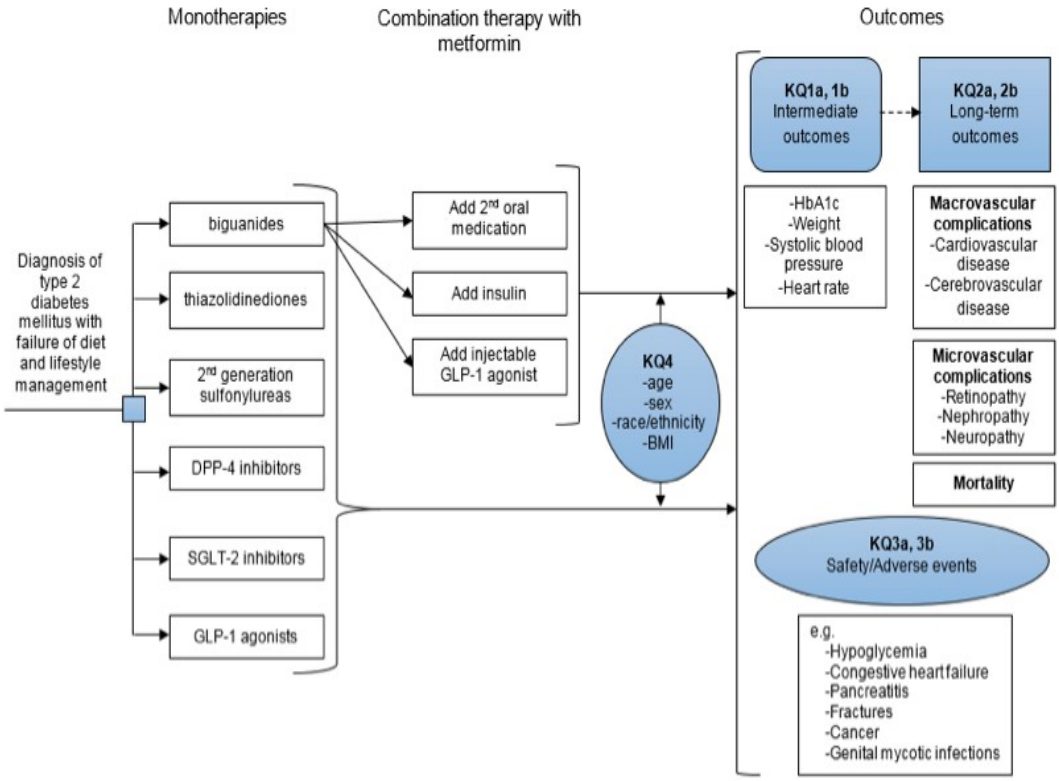
Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION • Type 2 diabetes is a condition of insulin insensitivity that causes higher than optimal blood glucose concentrations. The excess glucose causes a pro-inflammatory state leading to dyslipidemia resulting in increased cardiovascular disease risk;[1] pancreatic beta cell death; and death of pericytes, which line capillaries of endothelial cells.[2-4] When endothelial cells are damaged, the tissue does not receive adequate blood supply resulting in retinopathy, nephropathy and neuropathy. • The treatment of patients with type 2 diabetes usually begins with lifestyle modifications, such as changes to diet and exercise, and treatment with metformin, an oral medication that lowers glucose by reducing the production of glucose in the liver and helping with muscle uptake of glucose.[5 6] • When lifestyle modifications and metformin are insufficient to control the amount of glucose in the blood (as measured by Hemoglobin A1c), additional medications are added. Additional drug classes to lower glucose include:[7] **Oral treatments** o Sulfonylureas o Meglitinides o Thiazolidinediones o Dipeptidyl peptidase-4 (DPP-4) inhibitors o Sodium- glucose cotransporter 2 (SGLT2) Inhibitors o Alpha-glucosidase inhibitors o Bile acid sequestrants

	Other treatments o Injection treatments ▪ Insulin ▪ Glucagon-like peptide-1 (GLP-1) receptor agonists o Inhaled treatments ▪ Insulin • Approximately 60% of patients with type 2 diabetes are started on metformin monotherapy. Forty-five percent of patients who initiate metformin will require intensification of anti-hyperglycemic therapy within a year of first use.[8] • Existing guidelines do not clearly indicate which drug should be added if metformin alone is insufficient for controlling blood glucose concentrations or which drug should replace metformin if metformin is discontinued because of side-effects. • Existing guidelines and recommendations vary for these second-line treatments (after metformin is insufficient).). o The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) joint guidelines recommend a GLP-1 receptor agonist or a basal insulin as the second-line agents of choice. The guideline provides no suggestion on which medication should be added or what to do to replace a GLP-1 receptor agonist or basal insulin if they too are insufficient to normalize glucose levels.[6] o The American Association of Clinical Endocrinologists recommends a GLP-1 receptor agonist or a DPP-4 inhibitor in combination with metformin.[9] o The International Diabetes Federation recommends sulfonylurea, a glucosidase inhibitor, a DPP-4 inhibitor or a thiazolidinedione as second-line agents with metformin.[10,11]
Relevance to patient-centered outcomes	SYMPTOMS • Symptoms and signs of type 2 diabetes include increased urination, increased thirst, unexplained weight loss, fatigue, blurred vision, increased hunger, and sores that do not heal.[12] PATIENT-CENTERED OUTCOMES • When treatment with metformin fails, symptoms and signs remain the same or increase, and patients are likely to develop complications such as • Decreased quality of life • Hyperglycemia

