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 1:

Comparative effectiveness of drug treatment (antihyperglycemic drugs etc.) versus non-drug treatments (weight loss/exercise) in the treatment of patients with prediabetes. Do long-term outcomes differ across subgroups of adults?

Suggested/Modified Topic 1: Comparative effectiveness of drug treatments *as adjuncts to* non-drug treatments (weight loss/exercise) *versus non-drug treatments alone* in the treatment of *patients with prediabetes*. Do long-term outcomes differ across subgroups of adults?

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<tr><td>Overview/definition of topic</td><td>DESCRIPTION OF CONDITION
Prediabetes is a condition where blood sugar is higher than normal but not enough to be called diabetes mellitus. Prediabetes is sometimes called impaired fasting glucose or impaired glucose tolerance because of the tests used to make a diagnosis (Table 1).[1,2]

Table 1. Laboratory tests to diagnose diabetes and prediabetes
<table>
<tr><th></th><th>Hemoglobin A1c (percent)</th><th>Fasting Plasma Glucose (mg/dL)</th><th>Oral Glucose Tolerance Test (mg/dL)</th></tr>
<tr><td colspan="4">American Diabetes Association</td></tr>
<tr><td>Diabetes</td><td>6.5 and greater</td><td>126 and greater</td><td>200 and greater</td></tr>
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Estimates of progression from prediabetes to type 2 diabetes vary. Estimates range from less than 10% to 25% of individuals progress to diabetes within 3 years, with 40% to 60% progressing to diabetes 10 years after fasting glucose and glucose tolerance tests with prediabetes results.[2-5]</td></tr>
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	The 2015 Standards of Medical Care in Diabetes recommend measuring hemoglobin A1c and plasma glucose to test for prediabetes starting at age 45 and at younger ages for adults and children who are overweight and have other risk factors for diabetes such as a first degree relative with diabetes, cardiovascular disease, hypertension, abnormal cholesterol or triglyceride levels, polycystic ovarian disease, gestational diabetes, physical inactivity, or race other than white. Tests should be repeated every 3 years for individuals with normal results and more often for high-risk individuals and those with prediabetes results.[2] The standard management of prediabetes is based on life style changes (diet, exercise, behavioral modification, smoking cessation) and the use of metformin for high-risk individuals (*i.e.,* obese, gestational diabetes) or for those who do not respond to lifestyle modifications.
Relevance to patient-centered outcomes	SYMPTOMS • Prediabetes often has no symptoms.[6] Despite the absence of symptoms, high glucose levels and glycosylation end products create an inflammatory response at the cellular level that can lead to cardiovascular disease, neuropathy, and retinopathy.[7] PATIENT-CENTERED OUTCOMES • Quality of life • Cardiovascular disease • Neuropathy • Mortality.[8] • Increased risk of diabetes and its associated complications and long-term outcomes • Management of prediabetes with lifestyle modifications requires commitment and patient adherence
Burden on Society	
Recent prevalence in populations and subpopulations	PREVALENCE • In 2012, 86 million Americans age 20 and older had prediabetes.[9-12] Based on fasting glucose or hemoglobin A1c levels measured between 2009 and 2012, 37% of U.S. adults aged 20 years or older had prediabetes. Prediabetes is very common among the elderly, with 51% of those aged 65 years or older meeting the criteria for prediabetes. • Prediabetes does not appear to differ by race/ethnicity. Based on fasting glucose and

	hemoglobin A1c levels, 35% of non-Hispanic whites, 39% of non-Hispanic blacks and 38% of Hispanics have prediabetes. Prevalence of prediabetes estimates for other races are not available in the most recent National Diabetes Report.[13]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• Most people with prediabetes do not display symptoms. Despite the absence of symptoms, individuals with prediabetes have poorer quality of life and a shorter life span than the population without impaired glucose. Because individuals with prediabetes are more likely to be overweight and obese and have cardiovascular disease, they are more likely to use health care services.[14] • Preventing progression to type 2 diabetes can have substantial effects on the health care system. Individuals with diabetes have 2 times greater medical expenditures than the population without diabetes. Diabetes care cost the U.S. medical system 245 billion dollars in 2012.[15]
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• There is a large burden of prediabetes in the U.S. population, with 37% of the adult population having prediabetes. Therefore, high priority should be given to research to determine the best strategies to prevent the progression of prediabetes to diabetes.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	• The Diabetes Prevention Program, with results first published in 2002, is the landmark study on this topic. The Diabetes Prevention Program ultimately compared three arms in overweight individuals aged 25 and older with impaired glucose tolerance: 1) an intensive lifestyle intervention; 2) twice daily metformin with a standard lifestyle intervention; and 3) placebo with a standard lifestyle intervention. The primary outcome was diagnosis of diabetes. Participants were followed for 2.8 years on average. Lifestyle intervention was favored over metformin among those 45 and older and those with a body mass index (BMI) less than 35. There was no difference between lifestyle intervention and metformin for those aged 25-44 or those having a BMI greater than 35, and there was no difference in subgroups defined by sex, race, or baseline glucose levels. There were more gastrointestinal symptoms with metformin than lifestyle intervention or placebo, and fewer gastrointestinal symptoms with the lifestyle intervention than placebo. There were

	more musculoskeletal symptoms with the lifestyle intervention than placebo. There were no differences in need for hospitalization or death between the 3 groups.[16] • A recent post-hoc analysis of the Diabetes Prevention Program found that treatment effectiveness may vary by risk factors for diabetes with metformin having the strongest effect on those at highest risk of progression and the lifestyle intervention having a substantial effect on all individuals at risk of diabetes.[17] • Two reviews from the Evidence-based Practice Center Program are related to the topic, although none sought to directly compare drug versus non-drug treatment for prediabetes. o One review examined weight loss surgery in individuals with diabetes or prediabetes with BMI less than 35. Weight loss surgery resulted in greater weight loss and reduction in hemoglobin A1c than medications or behavioral interventions in non-randomized studies (no trials were identified).[18] o Another review aimed to examine factors to prevent weight gain and included individuals at risk of diabetes or cardiovascular disease. One study was included and found that a personalized goal-setting intervention did not affect progression to overweight or obesity, although adherence with the intervention was poor.[19] • Two relevant reviews were identified in the Cochrane Collaboration library, although neither included a medication group. o One review included nine trials and found that dietary changes, physical activity, weight loss and weight control interventions for adults with prediabetes decreased weight and prevented progression to diabetes.[20] o Another review compared diet and exercise interventions to standard recommendations to prevent diabetes in individuals at risk of type 2 diabetes. The diet and exercise interventions resulted in better weight outcomes and prevented progression to diabetes.[21]
What could new research contribute to achieving better patient-centered outcomes?	• Understanding the potential adverse effects of drug and non-drug treatments in the population with prediabetes will help patients make better decisions about which treatments are best for them, keeping in mind that patients must decide whether to make a commitment to long-term drug treatment despite not having any symptoms from prediabetes itself. • The risk-benefit profile of drugs may be different for individuals with prediabetes than diabetes. The risk-benefit results from the diabetes trials cannot be applied to prediabetes because more than 75% of individuals with prediabetes will not progress

