



# PROVIDER UPDATE

An Update for Highmark Health Options Providers and Clinicians

## THIS ISSUE

Page

### PROVIDER UPDATES

Quarterly Outreaches. . . . .	2
Provider Satisfaction Survey. . . . .	2
Community Resource Connection.....	2
Screening for Drug Interactions with Hepatitis C Meds. . . . .	3
Medications on Highmark Health Options Formulary: Preferred.....	5
Therapeutic Considerations for Use of Oral Hepatitis C Drugs.....	6
Aspirin for CV Primary Prevention and More.....	11
Pneumococcal Vaccine in Adults.....	18
Prediabetes FAQ's.....	21
Highmark Health Options Quality Improvement Program.....	26
CAHPS Satisfaction Scores.....	27
Reportable Conditions.....	28
Continuity of Coordination and Care.....	28
Member Rights and Responsibilities.....	28

### PRIOR AUTHORIZATION

Medications to Require Prior Medical Authorization . . . . .	29
Procedure Codes Requiring Authorization. . . . .	29
What if Medication Is Not On the List?. . . . .	32
Would You Prefer to Get Medication Through Pharmacy?.....	32
Submitting a Request.....	32
Additional Information.....	32



Important Phone Numbers

## PROVIDER UPDATES

### Quarterly Outreaches Via Atlas

Highmark Health Options is conducting quarterly outreaches to verify your provider data. Our Vendor, Atlas Systems, Inc. will perform the quarterly outreach on our behalf. Your cooperation in this process is extremely important to ensuring that your claims and other data are reflected correctly. You do not have to wait for the outreach call. You can and should check your own information on a consistent basis to make sure it reflects what it should.

### Provider Satisfaction Survey Launched!

Highmark Health Options recently launched the 2019 Provider Satisfaction survey. Your feedback is important to us. Please complete and let us know how we are doing.

### Reminder: Community Resource Connection System Facts and Updates

Community Resource Connection (CRC) is a tool to assist our members with accessing and learning about health and wellness support programs in their local community.

Providers can now select agencies they recommend to members directly in the provider portal. With your partnership, recommended agencies will be saved in the member's health record and we can work together to ensure members received the local support they need.



## SCREENING FOR DRUG INTERACTIONS WITH HEPATITIS C MEDS

**More patients taking hepatitis C antivirals (*Epclusa*, *Mavyret*, etc.) will have you contending with many potential drug interactions.** Interactions can lead to toxicity, or treatment failure. And this can be an expensive mistake, since antivirals cost up to \$95,000/course. Plus hepatitis C meds may fly under the radar if they're not filled at the local pharmacy. Ask patients about ALL medications, prescriptions, OTCs, supplements, etc. Suggest delaying any interacting meds that aren't critical, since hepatitis C treatment is usually just for 8 to 12 weeks.

Keep in mind, interactions vary based on the hepatitis C antiviral, but a few should raise red flags.

- **Acid reducers** can decrease antiviral absorption. Be aware of dosing limits and spacing with PPIs, H2-blockers, and antacids.
  - For example, usually avoid a PPI with *Epclusa*. Recommend using an H2-blocker instead. Should be dosed at the same time as *Epclusa* or 12 hours apart.
- **Statin** side effects (myopathy, etc.) may be more common, since antivirals can increase statin levels.
  - Generally suggest reducing or holding the statin with hepatitis C meds. For instance, limit rosuvastatin to 10 mg/day with *Mavyret* or *Zepatier*. Advise restarting the original statin dose after stopping the antiviral.
- **Anticonvulsants** can reduce antiviral levels. Avoid potent CYP3A4 inducers, such as phenytoin or carbamazepine, in combo with any hepatitis C antiviral. Think of valproic acid or lamotrigine as an option.
- **Supplements** should usually be avoided. For example, St. John's wort is a CYP450 inducer and lowers antiviral levels.

Evaluate drug interactions using the package label or the University of Liverpool's website at [Hep-DrugInteractions.org](https://www.hep-druginteractions.org). It's recognized as an authority by the Infectious Diseases Society of America. Visit: <https://www.hep-druginteractions.org/>

The chart below provides hepatitis C treatment options for treatment-naïve adults based on a genotype and presence of compensated cirrhosis.



Patient Population (treatment naive)	Regimens: frequency and duration
Genotype 1a (or unknown subtype), without cirrhosis	<ul style="list-style-type: none"> <li>• Epclusa once daily x 12 wks.</li> <li>• Harvoni once daily x 12 wks. (8 wks. if non-Black, not HIV positive, and HCV RNA &lt;6 million IU/mL)</li> <li>• Zepatier once daily x 12 wks. (only for patients without baseline NS5A polymorphisms)</li> </ul> <p>Alternatives Regimens</p> <ul style="list-style-type: none"> <li>• Daklinza once daily plus Sovaldi once daily x 12 wks.</li> <li>• Viekira XR (U.S.) once daily plus ribavirin twice daily x 12 wks.</li> <li>• Viekira Pak (U.S.) plus ribavirin twice daily x 12 wks.</li> <li>• Zepatier once daily plus ribavirin twice daily x 16 wks. (for patients with baseline NS5A polymorphisms)</li> </ul>
Genotype 1a (or unknown subtype), with compensated cirrhosis (Child-Pugh Class A)	<ul style="list-style-type: none"> <li>• Epclusa once daily x 12 wks.</li> <li>• Harvoni once daily x 12 wks.</li> <li>• Zepatier once daily (only for patients without baseline NS5A polymorphisms) x 12 wks.</li> </ul> <p>Alternative Regimens</p> <ul style="list-style-type: none"> <li>• Zepatier once daily plus ribavirin twice daily (for patients with baseline NS5A polymorphisms) x 16 wks.</li> </ul>
Genotype 1b, without cirrhosis	<ul style="list-style-type: none"> <li>• Epclusa once daily x 12 wks.</li> <li>• Harvoni once daily x 12 wks. (8 wks. if non-Black, not HIV positive, and HCV RNA &lt;6 million IU/mL)</li> <li>• Zepatier once daily x 12 wks.</li> </ul> <p>Alternative Regimens</p> <ul style="list-style-type: none"> <li>• Daklinza once daily plus Sovaldi once daily x 12 wks.</li> <li>• Viekira XR (U.S.) once daily x 12 wks.</li> <li>• Viekira Pak (U.S.) x 12 wks.</li> </ul>
Genotype 1b, with compensated cirrhosis (Child-Pugh Class A)	<ul style="list-style-type: none"> <li>• Epclusa once daily x 12 wks.</li> <li>• Harvoni once daily x 12 wks.</li> <li>• Zepatier once daily x 12 wks.</li> </ul> <p>Alternative Regimens</p> <ul style="list-style-type: none"> <li>• Viekira XR (U.S.) once daily x 12 wks.</li> <li>• Viekira Pak (U.S.) x 12 wks.</li> </ul>