	• Cancer
	• Cardiovascular disease
	• Cognitive impairment
	• Depression
	• Fatty liver disease
	• Fractures
	• Gastroparesis
	• Hearing impairment
	• Low testosterone in men
	• Nephropathy
	• Neuropathy
	• Obstructive sleep apnea
	• Periodontal disease
	• Retinopathy
	• Vision loss.[13,14]
	• The complications of diabetes have profound effects on normal living.
	  o The neurologic complications result in burning foot pain, difficulty walking, and falls.
	  o Vision loss affects the ability to do daily tasks like preparing meals for one's family.
	• The need for dialysis is very time consuming and many patients fear that once they are on dialysis that they are near death.[15,16]
	•

Burden on Society	
Recent prevalence in populations and subpopulations	PREVALENCE • In 2012, 29.1 million Americans (9.3% of the population) had type 2 diabetes. About 1 in 3 individuals with diabetes had not been tested or told by a doctor that they had diabetes as estimated from glucose measurements performed as part of a national survey on the health status of Americans. [18] • There were 1.7 million new cases of diabetes in 2012.[18] • There is no difference in type 2 diabetes prevalence between males and females. • American Indians and Alaska Natives are the population with the highest rate of diabetes (15.9%), followed by non-Hispanic blacks (13.2%) and Hispanics (12.8). Whites have the lowest rate of type 2 diabetes (7.6%).[18] • Approximately 60% of patients with type 2 diabetes are started on metformin

	monotherapy. Forty-five percent of patients who initiate metformin will require intensification of anti-hyperglycemic therapy within a year of first use. Intensification includes increased dose of metformin or the need of two or more drugs to achieve adequate glycemic control. The characteristics of patients requiring intensification (including change in dose or need for additional treatments) is described in the SUPREME-DM study.[8] o Younger age at first treatment use was a predictor of the need for intensification of treatment. Individuals aged 80 and older were less likely to increase dose or add additional treatments even with high A1c levels. o Women are more likely to intensify treatment than males. o Whites are more likely to intensify treatment than other races. o Past and current smokers are more likely to intensify treatment than never smokers. • Individuals who were adherent to the initial treatment (>90% proportion of days covered/medication possession ratio) were more likely to intensify.
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• The effects on quality of life, productivity, functional capacity, mortality and use of health care services for individuals who require second-line therapy are not well described. Presumably individuals who require second-line therapy have worse profiles for each of these outcomes than patients who do not require second-line therapy. • People with type 2 diabetes have decreased quality of life compared with the general population. Those who require oral medications for treatment have a decreased quality of life compared with those able to maintain their glucose levels with lifestyle modifications alone.[19] • Diabetes is the 7th leading cause of death in the U.S. Diabetes may decrease life expectancy by 10 to 15 years.[20,21] • Diabetes affects productivity. Of the $245 billion annual costs of diabetes (in 2007), $176 billion was due to direct medical costs and $69 billion was due to indirect costs including decreased productivity.[22] • Of the direct medical costs, 50% was spent on inpatient care.[22] • The numerous complications of type 2 diabetes affect functional capacity and use of health care services.

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• Type 2 diabetes affects nearly 10% of the population, is very expensive to manage, results in premature death and is expected to increase in prevalence by 2050.[23] • Sixty percent of patients with type 2 diabetes require a second-line treatment.[8] • To help patients decide between the numerous treatment options for second-line treatments, personalized medicine plans or options could be developed. The personalized treatment plans should incorporate patient preferences in addition to signs and symptoms.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	• AHRQ's Evidence-based Practice Center Program is currently updating its report on medications for type 2 diabetes. There are 4 key questions including the effectiveness of treatments on intermediate outcomes, long-term outcomes, safety, and the effectiveness and safety in subpopulations (Figure). Figure. Conceptual Model of the Systematic Review in Process (AHRQ EPC Program) 

	The draft report associated with the review includes 229 studies, published in 249 articles including monotherapy comparisons and the combination therapy comparisons relevant to this topic. The draft results (which may change modestly with inclusion of the most recent literature) relevant to metformin in combination with another therapy include: o *Combination therapy with metformin generally reduces hemoglobin A1c by 0.7 to 1 absolute percentage point compared to metformin monotherapy (Moderate to High strength of evidence, depending on the second-line treatment)* o *Metformin and the combination of metformin plus a DPP-4 inhibitor are associated with similar all-cause mortality.* o *The scant evidence on the comparative effectiveness of diabetes medications and microvascular outcomes (retinopathy, nephropathy, and neuropathy) precludes any substantive conclusions.* o *Metformin plus a GLP-1 agonist is associated with more gastrointestinal side-effects compared to metformin plus a thiazolidinedione or metformin plus a sulfonylurea.* o *Rates of pancreatitis are similar for metformin monotherapy and metformin plus a DPP-4 inhibitor.* o *There is little evidence about cancer risk.* o *Evidence on other adverse events including fractures, renal impairment, liver injury, lactic acidosis, macular edema, decreased vision, and severe allergic reactions was not conclusive in this report.* *The evidence on the comparative effectiveness of diabetes medications in subgroups defined by age, sex, race/ethnicity, and body mass index is considered inconclusive in the report.*