	to diabetes within 3 years. • Understanding the burden of treatment is needed. For example, the lifestyle intervention program tested in the Diabetes Prevention Program resulted in fewer individuals progressing to diabetes, especially among those age 60 or older, but the lifestyle program required intensive commitment with participants needing to maintain a 7% decrease in baseline body weight, a low calorie and low fat diet, and participate in a 24 week behavioral lifestyle curriculum followed by monthly counseling sessions. [16] New research is needed to evaluate less intensive regimens that are easier for individuals to adhere to. • New research could evaluate drugs other than metformin. Metformin was compared with lifestyle intervention in the Diabetes Prevention in 2002.[16] • Despite no difference in the prevalence of prediabetes across ethnicities, there are differences in type 2 diabetes by ethnicity. Examining why these differences in the progression to diabetes exist could be explored in future research.
Have recent innovations made research on this topic especially compelling?	• In December 2014, the Food and Drug Administration approved once-weekly injections with liraglutide for weight loss. Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist and is an established type 2 diabetes treatment. This treatment could be especially compelling as a treatment for prediabetes because it impacts a primary risk factor for diabetes, that is, obesity.[22] • Other medications for treatment of diabetes also contribute to weight loss such as the sodium-glucose cotransporter-2 (SGLT-2) inhibitors. It remains to be seen whether the manufacturers of SGLT-2 inhibitors will seek marketing authorization for a weight loss indication. The manufacturers of GLP-1 receptor agonists and SGLT-2 inhibitors may also pursue marketing authorization for prediabetes. • Wearable monitors, apps and web-based programs are available that are designed to facilitate lifestyle changes.
How widely does care now vary?	• The guidelines recommend metformin or lifestyle intervention for treatment, primarily based on results of the Diabetes Prevention Program. It is difficult to assess the variation in treatment for prediabetes because there is not always a record of the prescribed intensity level of the lifestyle intervention. There are no national estimates on the variation in prediabetes treatment with medications.
What is the pace of other research on this topic (as	ClinicalTrials.gov • On March 16, 2015, 408 studies were registered in ClinicalTrials.gov for the condition of prediabetes that included a drug, behavioral intervention, or intervention labeled

indicated by recent publications and ongoing trials)?	as other. o 168 of the studies were last updated prior to 2013, and 12 of these included results. Although none of the studies with results directly compared medications to non-drug treatments, 5 studied medications in adults (NCT00364377; NCT00417170; NCT00579813; NCT00990184) 1 studied medications in children (NCT00886626); and 1 studied lifestyle modification in adults (NCT00886340). o 84 studies were completed with updates since 2013, and 19 had results. Three of the completed trials without results were relevant to the topic, two of which compared medications with non-drug treatments: ▪ One study without results compared metformin or a thiazolidinedione with exercise training among males (NCT00510588). ▪ One compared a lifestyle intervention combined with a cholesterol-lowering medication (pitavastatin) to lifestyle intervention alone (NCT00301392). ▪ One compared a dietary supplement for weight loss with education and counseling for weight loss (NCT00129792). o 4 terminated or suspended studies were related to the topic but did not compare medications to non-drug treatments directly. One terminated study with results (only 3 individuals were enrolled in the study) compared 2 medications to prevent diabetes (NCT01006018). Another terminated study that enrolled 18 individuals used vitamin D supplementation to prevent progression to diabetes (NCT01425424). Another study compared an intensive exercise intervention with the standard exercise recommendations (3 enrolled participants). One suspended study (435 enrollees) compared lifestyle interventions of different intensities specifically designed for Chinese immigrants to New York (NCT02277509). o 36 studies were active, but not recruiting. None compared medications with non-drug treatments. o 6 studies were enrolling by invitation, 1 compared 2 exercise interventions (NCT01890876), 1 compared a medication with placebo (NCT02330549), and the remaining 4 were unrelated to the topic. o There are 78 actively recruiting studies aimed at preventing diabetes. None compare medications directly with non-drug treatment options. Fourteen examine medications (NCT02023918; NCT01876992; NCT01887691; NCT01856907; NCT01419535; NCT02008968; NCT01409993; NCT01845259;

	NCT02140983; NCT01475513; NCT01862029; NCT01960205; NCT01804049; NCT01977417), 7 examine diet (NCT02066948; NCT02234440; NCT02298790; NCT02148458; NCT02188823; NCT02203240; NCT02030249), 5 examine exercise (NCT02043405; NCT01296516; NCT02312843; NCT02060240; NCT02278939), 3 examine behavioral interventions or mindfulness (NCT01642355; NCT01831921; NCT01430221), one examines smoking cessation (NCT01926041) and 7 examine prebiotics or supplements (NCT01301521; NCT02330341; NCT02254317; NCT02366481; NCT01714102; NCT02129595; NCT02346838). Only one study uses web or app-based delivery of the intervention (NCT02188823). Special populations targeted in the actively recruiting studies include the elderly, male veterans, pre-menopausal women, women with gestational diabetes, cystic fibrosis, psychiatric disorder and cirrhosis. o Most studies that targeted children aimed to recruit children with a family history of type 1 diabetes, cystic fibrosis or a psychiatric disorder. No pediatric studies compared drug with non-drug treatments, although 2 studies examined metformin (NCT01394887; NCT01779375). o Of the 19 studies not yet recruiting, none directly compare medications to non-drug treatments although 6 studies are related to the topic. Three studies aim to prevent diabetes using medications among special populations including individuals with cystic fibrosis (NCT02239458), women who had gestational diabetes (NCT02338193) and individuals with kidney disease (NCT02284230). Two trials will compare dietary supplements or probiotics (NCT02082756; NCT02358668). One study will examine the effects of a pharmacist-led lifestyle modification program to prevent diabetes (NCT02384109). <u>NIH Reporter</u> • NIH Reporter was searched on March 17, 2015 and identified 54 studies that mentioned a trial and prediabetes. Ongoing relevant studies in NIH Reporter include predominantly behavior change interventions conducted in churches or community settings or interventions involving communication via the electronic medical record or the phone. o One study entitled *Improving Beta-Cell Function in Mexican American Women with Prediabetes* directly addresses the topic by comparing lifestyle intervention with or without a GLP-1 receptor agonist to prevent diabetes (1R01MD007867-01A1).

	o Several studies target high-risk individuals through communities or churches (5P60MD006917-04; 5R18DK083941-06; 5R18DK082401-05; 1R01DK099277-01A1; 1R01DK100900-01A1; 1R34DK097724-01A1; 5P20MD002316-09; 5R18DK083941-06; 5R24MD001691-11; 5R34DK094108-02) or use communication via the electronic medical record, phone, email or print to provide personalized recommendations (3R18DK091811-03, S1; 5R44NR012617-04; 1I21HX001323-01A1; 1R43DK097912-01A1; 3R18DK091811-03S1; 5R01DK064902-08; 5R03DK098162-02; 5R18DK069901-09; 5R18DK091811-03). o Four studies of specific age groups are using more traditional techniques. One targets resistance exercise in older adults (5R01DK082383-05), another targets diet and exercise to prevent diabetes in adolescents (5R01HL118734-02) and one targets a gardening and nutrition intervention for adolescents (5R21DK094066-02). One study examines microbiota changes with a prebiotic without a comparison group in adults aged 50-75 (5R21HL118668-02). One study examine a lifestyle intervention among employees of a company (5R34DK093907-02).
How likely it is that new CER on this topic would provide better information to guide clinical decision making?	• There are numerous studies for medications to treat diabetes (funded primarily by manufacturers) and ongoing research on non-drug treatments (funded primarily by NIH). However, there are no modern studies that directly compare all of the new medication treatments for diabetes to lifestyle interventions for this population of patients with prediabetes. One model that could be followed from type 2 diabetes is a public-private funded study called Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) (NCT01794143) that compares numerous medications in a single trial. A network meta-analysis could also be performed to identify the studied treatment options and identify the most reasonable for inclusion in a trial. New CER has the potential to meaningfully improve clinical decision-making even in this rapidly changing field. • The recently approved treatment for weight loss, liraglutide, has numerous studies but no systematic review. Systematically assessing the evidence with regard to preventing diabetes can help clinicians and clinical trial designers decide if liraglutide is a good candidate as a drug treatment to prevent diabetes compared with lifestyle intervention.