Patient Population (treatment naive)	Regimens: frequency and duration
Genotype 2 (with or without compensated cirrhosis [Child-Pugh Class A])	<ul style="list-style-type: none"> <li>Epclusa once daily x 12 wks.</li> </ul> <p>Alternative Regimen</p> <ul style="list-style-type: none"> <li>Daklinza once daily plus Sovaldi once daily x 12 wks. (16 to 24 wks. for compensated cirrhosis )</li> </ul>
Genotype 3 (with or without compensated cirrhosis [Child-Pugh Class A])	<ul style="list-style-type: none"> <li>Epclusa once daily x 12 wks. (without cirrhosis, or with compensated cirrhosis [Child-Pugh Class A])</li> </ul> <p>Alternative Regimen</p> <ul style="list-style-type: none"> <li>Daklinza once daily plus Sovaldi once daily x 12 wks. (without cirrhosis)</li> <li>Daklinza once daily plus Sovaldi once daily with or without ribavirin twice daily x 24 wks. (with compensated cirrhosis [Child-Pugh Class A])</li> <li>Vosevi once daily x 12 weeks (with compensated cirrhosis [Child-Pugh Class A] if Y93H is present)</li> </ul>
Genotype 4 (with or without compensated cirrhosis [Child-Pugh Class A])	<ul style="list-style-type: none"> <li>Epclusa once daily x 12 wks.</li> <li>Harvoni once daily x 12 wks.</li> <li>Zepatier once daily x 12 wks.</li> </ul>
Genotype 5 or 6 (with or without compensated cirrhosis [Child-Pugh Class A])	<ul style="list-style-type: none"> <li>Epclusa once daily x 12 wks.</li> <li>Harvoni once daily x 12 wks.</li> </ul>

## MEDICATIONS ON HIGHMARK HEALTH OPTIONS FORMULARY: PREFERRED

*EPCLUSA, MAVYRET, RIBAVIRIN, AND ZEPATIER ARE ALL PREFERRED BUT STILL REQUIRE A PRIOR AUTHORIZATION.*

### PRIOR AUTHORIZATION CRITERIA:

[https://fm.formularynavigator.com/FormularyNavigator/DocumentManager/Download?clientDocumentId=b0x8r7KGiU-Ia3\\_SBa5\\_ng](https://fm.formularynavigator.com/FormularyNavigator/DocumentManager/Download?clientDocumentId=b0x8r7KGiU-Ia3_SBa5_ng)

## THERAPEUTIC CONSIDERATIONS FOR USE OF ORAL HEPATITIS C DRUGS

SELECTED CONSIDERATIONS RELATED TO DRUG INTERACTIONS	COMMON ADVERSE EFFECTS	MONITORING
<b>ALL REGIMENS</b>		
<ul style="list-style-type: none"> <li>All may interact with certain anticonvulsants and HIV antivirals.</li> <li>All but sofosbuvir can reduce statin metabolism. This may necessitate statin avoidance, statin dose reduction, and/or monitoring for statin muscle symptoms. Recommendations are given below for specific antiviral/statin combinations.</li> <li>For all, frequent INR monitoring is recommended in warfarin-treated patients due to fluctuations in liver function.</li> </ul> <p><b>NOTE:</b> Detailed drug interaction information can also be found at <a href="http://www.hep-druginteractions.org/">http://www.hep-druginteractions.org/</a>, <a href="http://app.hivclinic.ca">http://app.hivclinic.ca</a> (HIV/HCV Drug Therapy Guide), or in the product labeling.</p>	See individual agents.	<p><b>Before starting</b> treatment, check hep C genotype, subtype, quantitative RNA (i.e., viral load). Due to risk of reactivation of hep B by hep C antivirals, screen for current or prior hep B infection before starting treatment. Management of hep B patients is addressed in the guideline.</p> <p><b>Within 12 weeks before starting:</b> CBC, INR, liver function, eGFR (calculated).</p> <p><b>After four weeks and as clinically indicated:</b> creatinine, eGFR (calculated), liver function.</p> <p><b>Discontinue treatment</b> in the event of 10-fold increase in ALT, or any increase that is accompanied by symptoms, or increased bilirubin, alkaline phosphatase, or INR. Consider discontinuation in the event of persistent elevation &lt;10-fold.</p>

## ELBASVIR/GRAZOPREVIR (*ZEPATIER*)

**Contraindicated** with OATP1B1/3 inhibitors (e.g., cyclosporine, atazanavir, darunavir, lopinavir, saquinavir, tipranavir).

**Contraindicated** with strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort, efavirenz).

Use with moderate CYP3A inducers (e.g., bosentan, etravirine, modafinil, nafcillin) is **not recommended**.

Use with certain strong CYP3A inhibitors (e.g., cobicistat, ketoconazole) is **not recommended**.

**Statins:** max daily atorvastatin dose is 20 mg. Max daily rosuvastatin dose is 10 mg.

Max daily fluvastatin, lovastatin, or simvastatin dose is 20 mg

>5% of patients: fatigue, headache, nausea with ribavirin, moderate to severe headache and anemia.

See "All regimens," above. Also check liver function tests at week 8 (and week 12 if receiving a 16-week course).

## Glecaprevir/pibrentasvir (*Mavyret*)

May increase plasma concentrations of substrates of P-glycoprotein (P-gp) e.g., dabigatran), BCRP, OATP1B1, or OATP1B3.