What could new research contribute to achieving better patient-centered outcomes?	• Understanding the efficacy, safety, patient preferences and ideal placement of the approved medications in the type 2 diabetes treatment algorithm is needed and makes research on this topic very compelling. • New research should focus on the safety of second-line treatments so that patients can make informed decisions about which treatment is best for them, given the comparable short-term efficacy of the available treatment combinations. Evidence on long-term effectiveness and safety is still needed. • Studying the patient-identified benefits, like decreased fear of walking or ability to participate in the preparation of family meals, in addition to measuring health care provider important benefits like hemoglobin A1c control, may help patients make better treatment decisions based on what is most important to them. • A systematic review of 10 studies evaluated patient preferences for selecting type 2 diabetes treatments, including second-line treatments. The authors reported that glycemic control, weight loss, weight maintenance, and the risk of treatment-related hypoglycemia and gastrointestinal effects are important drivers of patient treatment preferences. The systematic review noted that future work is needed to identify practical methods to incorporate patient preferences into treatment decision-making and patient-centered care.17
Have recent innovations made research on this topic especially compelling?	• The type 2 diabetes drug development pipeline is very active. In 2014, there were 180 medications in development.[24] • A PCORI-funded study *Advancing Stated-Preference Methods for Measuring the Preferences of Patients with Type 2 Diabetes* is currently comparing innovative methods to examine patient preferences with regard to diabetes medications. The preferred medications and the method of identifying preferences could be incorporated into future research.

How widely does care now vary?	• Over 100 million people from around the world are prescribed metformin each year.[5] Sixty percent of these people will require a second-line agent.[8] • In the U.S. based cohort study SUPREME-DM, within a year of initial treatment for type 2 diabetes, 55% of patients remain on the first oral treatment, 35% increase the dose of the initial treatment (35%), 8% added a second oral agent, 2% increased the dose and added a second oral agent and less than 1% switched to insulin.[8] • In the U.S. Medicare population and the United Kingdom's General Practitioner Research Database, metformin combined with sulfonylurea is the most common combination therapy. [25,26] The time periods of these studies were prior to the guidelines indicating that GLP-1 receptor agonists and basal insulin are the preferred second-line agents.
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	• The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Heart, Lung, and Blood Institute (NHLBI), Becton, Dickinson and Company, Bristol-Myers Squibb, Merck Sharp & Dohme Corp., Novo Nordisk A/S, Hoffmann-La Roche and Sanofi are currently funding a comparative effectiveness study to examine second-line treatments for diabetes when metformin alone is unable to control glucose levels. This public-private funded study is called Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). This study is registered in ClinicalTrials.gov as NCT01794143.[27] o GRADE is a randomized clinical trial of participants diagnosed with type 2 diabetes within the past 10 years who are already on metformin. Participants are randomly assigned to one of 4 commonly-used glucose-lowering drugs (glimepiride, sitagliptin, liraglutide and basal insulin glargine), plus metformin, and will be followed for up to 7 years. o The goal of the GRADE Study is to determine which combination of two diabetes medications is best for achieving good glycemic control, has the fewest side-effects, and is the most beneficial for overall health in long-term treatment for people with type 2 diabetes. o As of March 1, 2015, over 1,000 patients have been randomized from 44 nationwide sites. <u>ClinicalTrials.gov</u> • Our search of ClinicalTrials.gov in March 2015 identified 121 open studies that compare at least 2 drugs for type 2 diabetes and include metformin. Only 12 of these include a safety outcome of interest, often included as a primary outcome for

	"safety and tolerability" without specifying a safety outcome or focusing on hypoglycemic events (NCT02366377; NCT00658021; NCT02151461; NCT01766778; NCT02025907; NCT02280486; NCT01933256; NCT02053272; NCT02205528; NCT02000700; NCT02367066; NCT00964184). These studies are short-term safety studies; none is greater than 1 year in duration (NCT01766778). The 1-year trial of vildagliptin as a second-line therapy includes overall safety and death as the pre-specified safety outcome (NCT01766778). Vildagliptin is not currently approved by the FDA. <u>NIH Reporter</u> • Our search of NIH Reporter identified 614 studies related to type 2 diabetes, and 110 trials related to comparative effectiveness. Type 2 diabetes research is active within NIH. The GRADE trial funded by NIH is most similar to the topic.
How likely it is that new CER on this topic would provide better information to guide clinical decision making?	• The GRADE study does not include safety as a primary outcome. The results of the ongoing systematic review funded by AHRQ indicate that safety is a priority. Combining the systematic review recommendation with the absence of a primary safety outcome in the GRADE study indicates that CER to improve clinical decision making should focus primarily on safety. • Information combining patient preferences with effectiveness and safety to personalize treatments among the many second-line treatment options is 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: • Many patients require second-line treatment. Information to guide health care providers, patients and payers to the best treatment will be implemented right away. BARRIERS: • The drug development pipeline for diabetes is increasing rapidly. Identifying large, representative datasets or populations for study and rapid publication is needed to provide the most up-to-date information to stakeholders. These data sources may be rare. Even when they do exist (such as SUPREME-DM, a multi-site type 2 diabetes consortium), there may be a delay in use of new medications pending evidence about safety concerns, especially long-term safety concerns like cancer or vision loss. • If new medications are much more expensive than metformin and the existing

	treatment options, they may not be covered by all health care plans and will remain inaccessible to many patients
How likely is it that the results of new research on this topic would be implemented in practice right away?	• It is very likely that results will be implemented in practice right away because so many patients require second-line treatment for type 2 diabetes. The Standards of Medical Care guidelines are updated annually which will facilitate implementation.
Would new information from CER on this topic remain current for several years?	• Bariatric surgery and insulin pumps are emerging treatments for type 2 diabetes. Neither of these treatment options is likely to replace oral and injection based treatments in the near future. • Studies on the safety of medical treatments compared to each other or bariatric surgery or insulin pumps are unlikely to be rendered obsolete. • CER focusing on effectiveness may be largely duplicative with the ongoing GRADE study funded by NIH unless the CER uses new modifications on pragmatic trial design to generate important "real world" effectiveness information.[28] New CER should clearly identify intentional overlap with the GRADE study (to independently confirm findings) and novel aspects to answer independent patient-important questions.