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: • Health care providers are eager to help their patients avoid diabetes. • The increased burden of diabetes has made the public more aware of diabetes and individuals with a family history of diabetes may be particularly motivated to prevent diabetes. • There is a bill introduced to Congress called the Preventing Diabetes in Medicare Act that aims to provide more lifestyle intervention services to prevent diabetes in the Medicare population. However, this bill may not pass.[23] • A 2004 study aimed at identifying facilitators and barriers to meet the *Healthy People 2010* physical activity goal among underserved, ethnically diverse older adults identified a need for culture-specific physical activity programs.[24] Compliance with the existing lifestyle interventions may explain part of the difference in progression from prediabetes to diabetes by ethnicity. Several NIH-funded studies are examining interventions in specific ethnic groups which could serve as a base for culture-specific interventions once the results are made available. BARRIERS: • The cost of medications may prevent treatment initiation or persistence among individuals without symptoms. • Off-label use of hypoglycemic medications in patients without diabetes could conceivably be restricted by insurers. • Use of effective interventions could be limited by the costs and time burdens of intensive lifestyle interventions that may include counseling and exercise facility membership. • Many health care plans do not cover intensive lifestyle interventions like the intervention studied in the Diabetes Prevention Program. • Medicare acknowledges that it may not cover services recommended by providers on its page describing screening for diabetes.[25] • There may not be an existing workforce of individuals trained to deliver effective lifestyle interventions, especially interventions specific to individuals with chronic conditions.

How likely is it that the results of new research on this topic would be implemented in practice right away?	• The burden of prediabetes is great. It is very likely that results of new research on this topic will be implemented right away. • Low intensity interventions and technology assisted interventions (such as interventions delivered by apps or wearables) are of interest to the general public and are not being tested in registered clinical trials. Interventions delivered using these tools could be adopted even in the absence of clinic visits if proven effective. • Evidence on the risk-benefit ratio of medication versus lifestyle intervention for children and young adults, which was not assessed in the Diabetes Prevention Program, is especially needed.
Would new information from CER on this topic remain current for several years?	• Although there are numerous new drug candidates for diabetes that may also be candidates for prediabetes, the huge burden of prediabetes on society sets the stage for a comparison of new drugs versus lifestyle intervention despite the changing armamentarium. • Any evidence on prediabetes is likely to remain current for several years. At present, the Diabetes Prevention Program, published in 2002, is the best evidence on this topic.

References for Topic 1; Comparative effectiveness of drug treatment (antihyperglycemic drugs etc.) versus non-drug treatments (weight loss/exercise) in the treatment of patients with prediabetes. Do long-term outcomes differ across subgroups of adults?

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Topic 2:

Comparative effectiveness of early treatment (prediabetes stage) strategies versus treatment initiated after Type II diabetes has been diagnosed on long-term patient outcomes (B-cell function, cardiovascular morbidity, and mortality)

Suggested/Modified Topic 2: Comparative effectiveness of *treatment of prediabetes* versus treatment initiated after *diagnosis of* Type *2* diabetes on long-term patient outcomes

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITIONS Prediabetes is a condition where blood sugar is higher than normal but not enough to be called type 2 diabetes. Prediabetes is sometimes called impaired fasting glucose or impaired glucose tolerance because of the tests used to make a diagnosis (Table 1).[1,2] Type 2 diabetes is a condition where glucose builds up in the blood rather than going into the cells to provide energy. The excess glucose results in increased cardiovascular disease risk;[3] pancreatic beta cell death;[4] and death of pericytes which line capillaries of endothelial cells.[5,6] When endothelial cells are damaged the tissue does not receive adequate blood supply resulting in retinopathy, nephropathy and neuropathy. The glycemic changes associated with prediabetes can also lead to neuropathy.[7,8] **Table 1. Laboratory tests to diagnose diabetes and prediabetes** *Hemoglobin A1c (percent)* / *Fasting Plasma Glucose (mg/dL)* / *Oral Glucose Tolerance Test (mg/dL)* *American Diabetes Association* *Diabetes*: 6.5 and greater / 126 and greater / 200 and greater ***Prediabetes***: **5.7 to 6.4** / **100 to 125** / **140 to 199** *World Health Organization* *Diabetes*: 6.5 and greater / 126 and greater / 200 and greater ***Prediabetes***: Not considered suitable for diagnosis / **110 to 125** / **140 to 199** Complications of diabetes are often diagnosed at the same time that type 2 diabetes is

	diagnosed.[3] Newly diagnosed patients are recommended to undergo an extensive evaluation to identify complications of type 2 diabetes. Estimates of the progression from prediabetes to type 2 diabetes vary. After test results indicating prediabetes, the progression to diabetes within 3 years ranges from less than 10% to 25%. Forty to 60% progress to diabetes 10 years after prediabetes test results.[2,9,10 11] The 2015 Standards of Medical Care in Diabetes recommend measuring A1c or fasting glucose starting at age 45 and at younger ages for adults and children who are overweight and have other risk factors for diabetes such as a first degree relative with diabetes, cardiovascular disease, hypertension, abnormal cholesterol or triglyceride levels, polycystic ovarian disease, gestational diabetes, physical inactivity, or race other than white. Tests should be repeated every 3 years for individuals with normal results and more often for high-risk individuals and those with results indicating prediabetes.[2] When a patient is diagnosed with type 2 diabetes, a comprehensive evaluation should be performed. The evaluation should include a detailed medical history, thorough physical examination, and selected tests, with special attention to potential complications of diabetes which can be present at the time of initial diagnosis.[2] The standard management of prediabetes is self-management and lifestyle changes (diet, exercise, behavioral modification, smoking cessation). Pharmacotherapy with metformin is recommended by some professional organizations for individuals with a particularly high risk of progressing to diabetes (*i.e.,* obese, gestational diabetes) or who do not respond to lifestyle modifications.[2] However, there is limited evidence on real-world use of metformin and its long-term benefits and safety in prediabetes. Other pharmacotherapies are also effective for reducing diabetes risk in prediabetes but are not generally recommended because of side-effects or cost. Bariatric surgery is a more drastic intervention which can lower diabetes risk.[12] The standard initial management for type 2 diabetes is metformin combined with self-management and lifestyle changes or self-management and lifestyle changes without metformin in selected individuals. Insulin and other agents are recommended in patients with very high levels of hemoglobin A1c or blood glucose, severe symptoms, or who do not respond to metformin at the maximum dose.[2]