Weakly inhibits CYP3A, CYP1A2, and UGT1A1.

Drugs that inhibit P-gp, BCRP, OATP1B1, or OATP1B3 may increase plasma concentrations of glecaprevir and/or pibrentasvir.

Drugs that induce P-gp and CYP3A4 may decrease glecaprevir and pibrentasvir concentrations.

**Contraindicated** drugs: atazanavir, rifampin,

**Not recommended for use with** darunavir, lopinavir, ritonavir, efavirenz, carbamazepine, phenytoin, St. John's wort, and stable cyclosporine doses >100 mg/day.

**Statins:** reduce pravastatin dose by 50%. Do not exceed rosuvastatin 10 mg/day. Use the lowest necessary dose of fluvastatin or pitavastatin.

Reduce **digoxin** dose by 50% or extend dosing interval.

See **dabigatran** labeling for dosing with P-gp inhibitors

>10% of patients: headache, fatigue.

See "All regimens," above.

Note: may increase direct and indirect bilirubin via OATP1B1/3 and UGT1A1 inhibition.



## SOFOSBUVIR/VELPATASVIR (EPCLUSA)

Velpatasvir and sofosbuvir are P-gp and BCRP substrates. Velpatasvir is metabolized by CYP2B6, CYP2C8, and CYP3A4.

Use with inducers of P-gp and/or moderate or potent inducers of CYP2B6, CYP2C8, or CYP3A4 is **not recommended** (e.g., carbamazepine, efavirenz, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St. John's wort, tipranavir/ritonavir).

Separate from **antacids** by four hours. Give **H2-blockers** with or 12 hours apart from *Epclusa* at a dose not greater than famotidine 40 mg twice daily, or equivalent. Use with **proton pump inhibitors** not recommended per U.S. labeling. If use is necessary, give *Epclusa* with food four hours before omeprazole 20 mg. These interactions are due to the velpatasvir component, not sofosbuvir.

Use with **amiodarone** may result in serious bradycardia and is not recommended.

**Topotecan** levels may be increased; concomitant use not recommended (U.S. labeling).

Max daily **rosuvastatin** dose is 10 mg. Monitor muscle symptoms with atorvastatin.

Monitor **digoxin** levels.

≥10% of patients: headache, fatigue.

See "All regimens," above.

## RIBAVARIN( *REBETOL*)

<p>No CYP450 drug interactions.</p> <p>Contraindicated with didanosine.</p> <p>Patients taking azathioprine should have a CBC weekly for one month, twice monthly for two months, then at least monthly.</p>	<p>With <i>Sovaldi</i> and <i>Daklinza</i> &gt;20% of patients, anemia, fatigue, nausea, headache.</p> <p>With <i>Viekira Pak</i>, <i>Viekira XR</i> &gt;10% of patients, fatigue, nausea, dermatologic reactions, insomnia, weakness.</p> <p>Also see <i>Zepatier</i>, above.</p>	<p>Pregnancy test at baseline, then periodically and for six months after discontinuation.</p> <p>Patients with cardiac disease should have a baseline electrocardiogram (due to cardiac risk conferred by anemia).</p> <p>CBC at baseline, weeks two and four, and periodically. Biochemical tests (e.g., liver function, uric acid, TSH) at baseline and periodically</p> <p>Dose reduction or discontinuation may be indicated in the event of a drop in hemoglobin.</p> <p>Also see “All regimens,” above.</p>
--	--	--

## REFERENCES

Clinical Resource, Hepatitis C Treatment Overview. Pharmacist’s Letter/Prescriber’s Letter. July 2019.  
(<https://www.hcvguidelines.org/>,n.d.)

## ASPIRIN FOR CV PRIMARY PREVENTION AND MORE

In 2014, the FDA denied aspirin an indication for primary prevention of MI based on primary prevention studies. But practice guidelines, including recommendations from the USPSTF, continued to recommend aspirin for primary prevention in certain populations, largely based on meta- and other analyses of the primary literature. In 2018, three high-quality primary prevention studies were published. In light of these studies, guideline recommendations regarding aspirin for primary prevention may now be outdated. The table below provides information to assist clinicians in estimating aspirin's risk/benefit ratio in patients without CVD. Use for colorectal cancer prevention is also addressed.

### Acronyms/Definitions

- **American College of Cardiology (ACC):** The American College of Cardiology is a **52,000-member medical society** that is the professional home for the entire cardiovascular care team. The mission of the College is to transform cardiovascular care and to improve heart health.
- **American College of Chest Physicians (ACCP):** The American College of Chest Physicians is the global leader in advancing best patient outcomes through innovative chest medicine education, clinical research, and team-based care.
- **American Diabetes Association (ADA):** a network of more than 565,000 volunteers, a membership of more than 540,000 people with diabetes, their families and caregivers, a professional society of nearly 20,000 health care professionals, as well as more than 400 staff members.
- **American Heart Association (AHA):** The American Heart Association is a non-profit organization in the United States that funds cardiovascular medical research, educates consumers on healthy living and fosters appropriate cardiac care in an effort to reduce disability and deaths caused by cardiovascular disease and stroke.
- **A Study to Assess the Efficacy and Safety of Enteric-Coated Acetylsalicylic Acid in Patients at Moderate Risk of Cardiovascular Disease (ARRIVE):** The ARRIVE trial was a randomized controlled clinical **study** that compared elective induction of labor at 39 weeks to expectant management of labor with women who were nulliparous and met study criteria to be identified as low risk.
- **American Stroke Association (ASA):** The American Stroke Association is solely focused on reducing disability and death from stroke