References for topic 8: Comparative effectiveness of second-line drug therapies after failed metformin use (sulfonylureas, meglitinides, thiazolidinediones, acarbose, incretin agents, etc.) in type 2 diabetes treatment

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Topic 9:
Comparative effectiveness of optimal timing (early versus late) for reduced-intensity conditioning (RIC) allogeneic hematopoietic stem cell transplantation for older patients in reducing mortality risk and increasing survival in patients with myelodysplastic syndromes (MDS)

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION [1-3] • Myelodysplastic syndromes (MDS) are a group of hematologic stem disorders where the bone marrow fails to produce blood cells, resulting in pancytopenia, and characterized by inefficient hematopoiesis and increased apoptosis. • Complications from the disease include infection, bleeding, and anemia. With higher-risk MDS, there is a 30% risk of transformation to acute myeloid leukemia (AML), which is often refractory to standard treatments. • MDS may be idiopathic or associated with previous chemotherapy or exposure to environmental toxins like radiation or chemicals. A small percentage of cases are familial, and some specific mutations have been identified.[4] • Initially, patients may have mild cytopenias, but this can progress to more severe deficits requiring supportive treatment such as transfusions of red blood cells and/or platelets and use of growth factors to stimulate specific cell lineages production (e.g., granulocyte colony-stimulating factor (G-CSF) to stimulate granulocytes, granulocyte macrophage colony stimulating factor (GM-CSF) to stimulate white cells or erythropoietin to stimulate red blood cells. • At the time of progression to leukemia, chemotherapy can be used for treatment. • Recommendations for treatment are addressed by the MDS Practice Guidelines of the National Comprehensive Cancer Network (NCCN).[1] • Hematopoietic stem cell transplantation (HSCT) is the only curative treatment for MDS and is used with intermediate-2, high, or very high risk MDS (high risk for development of leukemia). The use of myeloablative conditioning (destroying the bone marrow and eradicating the disease with chemotherapy or radiation) before transplantation is limited by patients' age (generally up to age 60 years) given the potential toxicity. Reduced intensity conditioning (RIC) or non-myeloablative preparative regimens can be used with older patients with lower morbidity. RIC uses lower doses of chemotherapy and radiation immediately prior to a transplant.

	• For older populations, HSCT preceded by RIC is attempted now much more frequently than in the past, given advances in supportive care and lower toxicity with these regimens. The goal is to use graft-versus-tumor effect to combat the disease, as opposed to high doses of chemotherapy. In older populations with intermediate-2 or high-risk International Prognostic Scoring System- Revised (IPSS-R) scores, there is a higher rate of transformation to leukemia and survival is low without the use of transplantation. • The main complications from HSCT are graft versus host disease (GVHD), side effects from the chemotherapy and radiation, and complications from cytopenias and the disease itself. • Even if the transplantation is a success with RIC, not all patients are cured after it, and some patients can persist with MDS, relapse, or progress to AML. Maintenance therapy after transplantation is an important consideration in the post-transplant period, and research on better maintenance regimens is needed. The agent generally used, azacytadine, is a difficult agent to tolerate; regimens with a better adverse effect profile would improve quality of life. • A key current gap in the evidence is the optimal timing of stem cell transplantation with RIC (early versus late). Since older patients have a high risk of progression to leukemia, there is an increasing trend toward early transplantation, but because of the rarity of MDS, there are no data from large randomized clinical trials.
Relevance to patient-centered outcomes	SYMPTOMS[5] Impaired quality of life depends on specific cytopenias. • When red cells are affected, symptoms include: o Rapid heart rate o Shortness of breath with exertion o Weakness • When white cells are affected, symptoms include: o Fever o Higher risk of infections • When platelets are affected, symptoms include: o Easy, unexplained bruising o Nosebleeds and bleeding gums o Prolonged bleeding from cuts

	PATIENT-CENTERED OUTCOMES • Disease and treatment affects attendance and participation in activities at school or work. • Adverse effects from treatment affect quality of life. • Psychosocial concerns from future risks of leukemia also affect quality of life. • Caregiver burden due to disease and treatment is also substantial.
Burden on Society	
Recent prevalence in populations and subpopulations	INCIDENCE AND PREVALENCE[4,5] • MDS is not common; there are about 13,000 persons diagnosed each year in the United States, or 4.8 persons per 100,000 in the population. • MDS is more common in men. • The risk of developing MDS increases with age; there are very few cases of patients younger than 40 years old, and almost all patients are older than 60 years. • Some studies suggest a lower rate of response to stem cell transplantation for African-Americans than Caucasians.
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• Complications of untreated MDS, including infections, anemia, and leukemia, significantly impact quality of life. There are no studies quantifying this issue. • Both MDS and the leukemia that can develop have significant risk of mortality. • Transplantation in older patients also has significant impact on quality of life, functional status, and risk of mortality. • Symptomatic and curative treatments are expensive and burdensome and use large amounts of health care services. In 2012, 8,385 patients were hospitalized with myelodysplastic syndromes with an aggregate cost of 156,278,345 dollars.[6] There are no data for outpatient services costs.
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• MDS, although rare, causes significant and prolonged deficits in quality of life, has a high risk of mortality and is associated with high use of health care services. It is reasonable to give some priority to CER on alternative approaches to MDS because it has such high mortality and its prevalence is likely to increase as the average age of the U.S. population continues to increase.