Relevance to patient-centered outcomes	SYMPTOMS • Prediabetes often has no symptoms. Symptoms of type 2 diabetes include increased urination, increased thirst, unexplained weight loss, fatigue, blurred vision, increased hunger and sores that do not heal.[13] PATIENT-CENTERED OUTCOMES • Prediabetes increases the risk of diabetes and its complications and long-term outcomes.[14] • Diabetes is associated with numerous complications including cancer, cardiovascular disease, cognitive impairment, depression, fatty liver disease, fractures, gastroparesis, hearing impairment, low testosterone in men, nephropathy, neuropathy, obstructive sleep apnea, periodontal disease, decreased quality of life, retinopathy, and vision loss.[2,15] The practical effects of these complications include dizziness, limited mobility due to numbness in feet and poor vision. Complications can lead to amputations, blindness and falls, with many patients having anxiety of fear of developing one of these outcomes. • Attending the many health care visits for screening and treatment of complications can result in lost work time for the individual with type 2 diabetes and their family members or caretakers. • Costs of diabetes care are a patient-important outcome.[16] • Some individuals may not have the time, commitment or financial means to adhere to lifestyle modifications for the management of prediabetes or diabetes. • The adverse effects of medications may be less tolerated for individuals with prediabetes who are predominately asymptomatic.
Burden on Society	
Recent prevalence in populations and subpopulations	INCIDENCE & PREVALENCE [17] • 46% of adults in the U.S. have prediabetes or diabetes. o In 2012, 86 million Americans age 20 and older had prediabetes.[17-20] Based on fasting glucose or hemoglobin A1c levels measured between 2009 and 2012, 37% of U.S. adults aged 20 years or older had prediabetes. Prediabetes is very common among the elderly, with 51% of those aged 65 years or older meeting the criteria for prediabetes. o In 2012, 29.1 million Americans (9.3% of the population) had 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. There were 1.7 million new cases of diabetes in 2012. • Prediabetes does not appear to differ by race/ethnicity. Based on fasting glucose and hemoglobin A1c levels, 35% of non-Hispanic whites, 39% of non-Hispanic blacks and 38% of Hispanics have prediabetes. Prevalence of prediabetes estimates for other races are not available in the most recent National Diabetes Report. • The age-adjusted prevalence of diabetes does differ by race/ethnicity. Between 2010 and 2012, 15.9% of American Indians/Alaska Natives, 13.2% of non-Hispanic blacks, 12.8% of Hispanics, 9.0% of Asian Americans and 7.6% of non-Hispanic whites had diabetes. • Individuals at increased risk of prediabetes and diabetes include individuals that are overweight or obese, those who have a family member with diabetes, women who had gestational diabetes and children whose mothers had gestational diabetes. [13]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• Most people with prediabetes do not display symptoms. Despite the absence of symptoms, individuals with prediabetes have poorer quality of life and a shorter life span than the population without impaired glucose. Because individuals with prediabetes are more likely to be overweight and obese and have cardiovascular disease, they are more likely to use health care services. • Patients who progress to type 2 diabetes from prediabetes have greater health care costs than those who maintain prediabetes and individuals without glucose impairment.[21] • In 2011, there were 282,000 ER visits for hypoglycemia and 175,000 visits for hyperglycemic crisis. Among those with visits for hyperglycemic crisis, 2,361 died.[22] • Diabetes is the 7th leading cause of death in the U.S.[23] Individuals with prediabetes and diabetes have greater mortality rates than the population without diabetes. Those with diabetes have greater mortality than those with prediabetes (20 vs 14 per 1,000 person-years).[18] • Preventing progression to type 2 diabetes could have substantial effects on the health care system. Individuals with diabetes have 2 times greater medical expenditures than the population without diabetes. Diabetes cost the U.S. medical system 245 billion dollars in 2012: o 69 billion in reduced productivity[24] o 176 billion direct medical costs:[24] ▪ Hospital inpatient care (50% of total cost) ▪ Diabetes medication and supplies (12%)

	▪ Retail prescriptions to treat complications of diabetes (11%) ▪ Physician office visits (9%) • Many people with prediabetes will progress to type 2 diabetes (40-60%). Delaying diagnosis of type2 diabetes can delay the onset of the numerous complications of type 2 diabetes.
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• Nearly 50% of the adult U.S. population has prediabetes or diabetes. The proportion of the population with diabetes is expected to increase by 2050.[2] The large burden of disease justifies CER with 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?	• No systematic review in the Cochrane library aimed to examine long-term outcomes of prediabetes treatments. • There are no previous or ongoing systematic reviews conducted by the Evidence-based Practice Center that aimed to examine long-term outcomes of treatments for prediabetes. • The Diabetes Prevention Program is the landmark study to examine the effectiveness of treatments to prevent progression to type 2 diabetes.[25] o The intensive lifestyle modifications recommended for treatment of prediabetes and type 2 diabetes are not covered by most health plans despite evidence of their effectiveness. In the landmark Diabetes Prevention Program trial, an intensive lifestyle modification where participants aimed to reduce body weight by 7% and perform at least 150 minutes of moderate intensity physical activity per week prevented progression to diabetes better than metformin even after 10 years of follow up.[26] o The effectiveness of timing of medical treatment with metformin on the development of long-term complications is not well-studied. The Diabetes Prevention Program Outcomes Study plans to study the effects of metformin on cancer that have been described in other studies.[27] Long-term treatment with metformin has been associated with decreased risk of cancer, including breast, colorectal, liver, and pancreatic cancer.[28,29]

What could new research contribute to achieving better patient-centered outcomes?	• New weight-loss and type 2 diabetes drugs are available that may serve as alternatives or adjuncts to metformin. Understanding the safety of these medications and risk-benefit profile for prediabetes versus type 2 diabetes is needed. • Wearable technology may be able to increase compliance with lifestyle modifications or allow researchers to compare the intensity levels of different lifestyle modifications required to have an effect on long-term outcomes. These technologies may be especially useful to increase self-monitoring in individuals with prediabetes who do not want to take medications. • New research could help to improve understanding of when to start medication after "failed lifestyle intervention" for prediabetes. • Given the broad implications of prediabetes and diabetes and the fact that they are almost purely driven by lifestyle, research to promote population-level lifestyle change (*i.e.,* built environment, policy, behavior) are particularly important.
Have recent innovations made research on this topic especially compelling?	• Adaptive trial designs may facilitate comparison of lifestyle intervention intensities and medications in a more flexible manner.[30] • Trials on medications, surgical innovations and devices recently approved or in development for weight loss, which have implications for prediabetes treatment, and type 2 diabetes are very active and have resulted in numerous new treatment options.[31-33] • Wearable technology and mobile device monitors can collect biometric information and assist in implementing lifestyle changes. Some patients may be using these devices already despite the absence of high-quality information to support their accuracy and effectiveness.
How widely does care now vary?	• Estimates on the variation in metformin for prediabetes are not available. Metformin use in prediabetes likely occurs in <1% of patients.[34] • Among adults with type 2 diabetes during 2010-2012, 14% used no medication, 60% used oral medication only, 14% used insulin only and 15% used oral medication and insulin.[17]
What is the pace of other research on this topic (as indicated by recent	ClinicalTrials.gov Our search of ClinicalTrials.gov on March 17, 2015 identified 21 long-term studies of prediabetes. • The Diabetes Prevention Program Outcomes Study (the long-term follow-up to the trial that ended in 2001) aims to study the development of diabetes, microvascular

publications and ongoing trials)?	complications, cardiovascular risk factors, ageing related outcomes, subclinical atherosclerosis, quality of life, and economic analyses.[35] • One completed study without results compared two different formulations of voglibose with a primary outcome of diabetes prevention (NCT01993927). Although no specific long-term outcome of interest is mentioned, the trial register does mention that diabetes retinopathy will be measured and that other outcomes will be measured. This product is not currently approved by the FDA. • One study currently recruiting patients seeks to examine the effects of smoking cessation on development of type 2 diabetes and cardiovascular events over at least 3 years (NCT01926041). <u>NIH Reporter</u> Our search of NIH Reporter on March 17, 2015 identified twelve projects that mentioned long-term prediabetes trials. No study was longer than 2 years and none specifically mentioned long-term outcomes.
How likely it is that new CER on this topic would provide better information to guide clinical decision making?	• It is very likely that new CER on this topic will provide better information to guide clinical decision-making. According to our clinical expert there is insufficient information on when to consider lifestyle intervention a failure as a treatment for prediabetes. Clarity on when to start medication treatment after failed lifestyle changes is left to the discretion of providers. Definitive research on this topic could drastically change the use of metformin therapy for diabetes prevention.
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: • Health care reform may increase the availability of multidisciplinary type 2 diabetes clinics which facilitate single-site access to health care providers trained in the lifestyle interventions and medication treatments for prediabetes and type 2 diabetes.[36] • Primary care providers and diabetes experts are eager to help patients prevent type 2 diabetes. BARRIERS: • Methods to increase adherence to lifestyle modifications and medications are needed. Even with better evidence of effectiveness, not all patients adhere to their prescribed treatment. Identifying which patients increase adherence with treatment