## Acronyms and definitions cont.

- **A Study of Cardiovascular Events in Diabetes (ASCEND):** The ASCEND Aspirin trial showed that the absolute reduction in cardiovascular events from aspirin was offset by a similar absolute increase in major bleeding. The goal of the trial was to evaluate aspirin compared with placebo among diabetics with no known cardiovascular disease (CVD).
- **Aspirin in Reducing Events in the Elderly (ASPREE):** showed that aspirin did not prevent disability-free survival, but did increase major bleeding compared with placebo. The goal of the trial was to evaluate low-dose aspirin compared with placebo among healthy elderly patients.
- **Antithrombotic Trialists' Collaboration (ATT)**
- **Blood pressure (BP)**
- **Cyclo-oxygenase-2 (COX-2)**
- **C-reactive protein (CRP)**
- **Cardiovascular (CV)**
- **Cardiovascular disease (CVD)**
- **Food and Drug Administration (FDA or USFDA):** The FDA is a federal agency of the United States Department of Health and Human Services, one of the United States federal executive departments. The FDA is responsible for protecting and promoting public health through the control and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed<sup>[4]</sup> and veterinary products.
- **Gastrointestinal (GI)**
- **Hypertension Optimal Treatment (HOT)**
- **Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD)**
- **Myocardial infarction (MI)**
- **Nonsteroidal anti-inflammatory drug (NSAID)**
- **Prevention of Progression of Arterial Disease and Diabetes (POPADAD)**
- **Proton pump inhibitor (PPI)**
- **Peptic ulcer disease (PUD)**
- **Relative risk (RR)**
- **Transient ischemic attack (TIA)**
- **United States Preventive Services Task Force (USPSTF)**
- **Women's Health Study (WHS)**

Clinical Question	Guideline recommendation or other pertinent information
<p>Who might be a candidate for aspirin for primary prevention of CV disease, <b>per current guidelines?</b></p>	<p><b>See new, practice-changing data <u>below</u> that may obviate these guidelines.</b></p> <ul style="list-style-type: none"> <li>• <b>USPSTF (2016 recommendations):</b> <b>age 50 to 59 years</b> with <math>\geq 10\%</math> 10-year risk of CV disease, AND not at increased risk of bleeding, AND with a life expectancy of at least 10 years, AND willing to take low-dose aspirin for at least 10 years. Also consider for <b>age 60 to 69 years</b> with <math>&gt; 10\%</math> 10-year risk of CV disease. Evidence is insufficient to assess risk/benefit in younger or older adults.</li> <li>• <b>ACCP (2012):</b> age 50 and older</li> <li>• <b>AHA/ASA (2014):</b> adults with a 10-year CVD risk <math>&gt; 10\%</math> (i.e., potential benefit is high enough to outweigh potential aspirin risks) (to prevent CV events); women with stroke risk high enough that aspirin benefits outweigh risks (to prevent stroke); or patients with chronic renal disease with eGFR 30 to 45 mL/min/1.73 m<sup>2</sup> (to prevent stroke).</li> <li>• <b>ADA (2018):</b> consider for patients with diabetes and increased CV risk (e.g., patients <math>\geq 50</math> years of age with at least one additional major risk factor: family history of premature atherosclerotic CV disease, hypertension, dyslipidemia, smoking or albuminuria) who are not at increased risk of bleeding.</li> </ul>
<p>Why might recommendations differ among guidelines?</p>	<p>The <b>USPSTF 2016 recommendations</b> used a model based on findings from three systematic reviews to estimate net benefit. Results were stratified by age, gender, and 10-year CVD risk using the 2013 ACC/AHA pooled cohort equations calculator. This model was combined with primary trial data and meta-analyses. The number of MIs and ischemic strokes prevented, the number of colorectal cancer cases prevented, and the number of serious GI bleeding events caused by aspirin were considered. They also considered lifetime net life-years and net quality-adjusted life-years gained/lost due to aspirin use.</p> <p><b>AHA/ASA</b> guidelines focus on primary stroke prevention. They cite benefit in WHS, and subgroup analyses of JPAD, and HOT, and 2009 USPSTF analysis.</p> <p><b>ACCP</b> relied on a large 2009 meta-analysis by the ATT of individual data that they felt provided the best evidence regarding the benefit/risk of aspirin for primary prevention.<sup>5</sup> Benefit in ATT was largely driven by a reduction in nonfatal MI. ACCP chose not to make recommendations based on specific patient characteristics (e.g., sex, diabetes, older age) due to concerns about the validity of the subgroup analyses necessary to make such recommendations.</p>

What new studies inform the decision to use aspirin for CV primary prevention?

- **ARRIVE** (n = 12,546) was a multinational trial of enteric-coated aspirin 100 mg once daily vs placebo for primary prevention of CV events (CV death, MI, unstable angina, stroke, or TIA) in men  $\geq 55$  with two to four risk factors and women  $\geq 60$  years of age with three or more risk factors (an estimated 10-year CV risk of about 10% to 20% per the 2013 ACC/AHA pooled cohort equations calculator). Patients with a history of GI bleed, frequent NSAID use, antiplatelet or anticoagulant use, or **diabetes were excluded**. Aspirin was not beneficial during 5 years of follow-up (event rate 4.29% vs 4.48%, HR 0.96, 95% CI 0.81 to 1.13,  $p=0.6038$ ), but doubled the risk of GI bleeding (0.97% vs 0.46%, HR 2.11, 95% CI 1.36 to 3.28,  $p=0.0007$ ). The actual 10-year CV event rate in this study was lower than estimated (about 8% to 9%), perhaps due to optimization of modern medical therapies (e.g., statins, anti-hypertensives), making the study population essentially a low-risk population.<sup>14</sup> The GI bleed event rate was similar to the expected event rate.
- **ASCEND** (n = 15,480) compared enteric-coated aspirin 100 mg once daily to placebo in patients  $\geq 40$  years of age **with diabetes** (but no evidence of cardiovascular disease) for prevention of CV events (e.g., vascular death, MI, stroke, or TIA). Aspirin provided some benefit for prevention of serious vascular event (8.5% vs 9.6%, rate ratio 0.88, 95% CI 0.79 to 0.97,  $p=0.01$ , NNT = 91 over 7.4 years to prevent one event). No benefit was seen for any specific event (e.g., MI), and benefit was mainly seen in the first five years of use. This benefit was largely offset by bleeding events (NNH = 112 over 7.4 years to cause one major bleeding event).
- **ASPREE** (n = 19,114) was a multinational trial of enteric-coated aspirin 100 mg once daily vs placebo in patients  $\geq 70$  years of age (African Americans or U.S. Hispanics  $\geq 65$  years of age). Patients taking antiplatelets or anticoagulants were excluded, as were patients with BP  $\geq 180/105$  mmHg. Patients were allowed short-term use of NSAIDs at the lowest dose. Eleven percent of enrollees had diabetes. Aspirin did not reduce CV events, but increased the risk of major bleeding (8.6 vs 6.2 events per 1,000 person-years,  $p<0.001$ ). There was no evidence that any subgroup responded differently, including patients with diabetes.