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 systematic reviews or prospective studies evaluating the timing of reduced-intensity conditioning and transplantation in MDS. • Evidence for which populations benefit from early transplantation is from decision analyses based on observational studies (registry and large center databases). The decision analyses all concluded that those with high or very high risk IPSS-R are most likely to benefit from allogeneic transplantation, although the studies disagree on whether all those with intermediate scores or just those with intermediate-2 scores should undergo transplantation (details below). The study including only reduced-intensity conditioning concluded that intermediate-2 risk patients had better outcomes with transplantation. • The earliest analysis, done in 2004, included only standard conditioning, not reduced intensity conditioning, [7] and concluded that immediate transplantation for intermediate-2 and high risk patients was associated with maximal life-expectancy (quantitative results were not reported). • Alessandrino et al conducted a decision analysis evaluating the optimal timing of transplantation with data on 1137 patients from registry data, and concluded that, relative to supportive care, estimated life-expectancy increased with delayed transplantation for patients with IPSS risk as high as intermediate-1, and then decreased for higher risks. This analysis included both standard and reduced-intensity conditioning regimens together in the transplantation group with treatment dating from 1992 – 2009.[8] • Koreth et al. conducted a decision analysis including only reduced-intensity conditioning. This decision analysis concluded that for intermediate-2/high IPSS, transplantation offers both overall and quality-adjusted survival benefit: 36 compared to 28 months. For low/intermediate risk IPSS scores, supportive care is more beneficial: transplantation survival was 38 months with transplantation compared to 77 months with best supportive care. Including quality of life-adjusted survival with published utility estimates for relevant disease states did not change the favorability of transplantation for higher-risk patients. Data used in this study dated back to 1976, and data for outcomes of different regimens was obtained from different datasets.[9] • Since half of all MDS patients have intermediate-1 scores, the difference in conclusion between these studies has significant implications for treatment.

What could new research contribute to achieving better patient-centered outcomes?	• Given the rarity of this illness, clinical trials are small and take a long time to accrue, and no current research addresses the appropriate timing of transplantation. • Observational comparative effectiveness studies to provide better evidence for the timing of transplantation would therefore be useful. • Maintenance therapy after transplantation is an important consideration in the post-transplant period, and research on better maintenance regimens that have better side-effect profiles is needed.
Have recent innovations made research on this topic especially compelling?	• Advances in transplantation continue to reduce toxicity and make early transplantation a more viable option. • The development of haplo-identical (or half-matched) transplantation makes transplantation an option for nearly all persons and thus this is a treatment paradigm that is being explored more frequently in this population. (Haplo-identical means that the donor and recipient have the same set of closely linked HLA genes on one of the two number 6 chromosomes they inherited from their parents. They are a half-match instead of a perfect match for each other).
How widely does care now vary?	• NCCN guidelines for treatment of MDS recommend supportive care as first line of care for low/Intermediate-1 MDS, with consideration of transplantation if no response or disease progression for selected patients. The guidelines do not address the issue of timing of transplantation. • Currently, timing of care is institution-specific. • The guidelines recommend transplantation for intermediate-2 (IPSS-R, preferred risk categorization) for patients who are a candidate and have a donor available. • The guidelines do not specify when reduced-intensity conditioning approaches are indicated. • There are only four FDA-approved drugs in MDS which are difficult to tolerate (e.g., azacitidine) and there has not been a new drug approved in nine years, so treatment varies significantly in the United States and there is no evidence about second-line regimens. For example, a recent study found that 48% of patients had early discontinuation (less than 5 cycles) of a hypomethylating agent (azacitidine or decitabine) due to lack of response or intolerance. 70% of these had used azacitidine, 31% decitabine, and 4% lenolidamide.[10] Effective second-line therapies for these patients are not currently available.

What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	• We identified no relevant trials in NIH Reporter or clinical trials.gov or at the Aplastic Anemia & MDS International Foundation grants website. • The MDS Clinical Research Consortium, launched in 2012, is a 5-year, $16 million initiative of the Aplastic Anemia & MDS International Foundation across six centers "designed to undertake unique studies and trials to significantly advance treatments and improve outcomes for patients with Myelodysplastic Syndromes (MDS)." The goal is to build a sufficient cohort for Phase I and Phase II clinical trials along with pilot studies to identify and confirm new treatments and therapies for MDS.[11] None of these are transplantation studies. This collaboration could potentially allow for comparative effectiveness studies of MDS with sufficient sample size across the institutions. • The NHLBI (National Heart, Lung, and Blood Institute) is also sponsoring an MDS natural history study which has just been funded; this will provide an excellent resource for observational comparative effectiveness studies.[12] • Celgene is also sponsoring a new prospective registry for MDS addressing treatment regimens and sequencing in routine clinical practice (began December 2013), which includes patient-reported outcomes, particularly health-related quality of life and economic outcomes (Connect® MDS/AML).[13] • A scale has recently been evaluated and validated for quality of life measurement specifically for MDS – the QUALMS-1 (QUAlity of life in Myelodysplastic Syndromes) – and is ready for registry and comparative effectiveness studies. This scale includes the issues of disease information and uncertainty which are not included in other scales for oncology, as they are relatively specific issues for MDS.[14] • A refined version of the disease risk index (DRI) for predicting prognosis after transplantation was published in 2014, which can also help in research for risk stratification and improve interpretation of results across centers. However, like other risk indices for MDS, this does not include patient-reported outcomes. This study was based on data reported to the Center for International Blood and Marrow Transplant Research. Improvement in risk stratification is one factor that has improved providers' comfort with earlier transplantation.[15]