	choice and which do not may be needed.[37] • The limited time available during clinic visits may be insufficient to provide the screening and treatment plan information that patients need to make informed decisions about their prediabetes and type 2 diabetes risk and treatment plans. The average primary care visit lasts about 18 minutes.[38] • Patients with prediabetes may be hesitant to take a medication or modify their lifestyle to prevent a disease when they are asymptomatic.
How likely is it that the results of new research on this topic would be implemented in practice right away?	• With nearly 50% of the adult population affected and the growing number of treatment options, it is extremely likely that new information will be implemented in practice right away. • The American Diabetes Association annually updates its Standards of Care in Diabetes with the best available evidence on prediabetes and type 2 diabetes. New information will be distributed to providers in the annual update.[2]
Would new information from CER on this topic remain current for several years?	• It is unlikely that lifestyle interventions for prediabetes and type 2 diabetes will become obsolete. • Despite the rapidly growing armamentarium, there is limited information on the occurrence of long-term outcomes. • The results of comparative effectiveness research on this topic will remain current for at least several years. • Evidence on metformin will likely be enduring given its durability in treatment of type 2 diabetes and general benefit-risk profile.

References for topic 2: Comparative effectiveness of early treatment (prediabes stage) strategies versus treatment initiated after Type II diabetes has been diagnosed on long-term patient outcomes (B-cell function, cardiovascular morbidity, and mortality)

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Topic 4:

Comparative effectiveness of high-intensity statin versus low-intensity statin in the prevention of CVD

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION • Cardiovascular disease (CVD) refers to conditions of the heart and blood vessels. Two of the most serious and most common types of CVD are heart attack and stroke, both of which can be caused by narrowed or blocked blood vessels. • The main risk factors for CVD include high cholesterol levels, hypertension, obesity, physical inactivity, tobacco exposure, and diabetes mellitus. People with high levels of low-density lipoprotein cholesterol (LDL-c) may have a greatly increased risk of CVD.[1] • Beyond their cholesterol-lowering effects by directly reducing LDL-c and preventing cardiovascular events in people with or without established coronary artery disease, some research suggests that statins may play an immunomodulatory and anti-inflammatory function that involves other effects on blood vessels such as stabilization of arterial plaques and reduced susceptibility to formation of blood clots in the arteries.[2] • The 2013 American Heart Association/American College of Cardiology (AHA/ACC) guidelines used absolute 10-year atherosclerotic CVD risk estimates to guide decisions about initiation and choice of statin therapy. Unlike prior guidelines that focused on cholesterol levels, these guidelines focus on absolute risk of CVD, regardless of baseline LDL. [3] • The 2013 AHA/ACC guidelines define high-, moderate-, and low-intensity statin therapy as a daily dose that lowers LDL-c by 50%, 30% to 49%, and less than 30%, respectively (Table).[3] **Table. Guideline Recommended Statin Therapies** **Low-Intensity Statin Therapy** | **Moderate-Intensity Statin Therapy** | **High-Intensity Statin Therapy** Daily dose that lowers LDL-c < 30% | Daily dose that lowers LDL-c by 30% to 50% | Daily dose that lowers LDL-c ≥ 50% Simvastatin 10mg Pravastatin 10-20mg | Simvastatin 20-40mg Pravastatin 40-80mg | Atorvastatin 40-80mg Rosuvastatin 20-40mg

	Lovastatin 20mg Fluvastatin 20-40mg Pitavastatin 1mg	Lovastatin 40mg Fluvastatin 40mg Fluvastatin XL 80mg Pitavastatin 2-4mg Atorvastatin 10-20mg Rosuvastatin 5-10mg		

- For secondary prevention of CVD events (*i.e.,* in people with existing CVD), evidence from randomized controlled trials (RCTs) supports the benefit of a high-intensity statin compared to a lower intensity statin. The 2013 AHA/ACC guidelines recommend high-intensity statin therapy for adults with existing CVD up to the age of 75 years and moderate-intensity statin may be considered for those age >75 if the patient is not a candidate for high-intensity statin therapy. For older patients with CVD, the guidelines call for discussion of the risks and benefits of statin therapy relative to an individual's overall health status.
- For primary prevention of CVD-related events (*i.e.,* in people without known CVD), the incremental benefit of high-intensity statin compared to moderate- or low-intensity statin therapy is less well established and uncertainty remains. The 2013 AHA/ACC guidelines recommend a high- or moderate-intensity statin for adults 40 to 75 years old with an LDL-c between 70 and 189 mg/dl if they have an estimated 10-year CVD risk of 7.5% or more. Moderate-intensity statin is recommended as a reasonable option for those with a 10-year CVD risk between 5% and 7.5%. The guidelines emphasize the importance of having a discussion of the risks and benefits of statin therapy tailored to an individual's condition and risk factors.[3] Whether the management strategy should focus on cholesterol levels or cardiovascular risk remains under discussion.

Relevance to patient-centered outcomes	SYMPTOMS • People with high cholesterol levels generally have no associated symptoms, but high triglyceride levels can cause pancreatitis with abdominal pain. • High cholesterol is asymptomatic, but is generally associated with atherosclerosis and/or CVD. The first presentation of CVD may be myocardial infarction or sudden cardiac death. • Seventy to 80% of patients with sudden cardiac death have CVD,[4] emphasizing the importance of prevention.

	PATIENT-CENTERED OUTCOMES • Mortality • Cardiovascular events (including heart attack and stroke) • Chronic cardiovascular disease (including angina and congestive heart failure) • Quality of life • Adverse effects of statins (*e.g.,* muscle pain or weakness, gastrointestinal symptoms, or new onset of diabetes mellitus)
Burden on Society	
Recent prevalence in populations and subpopulations	INCIDENCE AND PREVALENCE • In the U.S., 720,000 persons have a heart attack each year. • 71 million adults (34% of the U.S. population) have high LDL-c, of whom less than half get treatment and less than a third have their LDL-c under control. • About 28% of the population older than 40 years old was using a cholesterol-lowering medication in 2011-2012, of whom 93% used a statin. Simvastatin was the most frequently prescribed statin (42%), followed by atorvastatin (20%), pravastatin (11%), rosuvastatin (8%), and lovastatin (7%).[5] • The use of statins increases with age but does not differ by sex, race, or ethnicity. The benefit of statins is comparable across demographic characteristics.[6-8] Using the 2013 ACC/AHA guidelines, the prevalence of people in the U.S. eligible for statin therapy has increased to 56 million compared to 43 million under the prior guidelines.[9]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• The effectiveness of statins to reduce the risk of CVD is well-established. Even in low-risk patients with a predicted 5-year CVD risk of less than 10%, each 1 mmol/L reduction in LDL-c with statin therapy can reduce absolute major vascular events by 11 per 1000 treated individuals over 5 years.[10] However, statin therapy may be associated with adverse effects, by causing muscle problems and an increased risk of developing type 2 diabetes mellitus.[11-13] • Not all individuals will benefit from treatment, especially those at low risk of CVD events.[14] • In 2011, 787,000 individuals died from heart disease and 380,000 died from CVD in the U.S.[15] An estimated 17.5 million people died from CVD in the world, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke. In the U.S, there were 787,650 deaths from CVD, 380,000 were due to CHD.[16]