**Bottom line: aspirin does not likely provide net benefit for primary prevention patients  $\geq 70$  years of age, or nondiabetics with an estimated 10-year event rate  $<20\%$ , especially those with bleeding risks.**

<p>Do patients with diabetes benefit from aspirin for primary prevention of cardiovascular disease?</p>	<p>See reviews of ASCEND and ASPREE, above.</p> <p>Older individual studies (e.g., JPAD, POPADAD) did not show a benefit of aspirin in diabetes patients. This may be due to low event rates, relatively small number of enrolled patients, use of statins and other medications with cardiac benefits, or other study limitations.</p> <p>A meta-analysis (ATT) that included patients with diabetes (~4%) suggested a modest benefit (12% reduction in relative risk of events). Based on two systematic reviews, benefit for patients with diabetes seems similar to that for the general population.</p> <p>The USPSTF also found no clear differences in outcomes based on diabetes status, and in the WHS, aspirin prevented stroke in women with and without diabetes.</p>
<p>Are there <b>gender-specific</b> differences in aspirin's benefits for primary CV prevention?</p>	<p>The USPSTF 2016 recommendations state there is not sufficient evidence to support any gender-specific differences in CV disease outcomes. This differs from their 2009 analysis. The apparent gender differences likely reflects data from the WHS, which was a young, healthy, female population. (The WHS found a benefit for stroke prevention, but not cardiac events or CV death).</p> <p>The ATT meta-analysis did not find a difference in proportional benefit from aspirin between men and women.</p>
<p>What can patients expect from aspirin for primary prevention?</p>	<p>Tables showing lifetime benefits and risks of taking aspirin are available at <a href="https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/aspirin-to-prevent-cardiovascular-disease-and-cancer">https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/aspirin-to-prevent-cardiovascular-disease-and-cancer</a>. <b>However</b>, this tool may be outdated in light of more recent evidence from large RCTs (described above), and may overestimate benefit for nondiabetic patients with an estimated CV risk of 10% to 20%.</p> <p>For nondiabetic patients with CV risk of 10% to 20% calculated using the 2013 ACC/AHA pooled cohort equations calculator, patients with diabetes, and patients ≥70 years of age, aspirin will not likely provide a net benefit [Evidence level A-1]. This may be especially true in patients with bleeding risks (e.g., anticoagulant use, history of GI bleed, uncontrolled BP).</p> <p>Based on the new information, use shared decision making to decide if starting/stopping aspirin for primary prevention may be appropriate in a given patient. Stopping aspirin for <b>primary prevention</b> might confer a small increased risk of a CV event: one per year for every 146 patients who discontinue it [Evidence level B-3]. Weigh baseline CV risk, potential benefit, bleeding risk, and CV risk of stopping (if pertinent) in light of patient's values and preferences.</p>



How do I assess CV risk for purposes of decision-making regarding aspirin?

The USPSTF used the 2013 ACC/AHA pooled cohort equations calculator available at <http://myamericanheart.org/cvriskcalculator>. However, this calculator might overestimate CV risk in modern nondiabetic patients, as seen in ARRIVE, discussed above. This may result in aspirin use in patients for whom benefit does not outweigh risk.

ADA suggests considering noninvasive tests such as coronary artery calcium score to help clarify the decision to start aspirin therapy in patients with diabetes, particularly in patients with low estimated risk.

Should aspirin be used for primary prevention in a patient with GI bleed risk?

The Aspirin-Guide app (available at <https://www.apple.com/itunes/> or <http://www.aspiringuide.com/nav/1>) takes into account risk in patients with a history of GI bleed. This app is based on the 2016 USPSTF recommendations. It calculates the patient's CV risk using the 2013 ACC/AHA pooled cohort equations calculator, and calculates a bleeding risk score based on the USPSTF analysis and published studies, and provides guidance for decision-making.<sup>10</sup> **However**, extrapolating from the results of ARRIVE, discussed above, this app might overestimate benefit in nondiabetic patients with a 10% to 20% estimated risk.<sup>14</sup>

Low-dose aspirin is linked to about 2 GI bleeds per 1,000 patients each year. But the risk is up to 10 times higher after a GI bleed. So in patients who have had a bleed, net benefit of aspirin for primary prevention is unlikely.

Use a PPI for GI prophylaxis in patients taking aspirin who have a history of ulcer disease or upper GI bleeding, are taking an additional antiplatelet (including an NSAID or COX-2 inhibitor), or who take an anticoagulant.<sup>11</sup>

Also use a PPI in patients who have **more than one** of the following GI bleed risk factors: age 60 years and older, corticosteroid use, or dyspepsia or gastroesophageal reflux symptoms.

Ensure patients with a history of peptic ulcer are treated for *H. pylori*, if appropriate.<sup>11</sup>

Note that the use of enteric-coated or buffered aspirin formulations does not mitigate bleeding risk, as it is due to aspirin's systemic effect. *Yosprala* (aspirin/omeprazole) is a convenience product that offers no proven benefit over the individual agents alone, but costs at least ten times more.