How likely it is that new CER on this topic would provide better information to guide clinical decision making?	• Given the paucity of existing high-quality evidence, particularly research including patient-reported outcomes, and the new development of U.S consortiums and a registry, new CER is likely to help guide clinical decision-making and recommendations for the NCCN guideline. • Given uncertainty on patients with intermediate risk for progression to leukemia, better evidence for the appropriate timing of transplantation is needed. • Research on regimens with a more tolerable side effect profile for maintenance therapy after transplantation is also 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: • Transplantation is conducted by a small number of clinicians at select institutions, so diffusion would not be a major issue. BARRIERS: • MDS affects an older population, often with comorbidities, and transplantation is expensive and very challenging for these patients in particular.
How likely is it that the results of new research on this topic would be implemented in practice right away?	• Rapid implementation is likely, since there is a small community of MDS experts and well-developed collaboration and consortiums across institutions. • NCCN guidelines are updated annually and used by experts.
Would new information from CER on this topic remain current for several years?	• At this point, reduced-intensity stem cell transplantation is likely to be the standard treatment for higher-risk populations for the foreseeable future, and there are no clinical trials of new drugs given the rarity of the disease. Thus, new CER about use of reduced-intensity conditioning is likely to be valuable for several years at least.

References for topic 9: Comparative effectiveness of optimal timing (early versus late) for reduced-intensity conditioning (RIC) allogeneic hematopoietic stem cell transplantation for older patients in reducing mortality risk and increasing survival in patients with myelodysplastic syndromes (MDS)

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Topic 10:

Comparative effectiveness of narrow-spectrum antibiotics versus broad-spectrum antibiotics in the treatment of community-acquired pneumonia in adults

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION[1-4] • Community-acquired pneumonia (CAP) is the acute infection of the lung in persons who have not been hospitalized recently and have not been regularly exposed to the health care system. A wide range of microorganisms can cause CAP, including bacteria (20-50%) and viruses (15-23%). In 30-65% of CAP cases, an etiologic organism cannot be identified. • Typical symptoms of CAP include fever, cough, sputum production, shortness of breath, with lung infiltrate or consolidation on chest imaging and, leukocytosis. However, the diagnosis of CAP can be challenging, as some patients, especially those who are elderly, may not present with these symptoms. • Antibiotics are only effective for CAP caused by bacteria, among which *Streptococus pneumonia*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are considered to be the most common. • Broad-spectrum antibiotics used to treat CAP include tetracyclines, fluoroquinolones, and third- and fourth-generation cephalosporins. Narrow-spectrum antibiotics used to treat CAP are penicillin, aminopenicillins, ampicillin sulbactam, and amoxicillin clavulanate. Some might consider azithromycin to be narrow-spectrum in this context. • According to the 2007 consensus based Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines, empirical treatment of CAP with narrow-spectrum antibiotics is recommended in young patients with no previous history of antimicrobials and no comorbidity.[2] Broad-spectrum antibiotics are used empirically in older patients, patients who received antibiotics within the previous 3 months, those with comorbidity, patients with severe disease who require hospitalization or an intensive care unit (ICU), and when there is concern for Pseudomonas infection.[2] • There is a general trend towards broader and longer duration antibiotic therapy for CAP. Public health experts are concerned about the use of antibiotics in patients who do not really have pneumonia, especially because excess use of broad-

	spectrum antibiotics can lead to emergence of multidrug-resistant bacteria. Using narrow-spectrum antibiotics is one of several ways to reduce bacteria resistance.
Relevance to patient-centered outcomes	SYMPTOMS[1] • Tiredness and weakness • Cough • Body aches • Wheezing • Weak appetite • Fever and chills • Shortness of breath PATIENT-CENTERED OUTCOMES • Hospital admission rate • ICU admission rate • Length of hospital stay • Hospital readmission rate • Days away from work/school/normal activities • Short-term disability and productivity lost • Cost of care • Patient satisfaction, including emergence of antibiotic resistance (patients often are upset when they learn they have a drug-resistant organism, and they may be subjected to special contact precautions as a result) • Infection (e.g., *Clostridium difficile* infection) as a result of antibiotic treatment • Drug toxicity and adverse effects • Mortality
Burden on Society	
Recent prevalence in populations and subpopulations	INCIDENCE AND PREVALENCE • One study estimated that 915,900 episodes of CAP occur in adults greater than or equal to 65 years of age each year in the U.S.[5] • The estimated CAP incidence is between 5-10 cases per 1000 person-years in a working population[6,7] and increases to over 20 cases per 1000 person-years among individuals aged 65-69 years, and to over 50 cases per 1000 person-years among those 85 years old or older.[8]

Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• Patients diagnosed with CAP have a significant short-term decrease in quality of life due to symptoms, and typically miss at least one week of work or school even when not admitted. If admitted to a hospital, loss of productivity can go up to 2 or 3 weeks.[9] Older age, non-white race, low education, low income, and unemployment were associated with worse outcomes.[12] • In 2013, CAP was the 9th leading cause of death in the US, causing around 53,000 deaths (the mortality rate is 16.9 per 100,000). Despite recommendations to use broad-spectrum antibiotics for CAP, mortality from CAP has not decreased significantly over years. • In 2012, 1.1 million persons were diagnosed with CAP, resulting in 327,840 hospital admissions.[13] • In the working population, CAP is a frequent and costly event with a national cost of $10.6 billion a year. The cost is higher in individuals with comorbid conditions, and in individuals admitted to hospitals.[6,7,10]
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• CAP is a major cause of death and bears substantial clinical and economic burden. CER on alternative approaches to treating CAP should be given high priority, taking into consideration that broad-spectrum antibiotics are frequently used because it often is difficult to identify a causative organism. • High priority also should be given to CER on the new techniques that have been under development to better determine the pathogen and establish a faster diagnosis in patients presenting with symptoms of CAP. This would help clinicians better differentiate colonization from infection, and help them choose the most appropriate antibiotic for patients most likely to have bacterial CAP, and help avoid unnecessary treatment of patients unlikely to benefit from antibiotics.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	• A 2014 Cochrane systematic review evaluated the efficacy and safety of different antibiotic treatments for CAP in patients more than 12 years of age treated in outpatient settings. Although this review included 11 randomized controlled trials (RCTs) of good quality with 3352 participants, many different antibiotics pairs were examined, including clarithromycin vs. amoxicillin, clarithromycin vs. amoxicillin vs. azithromycin vs. levofloxacin, erythromycin vs. clarithromycin, clarithromycin vs. azithromycin microspheres, clarithromycin vs. telithromycin, azithromycin microspheres vs. levofloxacin, telithromycin vs. levofloxacin, cethromycin vs. clarithromycin, solithromycin vs. levofloxacin, and nemonoxacin vs. levofloxacin

	(narrow spectrum antibiotics for CAP are underlined). The variable comparisons have limited the ability to pool data across RCTs. In the individual RCTs, there was no significant difference in the comparative efficacy of various antibiotics for the treatment of CAP in outpatient settings. The authors concluded that there is insufficient evidence to recommend the choice of antibiotics for the treatment of CAP in outpatient settings.[3] • A 2012 Cochrane systematic review evaluated the comparative effectiveness of antibiotic regimens containing coverage for atypical bacteria relative to those regimens not covering atypical bacteria for the treatment of CAP in hospitalized adults. Atypical bacteria include Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydia pneumoniae. The main typical bacteria causing CAP is Streptococcus pneumoniae. The review included 28 RCTs with a total of 5939 participants. The antibiotics with activity against atypical organisms were administered as monotherapy in all but three RCTs (mostly the comparison between quinolone and beta-lactam monotherapy). One RCT assessed a beta-lactam combined with a macrolide compared to the same beta-lactam. The authors concluded that there is no evidence of benefit in survival or clinical efficacy with empirical atypical coverage in hospitalized patients with CAP.[14] • A 2012 systematic review including both RCTs and observational studies found that macrolide-based regimens were associated with survival benefit in observational studies but not in RCTs for the treatment of CAP in hospitalized patients. Also, there was no mortality benefit for patients treated with IDSA/ATS guideline-concordant antibiotics (macrolide and beta-lactam combination) compared with fluoroquinolones.[15] • The duration of antibiotics is relevant to reducing bacteria-resistant. A 2012 systematic review including 5 RCTs compared short-course (3-7 days) versus long-course (7-10 days) antibiotic therapy for CAP. The review found no difference in effectiveness and safety in patients with CAP of mild to moderate severity.[16] • A 2009 systematic review including 13 cohort studies found that blood cultures for patients hospitalized with CAP had limited value: the blood cultures were true-positive in 0-14% of cases, and that led to antibiotic narrowing in 0 -3% of patients. The review concluded that hospital quality measures that include blood cultures should be reassessed.[17]

What could new research contribute to achieving better patient-centered outcomes?	• Diagnostic tests with high sensitivity and specificity are available to detect the causative organisms.[18] However, whether these new diagnostic tests could improve patient-centered outcomes is unclear. There is a need for further research on establishing CAP diagnosis rapidly in clinical practice with respect to whether CAP is present, whether hospital admission is required, the type of pathogen (i.e., bacteria or virus, colonization or infection), and the causative bacteria, with a focus on patient-centered outcomes. • In patients with CAP, new research could help to improve patient-centered outcomes by providing information about the comparative effectiveness of o narrow versus broad-spectrum antibiotic for empiric therapy and/or definitive therapy, o shorter versus longer antibiotic therapy, and o approaches to de-escalate antibiotic therapy on patient-centered outcomes including measures of the success of therapy, reducing the days of treatment according to patient's response, association of therapy with side-effects such as *C. difficile* infection, and emergence of antibiotic resistance.
Have recent innovations made research on this topic especially compelling?	• A recent cohort study from Australia found that, based on the etiology results, broad-spectrum antibiotics are not necessary for the vast majority of Australian patients with CAP.[19] Furthermore, the choice of antibiotics and outcomes were comparable regardless of whether a pathogen was isolated. This study has stimulated discussion and interest in the U.S. • The availability of sensitive diagnostic tests such as procalcitonin (a marker of bacterial infection with a sensitivity of up to 89% and a specificity of up to 94%)[18] is likely to reduce unnecessary antibiotic therapy and reduce the length of antibiotic therapy. However, clinicians must be trained in how to interpret and respond correctly to the tests for them to be of value.