	• Direct and indirect costs of CVD, including health expenditures and lost productivity, total more than $320.1 billion annually.[5,17]
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• The societal burden is high because of the high prevalence of CVD and serious nature of the complications of CVD, as well as the large proportion of the population that is eligible for statin therapy based on current guidelines. • Statins are among the most prescribed drugs in the U.S. and the world. • Low- and moderate-intensity statin therapies are available in generic forms and are associated with fewer adverse events than high-intensity statin therapy. Because many more people became eligible for statins under the 2013 ACC/AHA guidelines, it is especially compelling to compare the benefits and risks of high- versus low-intensity statin therapy for primary prevention. • The benefits of CVD event reduction should also be placed in the context of patient preferences, costs and the risks of adverse effects of statin therapy.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	• Lifestyle modifications including healthy diet, exercise, avoidance of tobacco products, and maintenance of a healthy weight should be considered prior to and in concert with the use of statin therapy of any intensity.[18] • Evidence from systematic reviews and RCTs indicated a consistent reduction in atherosclerotic CVD events from statin therapy in both primary and secondary prevention for various patient subgroups (except in those with New York Heart Association class II-IV heart failure or receiving maintenance hemodialysis). Statin therapy reduces atherosclerotic CVD events across the spectrum of baseline LDL-C levels greater than or equal to 70 mg/dL. The absolute reduction in atherosclerotic CVD events is proportional to baseline absolute risk.[12,19,20] • In terms of different intensities of statin therapy, 5 RCTs[21-24] directly compared high- vs. moderate-intensity statin therapies for secondary prevention, and a meta-analysis of these 5 RCTs found that high-intensity statin therapy reduces atherosclerotic CVD risk more than moderate-intensity statin therapy (major vascular events per year: 3.27% vs 4.04%; RR=0.79, 95% CI 0.77–0.81, p<0.00001)[12] • Adverse events including muscle complaints occur more commonly with high-intensity statin therapy (0.5 versus 0.1 cases per 1000 persons when high intensity is used in comparison with low intensity). Patients receiving high-intensity regimens have a 12% increased risk of developing diabetes.[12,25] The guidelines concluded that the risk of adverse events "*appears to be small, compared with the benefit from atherosclerotic CVD reduction.*" [26]

	• In primary prevention, all trials compared statins (at various intensities) to placebo.[27-31] In these placebo-controlled trials, one trial used a high-intensity statin,[28] and the other trials used moderate- or low-intensity statin therapy. • On a background of statin therapy, non-statin therapies such as niacin, fibrates, and cholesterylester transfer protein inhibitors have not been shown effective in the primary prevention of atherosclerotic CVD events. For secondary prevention, one trial found that ezetimibe plus simvastatin reduced the rate of cardiovascular death, myocardial infarction, or stroke by 2% (35% for simvastatin alone versus 33% for ezetimibe plus simvastatin) in patients with stabilized acute coronary syndrome.[32]
What could new research contribute to achieving better patient-centered outcomes?	• Benefits for "lower intensity is better" for primary prevention are extrapolated from secondary prevention and from the meta-analyses showing incremental reduction in atherosclerotic CVD risk of 11 per 1000 persons over 5 years for every 1 mmol/L reduction in LDL-c. However, there are little data for those in the very low risk group (10-year predicted atherosclerotic CVD risk below 5%).[12] • Anti-PCSK9 is a new agent under investigation for lowering LDL-c.[33] Investigating the role of Anti-PCSK9 combined with different intensities of statin therapy is needed. • Studying differences in risk/benefit profiles of statin therapy based on the recent modifications to the ACC/AHA risk estimator tool are needed.
Have recent innovations made research on this topic especially compelling?	• Ongoing research has focused primarily on 3 areas: validating the ACC/AHA risk estimator tool; the adverse effects associated with statin therapy (*e.g.,* risk of diabetes and muscle pain); and treating individuals earlier in life. • Using the 2013 ACC/AHA guidelines, 56 million people, nearly half of the US population between the ages of 40 and 75, are eligible to take statin therapy compared to 43 million under the prior ATP-III guidelines.[9] • The risk of diabetes is greater for high- compared to low-intensity statin therapy, giving some pause of whether providers should be prescribing so many patients high-dose statin therapy for primary prevention.[10] • The development of new medications such as antibodies to proprotein convertase subtilisin/kexin-9 (PCSK9), antisense oligonucleotide inhibitors of apolipoprotein production, microsomal transfer protein inhibitors, and acyl-coenzyme A cholesterol acyl transferase inhibitors have provided an evidence base for renewed interest in the hypothesis that lower LDL-c is better.[39] • The growing data on the benefits of coronary artery calcium scores to refine risk prediction to better estimate CVD risk makes this a compelling topic.

How widely does care now vary?	• The compliance with the 2013 AHA/ACC guidelines are unknown. The guidelines recommend: *"Primary prevention in individuals with LDL-c ≥ 190 mg/dL: use high-intensity statin therapy unless contraindicatedcontraindicatedcontraindicated (moderate recommendation); for individuals unable to tolerate high-intensity statin therapy, use maximum tolerated statin intensity (moderate recommendation).* *Primary prevention in individuals with diabetes and LDL-c 70-189 mg/dL: moderate-intensity statin therapy should be initiated or continued for adults 40-75 years of age (strong recommendation); high-intensity statin therapy is reasonable for adults 40-75 years of age with a ≥7.5% estimated 10-year atherosclerotic CVD risk (expert opinion); in adults who are <40 or >75 years of age, it is reasonable to evaluate the potential for atherosclerotic CVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy (expert opinion).* *Primary prevention in individuals without diabetes and with LDL-C 70-189 mg/dL: used the Pooled Cohort Equations to estimate 10-year atherosclerotic CVD risk to guide initiation of statin therapy (expert opinion); individuals with estimated risk ≥7.5% should be treated with moderate- to high-intensity statin therapy (strong recommendation); individuals with estimated risk of 5% to 7.5% could be treated with moderate-intensity statin therapy (weakweakweak recommendation)."* • Despite the new recommendations, some providers are still treating patients based on the previous LDL target and some feel more comfortable with lower- than higher-intensity statin therapy. Some physicians may prefer adding other lipid-modifying agents (*e.g.,* fibrates, niacin, ezetimibe) instead of increasing the dose of statin therapy.[40-42]
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	• We searched ClinicalTrials.gov on February 27, 2015 and found 157 studies using the strategy "("("(atorvastatin OR rosuvastatin) AND (simvastatin OR pravastatin OR lovastatin OR fluvastatin OR pitavastatin)".)".)". Almost all of these studies registered CVD or hypercholesterolemia or dyslipidemia as the conditions of interest. A quarter of these studies registered diabetes mellitus as the condition. Three quarters of studies (114/157; 73%) have completed recruitment and one fifth (30/157; 19%) have results available. In terms of outcomes, almost all studies have focused on cholesterol level as the primary outcome. • None of the trials compares high-intensity vs. low-intensity statin therapy for

	primary prevention of CVD. • 16 trials compared atorvastatin or rosuvastatin versus a less potent statin for cholesterol control or secondary prevention of CVD. The dose of the statin therapy varied across trials and some may not be considered as "low" intensity statin therapy using the 2013 AHA/ACC guidelines (NCT00249249, NCT00309751, NCT00344370, NCT00631189, NCT00382460, NCT00159835, NCT00380939, NCT00654537, NCT00654173, NCT00654407, NCT01166633, NCT00141141, NCT00889226, NCT00861861, NCT01223586, NCT01386853). • 11 trials compared ezetimibe/simvastatin versus another statin therapy in various patient populations (NCT00862251, NCT00782184, NCT00166504, NCT00496730, NCT00442897, NCT00525824, NCT01164397, NCT00157924, NCT00092690, NCT01185236, NCT00267267). None of these trials registered CVD events as the primary outcome.
How likely it is that new CER on this topic would provide better information to guide clinical decision making?	It is very likely that new comparative effectiveness research on this topic will provide better information to guide clinical decision-making. The most recent guidelines recommend statin therapy for a much larger number of patients than the previous guidelines. Detailing the comparative effectiveness of statin therapy in the population newly recommended for treatment may increase adherence with the guidelines.
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 a lot of interest in this topic because of the recent changes to the guidelines. • Patients and providers seem to be more interested in lower-intensity statin. BARRIERS: • Some patients do not want to take a daily prescription for statins, and low-risk individuals may not want to take any statin therapy. • There exists discomfort with current recommendations.[43,44] Some doctors are not comfortable with prescribing a statin therapy for primary prevention in the low risk group or basing treatment on the 10-year atherosclerotic CVD risk estimate. Implementation of the current recommendations in primary care setting has been challenging. • Primary prevention trials require a large sample size and long follow-up time.