<p>What is the aspirin dose for primary prevention of CV disease?</p>	<p><b>USPSTF (2016 recommendations):</b> 81 mg daily</p> <p><b>AHA/ASA:</b> dose not explicitly stated except that 81 mg daily or 100 mg every other day suggested for preventing first stroke in women.</p> <p><b>ADA:</b> 75 to 162 mg daily</p> <p><b>ACCP:</b> 75 to 100 mg daily</p> <p><b>CCS:</b> 75 to 162 mg daily</p> <p>An analysis of individual data from RCTs suggests that currently recommended aspirin doses may not be high enough for primary CV prevention or colorectal cancer prevention for many patients weighing <math>\geq 70</math> kg. Interestingly, doses <math>\geq 325</math> mg reduced CV events only in larger patients. However, these higher doses increase bleeding risk.</p>
<p>Who qualifies for aspirin for primary prevention of colon cancer?</p>	<p>Five to ten years' of daily aspirin use is needed to reduce the incidence of colorectal cancer, and this benefit may not be seen for ten to 20 years. Patients with a low risk of bleeding, a life expectancy of at least ten years, and high 10-year CV risk are most likely to receive net benefit.</p> <p>Analysis of data from the Nurses' Health Study and the Health Professionals Follow-up Study suggests that for every 100,000 people <math>&gt;50</math> years, aspirin may prevent 33 colorectal cancers each year in patients who did not receive colonoscopy. There was a smaller benefit seen in people who were screened with colonoscopy (18 colorectal cancers prevented). These benefits were seen when low-dose aspirin was taken each day for at least six years.</p>

## References

1. U.S. Preventive Services Task Force. Final recommendation statement. Aspirin to prevent cardiovascular disease and colorectal cancer: preventive medication. April 2016. <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/aspirin-to-prevent-cardiovascular-disease-and-cancer>. (Accessed September 27, 2018).
2. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:3754-832.
3. American Diabetes Association. Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018;41(Suppl 1):S1-159.

## References cont.

4. Bell AD, Roussin A, Cartier R, et al. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society guidelines. *Can J Cardiol* 2011;27:S1-59.
5. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008;300:2134-41.
6. Anon. Aspirin Guide Background. <http://www.aspiringuide.com/nav/4>. (Accessed September 27, 2018).
7. Mora S, Manson JE. Aspirin for the primary prevention of atherosclerotic cardiovascular disease: advances in diagnosis and treatment. *JAMA Intern Med* 2016;176:1195-204.
8. Gaziano JM, Brotons C, Copolechia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomized, double-blind, placebo-controlled trial. *Lancet* 2018;392:1036-46.
9. ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 2018 Aug 26. doi: 10.1056/NEJMoa1804988.
10. McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med* 2018 Sep 16. doi: 10.1056/NEJMoa1805819.
11. Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomized trials. *Lancet* 2018;392:387-99.

## PNEUMOCOCCAL VACCINATION IN ADULTS

*Prevnar 13* is often thought of as a childhood vaccine, but it is also FDA-approved for use in adults 18 years of age and older (condition unspecified). The CDC recommends its use in adults 65 years and older and in younger adults with immunocompromising conditions, cerebrospinal fluid (CSF) leak, or cochlear implant, in addition to *Pneumovax 23*. Both vaccines cover 12 of the same serotypes, plus *Prevnar 13* covers one more, and *Pneumovax 23* covers 11 others. Immune response to *Prevnar 13* (a conjugate vaccine) is as good as or better than *Pneumovax 23* (a polysaccharide vaccine). There is a slightly lower immune response to *Prevnar 13* when it is given at the same visit as the influenza vaccine in the elderly. **However**, either *Prevnar 13* or *Pneumovax 23* can be given at the same visit as the influenza vaccine (live or inactivated), or other vaccines in adults, at separate injection sites. Although *Prevnar 13* and *Pneumovax 23* should not be given at the same visit, they should not be repeated if accidentally given sooner than the recommended interval. The CDC's recommendations for pneumonia vaccination in adults are summarized in the table below. If the following recommendations are followed correctly, no adult will receive more than three doses of 23-valent pneumococcal vaccine, and not more than one dose

Who	What and When
<p>Immunocompromised adults 19 to 64 years of age:</p> <ul style="list-style-type: none"> <li>Asplenia (functional or anatomic)</li> <li>Hemoglobinopathy (e.g., sickle cell disease)</li> <li>Congenital or acquired immunodeficiency (includes complement deficiency, B- or T-cell deficiency, and phagocytic disorders [excluding chronic granulomatous disease])</li> <li>Cancer (e.g., leukemia, lymphoma, Hodgkin's disease, multiple myeloma)</li> <li>HIV</li> <li>Chronic renal failure or nephrotic syndrome</li> <li>Organ transplant</li> <li>Iatrogenic immunosuppression (e.g., systemic corticosteroids 14 days or longer, radiotherapy, chemotherapy)</li> </ul>	<p>Single dose of <i>Prevna</i> 13 (if not previously given), followed by <i>Pneumovax</i> 23 at least eight weeks later.</p> <p>Wait until at least one year has passed since any previous <i>Pneumovax</i> 23 dose to give <i>Prevna</i> 13.</p> <p>A second <i>Pneumovax</i> 23 should be given at least five years after the first, but at least eight weeks after <i>Prevna</i> 13.</p>
<p><b>Immunocompetent</b> adults 19 to 64 years of age with <b>CSF leak</b> or <b>cochlear implant</b></p>	<p>Single dose of <i>Prevna</i> 13 (if not previously given), followed by <i>Pneumovax</i> 23 at least eight weeks later.</p> <p>Wait until at least one year has passed since any previous <i>Pneumovax</i> 23 dose to give <i>Prevna</i> 13.</p>
<p><b>Immunocompetent</b> adults 19 to 64 years of age or older with <b>diseases, habits, or living conditions</b> that put them at high risk of pneumococcal disease:</p> <ul style="list-style-type: none"> <li>Heart disease (including heart failure or cardiomyopathy)</li> <li>Pulmonary disease (including COPD, emphysema, or asthma)</li> <li>Diabetes</li> <li>Alcoholism</li> <li>Cigarette smoking</li> <li>Chronic liver disease</li> </ul>	<p>Single dose of <i>Pneumovax</i> 23.</p>

## Adults 65 years of age and older

Single dose of *Prevnar 13* (if not previously given, or vaccination history is unknown), followed by *Pneumovax 23* at least one year later (at least eight weeks later for adults who are immunocompromised, with functional or anatomic asplenia, or who have CSF leak or cochlear implant). Wait until at least one year has passed since any previous *Pneumovax 23* dose to give *Prevnar 13*.

**ACIP recommendation, 2019 (final CDC guidance pending):** *Pneumovax 23* is recommended. For patients 65 years of age and older without an immunocompromising condition, *Prevnar 13* (if not previously given), based on shared clinical decision-making. The addition of *Prevnar 13* prevents one case of outpatient pneumonia for every 2,600 immunocompetent seniors and one case of invasive pneumococcal disease for every 26,300 immunocompetent senior's vs giving *Pneumovax 23* alone.