How widely does care now vary?	• The 2007 IDSA/ATS guidelines recommend that once the diagnosis of CAP is made, antimicrobial therapy should be initiated promptly and at the point care where the diagnosis is first made. Outpatients with CAP are generally treated empirically because of the substantial cost and inadequacies of diagnostic testing for pneumonia. For outpatients without coexisting illnesses or recent use of antibiotics, IDSA/ATS guidelines recommend the administration of a macrolide or doxycycline; for those with coexisting illnesses or recent use of antibiotics, the guidelines recommend the use of levofloxacin or moxifloxacin alone or a beta-lactam plus a macrolide.[20] • Hospital CAP core measures (a set of measurements developed by the Centers for Medicare and Medicaid Services to reflect the quality of care in hospitals) have contributed to a greater uniformity of empiric treatment, although this treatment has been with broad-spectrum antibiotics as described in the bullet point above. However, because diagnosis of CAP is difficult and not always accurate, care still varies across hospitals and centers.[21-24] In addition, the core measures did not address management of CAP, including antibiotic management, after the initial selection of antibiotics. • In practice, the duration of treatment varies from 5-7 days to 10-14 days; the doses and choice of antibiotics also vary.[21-24] • The use of antibiotics for CAP may also vary according to patient comorbidity, with clinicians likely to favor broad-spectrum antibiotics when patients have serious comorbidity that could increase their risk of having complications.
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	• We searched clinicaltrials.gov on March 18, 2015 and found 75 studies using the strategy “community acquired pneumonia” as the condition AND “antibiotics” as the interventions AND “adults OR senior” as the age groups. Forty (64%) trials have completed recruitment and 11 (15%) have results available. Most of these trials have focused on clinical cure/response or duration of antibiotic therapy as the primary outcome. Fifty-four (72%) trials received industry funding. • In terms of the comparisons, 30 (40%) trials compared different monotherapies; 10 (13%) trials compared combination antibiotic therapy versus monotherapy or another combination therapy; 3 (4%) trials compared different durations of antibiotic therapy. • Five (7%) studies, some observational, evaluated the use of diagnostic tests (polymerase chain reaction) or procalcitonin level for guiding antibiotic therapy. • Two (3%) studies evaluated programs/strategies to improve antibiotic use

	(antimicrobial stewardship) at hospitals. • It is important to note that new antibiotics for CAP are all broad spectrum. Only one trial (1%) compared a narrow against a broad-spectrum antibiotic (ampicillin/amoxicillin vs moxifloxacin) in hospitalized patients with non-severe CAP (NCT00887276). Pharmaceutical companies have great interest in research on these new antibiotics, but less interest in research on older narrow-spectrum antibiotics.
How likely it is that new CER on this topic would provide better information to guide clinical decision making?	• CAP is a common disease, even with guidelines and hospital core measures, both broad and narrow treatment have potential pitfalls and evidence gaps exist. If new CER could show that selected narrow-spectrum antibiotics are non-inferior to broad-spectrum antibiotics, that would give clinicians a stronger evidence-based rationale for using narrow-spectrum antibiotics at least for certain subsets of patients who may not need a broad-spectrum antibiotic. • It is important to minimize inappropriate use of antibiotics to reduce the risk of developing more resistant organisms, which could in turn reduce future effectiveness of the available antibiotics. Thus, studies of strategies to reduce inappropriate use of antibiotics (and unnecessary use of broad-spectrum antibiotics) would help provide information that could improve clinical decision-making. Given the paucity of new antibiotics in development, approaches to prolong the useful lifespan of antibiotic classes should be encouraged.[19]
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: • Recent studies from Europe and Australia have demonstrated that narrower and shorter duration antibiotics are as good as broader and longer duration antibiotic therapy.[19,25] Guidelines from the United Kingdom and Sweden also recommend amoxicillin or penicillin as empirical therapy for CAP in outpatients.[26,27] Although the epidemiology of CAP differs between the U.S. and Europe/Australia, experience from these countries still may help to facilitate implementation of new approaches to the management of CAP in the U.S.[20] • Use of narrow-spectrum antibiotics and shorter durations of antibiotics are associated with a lower risk of *C. difficile* infection and lower risk of antibiotic resistance, and that information could help to facilitate greater use of narrow-spectrum antibiotics and shorter durations of antibiotics if new research shows that they also are non-inferior in effectiveness. • The increasing interest of public health experts in preventing antibiotic resistance

	could help to facilitate implementation of new strategies for treating CAP. BARRIERS: • Previous adoption of hospital core measures (abandoned on 1/1/2014) and existing practice guidelines have made research on use of narrow-spectrum empiric therapy challenging. There is a general trend toward broader and longer duration antibiotic therapy. • The trade-off between the societal benefit of using narrow-spectrum antibiotics and the potential individual benefit (whether real or perceived) of using broad-spectrum antibiotics may not be well understood by prescribers and/or patients. • It can be challenging to standardize treatment for CAP in populations having different comorbidity and different risks of complications. • Changes in the recommended choice of antibiotics for CAP need to account for potential local/regional variation in the epidemiology of CAP and the prevalence of antibiotic resistance.
How likely is it that the results of new research on this topic would be implemented in practice right away?	• Implementation of new findings in this area likely would depend on how the new research findings are incorporated into practice guidelines at the national and local level, and could be affected by the quality of care measures being used by hospitals and health systems at the time that new research is reported. • Recommendations for hospital-based care of CAP will be easier to implement than recommendations for outpatient-based care because hospitals tend to devote more resources to quality improvement activities than community-based practices. It is challenging to influence antibiotic prescribing practices in diverse outpatient settings. • Depending on the strength of evidence from new research, hospitals and health systems could make changes in guidelines and quality of care measures within a relatively short period of time. The IDSA/ATS guidelines on the management of CAP are being updated and are projected to release in fall 2015.
Would new information from CER on this topic remain current for several years?	• If new information from CER supported a paradigm shift toward greater use of a narrow-spectrum antibiotic, or shorter course of antibiotic therapy, it would take time to be widely embraced in practice, but could remain current for many years.

References for topic 10: Comparative effectiveness of narrow-spectrum antibiotics versus broad-spectrum antibiotics in the treatment of community-acquired pneumonia in adults

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