How likely is it that the results of new research on this topic would be implemented in practice right away?	Evidence that addresses the controversy surrounding the new guidelines will likely be implemented into practice right away.
Would new information from CER on this topic remain current for several years?	New information from comparative effectiveness research is likely to remain current for several years. Statin therapy is likely to remain a treatment for CVD prevention for the foreseeable future.

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Topic 5:
Comparative effectiveness of antiretroviral (ARV) drugs (3TC/FTC + boosted PI versus 2NRTI + boosted PI) in the treatment of HIV infection

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION[1,2] • HIV or human immunodeficiency virus is the virus that can lead to acquired immunodeficiency syndrome (AIDS). HIV attacks the host immune system, especially the T cells (CD4) which defend against infections. As CD4 numbers drop and viral burden (viral load) goes up, the immune system weakens and the patient develops infections and other complications. AIDS is diagnosed when HIV infection is associated with one or more infections, certain cancers, or a very low number of CD4 cells. • To date there is no treatment that cures HIV infection. HIV infection is a lifelong disease. • All treatments are designed to control the disease and its manifestations. The purpose of treatment is to stop the virus from replicating, diminish viral load and increase the CD4 count. • As more potent and less toxic drugs have become available, the guidelines for antiretroviral therapy (ART) have recommended initiating treatment as soon as the diagnosis of infection is made, no matter the CD4 count. This contradicts past guidelines that recommended treatment only when CD4 counts dropped below a certain number. Today there are 28 approved antiretroviral drugs and 7 first-line regimens. All of the recommended regimens involve use of at least 3 drugs to achieve a synergistic effect. • Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are generally given in pairs as advised in guidelines, and this is the backbone of therapy. The NRTIs tenofovir (TDF) and emtricitabine (FTC, which stands for 2',3'-dideoxy-5-fluoro-3'-thiacytidine) have been used in most studies, with a variety of different third agents. Another option is the combination of the NRTIs abacavir (ABC) and lamivudine (3TC, which stands for 2',3'-dideoxy-3'-thiacytidine) with a third agent. 3TC (lamivudine) and FTC (emtricitabine) are pharmacologically equivalent NRTIs. • The other types of drugs included in recommended regimens include: protease inhibitors (PIs) such as darunavir, lopinavir, or atazanivir (ATV), which are given with another agent (booster) to improve drug concentrations (*e.g.,* lopinavir + ritonavir

	or LPV/r); non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as efavirenz; or integrase strand transfer inhibitors (INSTIs) such as raltegravir. • This topic addresses the issue of simplified therapy using only one NRTI (referred to in this brief as single NRTI therapy). The recent GARDEL study found improved outcomes with this regimen compared to a regimen with 2 NRTIs, but this study had the drawback of using an older PI combination that is no longer considered the PI of choice due to toxicity and tolerability. A study using a better-tolerated additional agent is needed. • Regimens can be complex and pill burden substantial. Some simplified strategies combine multiple medications into one pill and others use fewer medications; both might improve adherence. A pill combination for a single NRTI regimen is not currently available and the impact on adherence has not been studied for a one NRTI regimen. Simpler regimens including fewer active agents could also potentially reduce adverse effects and therefore improve adherence as well. The key guidelines used in the U.S. are: • Panel on Antiretroviral Guidelines for Adults and Adolescents from the Department of Health and Human Services.[3] • The Recommendations of the International Antiviral Society-USA 2014 Panel.[4] • World Health Organization (WHO) recommendations.[5,6]
Relevance to patient-centered outcomes	SYMPTOMS • Symptoms depend on stage of infection. Initial symptoms of HIV infection are usually flu-like symptoms. • As viral loads increase and CD4 counts decrease, other infections and cancers may develop with associated symptoms. PATIENT-CENTERED OUTCOMES • Social isolation and stigma • Adverse events and toxicity from treatment • Disability (with greater impact in working-age adults) • Risk of transmission for partners and family • Risk of mother-child transmission • Psychosocial and educational needs • Adherence or pill burden (regimen complexity) • Major limitations of treatment are toxicity and lack of adherence • Drug resistance

	• Opportunistic infections and adverse effects of their treatment
Burden on Society	
Recent prevalence in populations and subpopulations	PREVALENCE • In 2013, there were about 35 million people infected with HIV in the world, including 3.2 million younger than 15. That same year, there were 2.1 million people newly infected with HIV and 1.5 million people died from AIDS.[7] • In 2012, there were about 1.2 million people infected with HIV in the U.S, including 14% who are unaware of the infection. That same year, there were 50,000 people newly infected with HIV and 13,172 people died from AIDS.[8] • In the U.S. 44% of HIV-infected people are African Americans, 31% are whites and 21% are Latinos. Males comprise 88% of HIV-infected population. INCIDENCE • About 50,000 people are infected every year with HIV, but there are only 32,000 confirmed diagnoses per year. • 26% of new cases each year are adolescents and young adults between the ages of 13 and 24 years, 31% are young adults between the ages of 25 and 34 years, 24% are 35 to 44 years old, 15% are 45 to 54 years old and 4% are 55 years or older. • The incidence of HIV infection among African Americans is about 8 times higher than among whites. • 80% of HIV transmission is due to sexual contact (50% homosexual, 30% heterosexual). Twelve percent of transmission is due to injection drug use.[9]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• Patients infected with HIV have lower perceived quality of life, poorer physical and social functioning and, as disease progresses, chronic debilitation. Quality of life is affected not only by the disease itself but by the adverse events of treatments available. The social stigma carried by the HIV infection adds to the burden of a chronic disease.[10] • Coverage of HIV treatment is available through Medicare, Medicaid, the Ryan White Program, and the AIDS Drug Assistance Program (ADAP), a state-administered program that provides HIV-related medications to low-income individuals with HIV/AIDS who are uninsured or have limited access to prescription drug coverage. In June 2013, 210,000 HIV patients were enrolled in ADAP. • The ADAP budget for 2015 is $30.4 billion for HIV and AIDS spending; 57% of the

	budget is planned for care and treatment programs.[9] • Since the HIV epidemic started, 648,459 people have died in the U.S. with a diagnosis of AIDS. • The death rate for HIV has been estimated at 6.7 persons per 100,000 per year.
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• The societal burden of HIV infection is enormous. As people are generally infected with HIV at relatively young ages and HIV is now considered a chronic illness in the U.S., patients are affected by HIV for decades. • Although many treatment options are available, there are many side effects and long-term consequences of HIV treatment. Non-adherence is a major concern because of the potential to develop resistance to HIV medications. Thus, CER on alternative approaches to improving medication adherence and compare the effectiveness of different regimens on resistance could have a great impact in reducing the societal burden.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	We identified no systematic reviews on the specific topic of single NRTI therapy, Older studies found worse outcomes with simplified regimens, but there are some newer studies with equivalent or better outcomes, although all have significant drawbacks. • The topic is based on the GARDEL (Global AntiRetroviral Design Encompassing Lopinavir/r and Lamivudine vs LPV/r based standard therapy) clinical trial and several similar studies. The GARDEL study was an open-label, randomized clinical trial in 426 treatment-naive patients. Patients had to be over the age of 18, in otherwise good health, with no other abnormal laboratory results and no alcohol or substance misuse. Randomization was to a single NRTI (3TC) 150 mg twice a day or 3TC plus an investigator-selected second NRTI. All study participants received lopinavir/ritonavir twice daily. At 48 weeks, 88% of the one NRTI group and 84% of the two NRTIs group achieved HIV viral loads of less than 50 RNA (ribonucleic acid) copies per mL. One percent of the one NRTI group had missing data at week 48 due poor adherence compared with 5% in the two NRTI group (p = 0.03). The rates of virologic failure and resistance were not significantly different between study groups. Among patients with high viral load (>100,000 RNA copies per mL), 87% vs 78% had less than 50 RNA copies at week 48.[11] However, this study had the drawback of using an older PI combination (lopinavir/ritonavir) that is no longer considered the PI of choice due to toxicity and tolerability. Newer 3rd agent options are also very effective with low toxicity.