Those who received one or more doses of the 23-valent vaccine before age 65 for any indication should receive another dose at age 65 or older after at least five years have elapsed since their previous *Pneumovax 23* dose.

## References

1. CDC. Pneumococcal vaccine timing for adults. November 30, 2015. <https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf>. (Accessed August 1, 2019).
2. CDC. General Recommendations on immunization. In: Epidemiology and prevention of vaccine-preventable diseases. The Pink Book: Course Textbook. 13<sup>th</sup> Ed. 2015. <https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/genrec.pdf>. (Accessed August 1, 2019).
3. CDC. Pneumococcal disease. In: Epidemiology and prevention of vaccine-preventable disease. The Pink Book: Course Textbook. 13<sup>th</sup> Ed. 2015. <https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/pneumo.pdf>. (Accessed August 1, 2019).
4. ACIP Recommendations. June 2019 meeting recommendations. <https://www.cdc.gov/vaccines/acip/recommendations.html>. (Accessed August 1, 2019).

## PREDIABETES FAQ's

Clinical Question	Response
Who should be evaluated for prediabetes?	<p>Screening for prediabetes should be conducted in adults <math>\geq 45</math> years (ADA-American Diabetes Association) who are overweight or obese (<math>\text{BMI} \geq 25 \text{ kg/m}^2</math> or <math>\geq 23 \text{ kg/m}^2</math> [Asian Americans]) who have one or more additional risk factor for diabetes including:</p> <ul style="list-style-type: none"> <li>Physical inactivity</li> <li>First-degree relative with type 2 diabetes</li> <li>High-risk ethnicity such as African American, Asian American, Aboriginal, Latino, Native American, Pacific Islander</li> <li>Women who delivered an infant nine pounds or greater or who were diagnosed with gestational diabetes during pregnancy</li> <li>Hypertension</li> <li>HDL cholesterol <math>&lt; 35 \text{ mg/dL}</math> (<math>0.9 \text{ mmol/L}</math>) and/or triglycerides <math>&gt; 250 \text{ mg/dL}</math> (<math>2.82 \text{ mmol/L}</math>). (CDA recommends screening in those with HDL <math>&lt; 39 \text{ mg/dL}</math> [<math>1 \text{ mmol/L}</math>] in males or <math>&lt; 50 \text{ mg/dL}</math> [<math>1.3 \text{ mmol/L}</math>] in females and triglycerides <math>\geq 150 \text{ mg/dL}</math> [<math>1.7 \text{ mmol/L}</math>].)</li> <li>Women with polycystic ovary syndrome (PCOS)</li> <li>A1C of <math>\geq 5.7\%</math> and IGT or IFG (Impaired Glucose Intolerance and Impaired Fasting Glucose)</li> <li>Conditions associated with insulin resistance such as severe obesity or acanthosis nigricans</li> <li>History of cardiovascular disease</li> <li>Taking medications associated with hyperglycemia such as glucocorticoids or atypical antipsychotics</li> </ul> <p>The USPSTF recommendations differ from the ADA in that the former groups include age AND obesity AND at least one risk factor. However, the USPSTF recommendations suggest screening for prediabetes in adults' age 40 to 70 years who are overweight or obese. Screening can be considered at a younger age or normal weight for patients who have one or more of the following diabetes risk factors: family history of diabetes, history of gestational diabetes or polycystic ovary syndrome, or member of certain racial/ethnic minorities (African Americans, American Indians/Alaska Natives, Asian Americans, Hispanics/Latinos, and Native Hawaiians/Pacific Islanders).</p> <p>If results are normal, testing should be repeated at a minimum of every three years.</p>

How is the diagnosis of prediabetes made?

The ADA considers prediabetes as:

- IFG defined as a fasting plasma glucose of 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) or,
- IGT defined as a two-hour plasma glucose during a 75 g oral glucose tolerance test of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11 mmol/L) or,
- A1C 5.7% to 6.4%

The USPSTF recommendations use slightly different definitions for IFG or IGT and do not differentiate between IFG and IGT.<sup>5</sup>

- IFG or IGT are defined as an A1C 5.7% to 6.4% or a fasting plasma glucose of 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) or a two-hour plasma glucose during a 75 g oral glucose tolerance test of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11 mmol/L).

The USPSTF recommendations suggest the diagnosis of IFG or IGT must be confirmed unless symptoms of hyperglycemia are present. Repeat testing (within about a month) using the same test on a different day is the preferred method of confirmation. If diagnosis cannot be confirmed by the results of two tests, but at least one test indicates high risk, clinicians should monitor the patient and consider retesting in 3 to 6 months. Random blood glucose measurements should not be used for screening purposes.

What is the role of diet and exercise in the treatment of prediabetes?

Lifestyle interventions including dietary changes and exercise (at least 150 minutes/week) have been shown to be beneficial in the treatment of prediabetes.

- In the United States Diabetes Prevention Program evaluating intensive lifestyle intervention aimed at reducing weight, it was found that lifestyle intervention resulting in weight loss of 5% to 10% may prevent or delay diabetes diagnosis in about 1 in 7 patients when maintained for 3 years (absolute risk reduction 14.5%).
- In the Finnish Diabetes Prevention Study, in patients with prediabetes, patients randomized to lifestyle intervention were given the following goals: weight loss >5%, reduction in total fat consumption <30% daily calories, saturated fat intake of <10% of daily calories, fiber intake of ≥15 g per 1000 kcal daily, and exercise >4 hours per week. The study found that seven to eight patients would need to comply with lifestyle intervention for one year to prevent one case diabetes (absolute risk reduction 11%).

The USPSTF recommendations identified 10 studies that assessed lifestyle interventions to prevent or delay progression to type 2 diabetes. A meta-analysis of these trials found a relative risk (RR) of 0.53 (95% CI, 0.39 to 0.72). The USPSTF determined that there is adequate evidence that lifestyle interventions can prevent or delay progression to type 2 diabetes.

Consider drug therapy if lifestyle changes aren't enough after three to six months.