	• The OLE (Open Label Extension) trial randomized 250 patients already on therapy with lopinavir/ritonavir plus two NRTIs to either continue this regimen or switch to therapy with lopinavir/ritonavir plus only 3TC. In 2014, the 48-week follow-up results were published in abstract form. Rates of virologic failure, viral load, and adverse events were not statistically significantly different between the two groups.[12] This study has the same drawback as the GARDEL study. • The SALT (Simplification to Atazanavir/Ritonavir + Lamivudine) trial, published in abstract form in 2014, randomized 286 patients to a regimen including atazanavir/ritonavir and 3TC versus standard therapy with atazanavir/ritonavir plus 2 NRTIs. The outcomes were similar in the two groups for virologic failure and adverse events.[13] • ACTG (AIDS Clinical Trials Group) 5142, published in 2008, evaluated regimens using efavirenz (an NNRTI), but did not evaluate therapy using only one NRTI. This trial evaluated three regimens: efavirenz plus 2 NRTIs, lopinavir/ritonavir plus 2 NRTIs, and lopinavir/ritonavir plus efavirenz (the NRTI-sparing group). The group with efavirenz plus 2 NRTIs had statistically significantly improved time to virologic failure and viral load than the group with lopinavir/ritonavir plus 2 NRTIs. Virologic failure outcomes were similar with the NRTI-sparing regimen compared with the efavirenz plus 2 NRTI regimen, but there was a higher rate of drug resistance.[14] This study provides some evidence for equivalence of simplified therapy for one outcome but did not use a single NRTI regimen.
What could new research contribute to achieving better patient-centered outcomes?	• As the population with HIV ages, side effects and the impact of treatment on diseases of aging (*e.g.,* heart disease) is of increasing importance, leading to need for continued development of regimens that are better tolerated with fewer side effects. • Future research could address patient preferences regarding the choice of different first-line therapies, taking into consideration side-effect profiles. • Better studies on adherence could quantify the impact of patient-reported side effects on adherence. In particular, some combinations are available in once-daily single-pill combinations, which may be favored by patients and have been shown to be associated with significantly better adherence. One study found that patients receiving once-daily single-tablet therapy had not only significantly higher adherence than those taking more complex regimens, but significantly fewer hospitalizations (by 23%) and lower costs.[15] Adherence is important because of the implications for development of resistant HIV, which affect the overall effectiveness

	of treatment for the patient and long-term outcomes. • In general, studies and guideline recommendations are based on clinical outcomes, including virologic response and clinical adverse events such as jaundice or lipids, not on patient-reported outcomes.[3] Studying patient-important outcomes to improve adherence and decrease resistance is needed.
Have recent innovations made research on this topic especially compelling?	The most important new finding from recent research is that the GARDEL study demonstrated improved outcomes with therapy using only one NRTI and other studies have shown non-inferiority of a regimen using only one NRTI. The one NRTI regimen might increase adherence, which should have downstream effects on resistance, although this has not been studied. However, the GARDEL study had the drawback of using an older PI combination (lopinavir/ritonavir) that is no longer considered the PI of choice due to toxicity and tolerability. Other newer 3rd agent options are also very effective with low toxicity. New research with a different combination would therefore be needed to include a one NRTI regimen in guidelines.
How widely does care now vary?	• Established guidelines are used as the basis for care, but appropriate indications for simplified regimens are not addressed in current guidelines. Simplified therapy is not generally used due to lack of sufficient evidence from clinical trials and lack of recommendation in guidelines except for particular cases where resistance, comorbidity, or side effects are an issue. However, the currently prescribed simplified therapies are often NRTI-sparing regimens, not regimens containing a single NRTI. • Little is known about actual patterns of use of these simplified regimens. One recent study evaluated practice patterns in Medicaid patients in 15 states and found that about half were receiving drug combinations not recommended in guidelines, but did not specify the frequency of those combinations (such as use of regimens with only 1 NRTI).[16]
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	Few studies were identified addressing this specific single-NRTI regimen, although many other studies evaluating new HIV medications and regimens are ongoing. <u>Clinicaltrials.gov</u> Our search in Clinicaltrials.gov identified one relevant single-NRTI study. • In the Atazanavir and Lamivudine for Treatment Simplification (AtLaS-M) study, atazanavir/ritonavir plus 3TC was compared to atazanavir/ritonavir plus 2 NRTIs, and

	was found to be non-inferior, but with a greater increase in CD4 count, increased cholesterol levels, and improvement in renal function within 24 weeks, according to preliminary results published in November 2014. Results of the 48-week trial results are not yet available.[17] <u>NIH Reporter</u> Our search in the NIH Reporter identified no other studies on this specific therapy simplification topic.
How likely it is that new CER on this topic would provide better information to guide clinical decision making?	• Pragmatic trials or observational studies might be useful as patients treated with these regimens in clinical practice are likely to be different than those included in clinical trials. CER should address issues with adherence, resistance to other HIV medications, and optimal treatment regimens in patients with comorbidities. • There is insufficient evidence on these new treatment regimens due to drawbacks of current research. New CER will provide important information to guide clinical decisions.
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 interest in the results of trials of single NRTI regimens, and providers are interested in using these regimens if they have improved outcomes over existing regimens. • Some patients cannot tolerate or cannot receive current standard regimens for a variety of reasons. Simplified regimens may be attractive to this population. BARRIERS: • Simplified regimens may not significantly improve adherence by reducing pill burden or reducing side effects. • Differences in outcomes are likely to be small and effectiveness uncertain, given that patients treated in actual practice are often very different from those included in clinical trials, who have fewer comorbidities and are more likely to be adherent.

How likely is it that the results of new research on this topic would be implemented in practice right away?	• Guidelines and practice are based on randomized, controlled trials, and therefore comparative effectiveness research not using a randomized trial design is unlikely to change practice. • Because improved outcomes are likely to be small in magnitude and mixed based on the existing randomized trial results (*e.g.,* new regimens might have better results on CD4 count but increase cholesterol, as in the Atlas-M study), new results from clinical trials without clear benefits on outcomes, adherence or resistance may not lead to changes in practice.
Would new information from CER on this topic remain current for several years?	• There is a strong pace of ongoing research and drug development in HIV, so it is possible that subsequent studies and new medications would make new information obsolete. However, at this point, chronic drug therapy is likely to be the standard treatment for most patients for many years, as treatments to cure HIV are not on the near horizon. • Tenofovir is being reformulated and this will be released in the next year. The reformulated version purportedly has fewer renal and bone side effects than the currently approved formulation, and may be substituted in the combined regimens. The release of these new treatment will likely change the field within the next year and may make current ongoing studies less relevant.[18]

References for topic 5: Comparative effectiveness of antiretroviral (ARV) drugs (3TC/FTC + boosted PI versus 2NRTI + boosted PI) in the treatment of HIV infection

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