What is the drug of choice for prediabetes?

The ADA recommends metformin as the drug of choice for patients with prediabetes who are very high risk (e.g., those with a history of gestational diabetes, those who are very obese, and/or those with more severe or progressive hyperglycemia) because it has the strongest evidence and demonstrated long-term safety for diabetes prevention. According to the ADA, metformin is preferred because for other medications, cost, side effects, and lack of persistent effects may limit their use.

The American Association of Clinical Endocrinology (AACE) suggests either metformin, acarbose, or a thiazolidinedione for the treatment of prediabetes.

The USPSTF recommendations do not make recommendations on the drug of choice for prediabetes.

As of July 2015, no drug is officially approved by the FDA for treating prediabetes.

What is the evidence to support metformin in the treatment of prediabetes?

In the United States Diabetes Prevention Program evaluating intensive lifestyle intervention aimed at reducing weight, it was found that metformin therapy may prevent or delay diabetes diagnosis in about 1 in 14 patients when maintained for 3 years (absolute risk reduction 7.2%).

In a meta-analysis of three randomized, controlled trials of metformin to delay or prevent type 2 diabetes in patients with IGT or IFG, metformin was effective in delaying the progression to diabetes (NNT=7 to 14; over a three-year period).

In certain patient subgroups, metformin may be even more effective (e.g., those with a history of gestational diabetes or those with a BMI of 35 or greater).

The USPSTF recommendations identified eight studies published since the prior USPSTF review that assessed the effects of pharmacological interventions to prevent or delay progression to diabetes. In this review, metformin was one of the agents that was found to be effective in preventing or delaying progression to type 2 diabetes.

What is the correct dose of metformin in the treatment of prediabetes?

In the three randomized, controlled trials of metformin to delay or prevent type 2 diabetes in patients with IGT or IFG which showed a beneficial effect, the dose of metformin was 850 mg twice daily (United States Diabetes Prevention Program, n=1073) or 250 mg twice daily (two studies, n=45 and n=136).<sup>4</sup>

- The relative effectiveness of the lower dose compared with the higher dose is unknown.
- The two smaller studies which used the lower dose were conducted in Asia, where general rates of conversion to diabetes are different than the rates in the U.S.

The effect of other doses in the prevention of the progression to type 2 diabetes is not known.

Some clinicians start with metformin 500 mg daily, and increase up to 850 mg twice daily if A1C is still  $\geq 5.7\%$  after three months.

What is the evidence to support the use of acarbose in the treatment of prediabetes?

The largest study to evaluate the use of acarbose in the prevention of type 2 diabetes in patients with IGT was the STOP-NIDDM trial.

- Over the 3.3 year follow-up, 11 to 12 patients with IGT would need to be treated with acarbose in order to prevent 1 case of diabetes.
- Of note, 31% of those treated with acarbose dropped out of the treatment arm due to adverse effects, most commonly due to severe GI effects such as flatulence and diarrhea.

The USPSTF recommendations identified eight studies published since the prior USPSTF review that assessed the effects of pharmacological interventions to prevent or delay progression to diabetes. In this review, acarbose was one of the agents that was found to be effective in preventing or delaying progression to type 2 diabetes.

What other medications have been shown to be beneficial in the treatment of prediabetes?

Other agents which have studied in the treatment of prediabetes include the thiazolidinediones and GLP-1 analogs.

- Although rosiglitazone and pioglitazone appear to be effective, safety concerns such as weight gain, heart failure and fracture risk, and a possible link to bladder cancer (pioglitazone) limit their use in the treatment of prediabetes.
- GLP-1 agonists such as exenatide and liraglutide have been shown to reduce the prevalence of prediabetes over a one to two year follow-up period, but because they are injectable agents (and expensive), they are not considered first-line agents for this indication.

The USPSTF recommendations identified eight studies published since the prior USPSTF review that assessed the effects of pharmacological interventions to prevent or delay progression to diabetes. In this review, in addition to metformin and acarbose, the thiazolidinediones were found to be effective in preventing or delaying progression to type 2 diabetes.

Does screening and treating prediabetes reduce the incidence of cardiovascular disease?

The USPSTF recommendations state that there is no direct evidence that SCREENING for type 2 diabetes, IFG, or IGT among asymptomatic adults improves health outcomes.

The USPSTF recommendations found that pharmacological TREATMENT for screen-detected IFG, IGT, or diabetes showed no reduction in cardiovascular mortality, based on a meta-analysis of five trials with three to six years mean follow-up (risk ratio, 1.07 [95% CI, 0.84 to 1.35]).

Therefore, although screening and treating prediabetes has been shown to delay progression to diabetes, this has not been shown to reduce cardiovascular mortality.



## References:

1. American Diabetes Association. Standards of Medical Care in Diabetes—2015. *Diabetes Care* 2015;38(Suppl 1):S1-S93.
2. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion. Division of Diabetes Translation National diabetes statistics report, 2014. <http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf>
3. U.S. Preventive Services Task Force. Final recommendation statement. Abnormal blood glucose and type 2 diabetes mellitus: screening. December 2015. <http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/screening-for-abnormal-blood-glucose-and-type-2-diabetes>.
4. Knowler WC, Barrett-Connor E, Fowler SE, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.
5. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among patients with impaired glucose tolerance. *N Engl J Med* 2001;344:1343-50.
6. The Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care* 2012;35:723-30.
7. Ratner RE, Christophi CA, Metzger BE, et al. Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008;93:4774-9.
8. Chiasson JL, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359:2072-7.
9. Chiasson JL, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003;290: 486-94.
10. DeFronzo RA, Tripathy D, Schwenke DC, et al. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med* 2011;364:1104-15.
11. Zinman B, Harris SB, Neuman J, et al. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. *Lancet* 2010;376:103-11.

## HIGHMARK HEALTH OPTIONS QUALITY IMPROVEMENT PROGRAM

The purpose of the Highmark Health Options Quality Improvement/Utilization Management (QI/UM) Program is to assure quality, safety, appropriateness, timeliness, availability, and accessibility of care and services provided to Highmark Health Options members. The comprehensive evaluation and assessment of clinical, demographic and community data – in conjunction with current scientific evidence – is paramount to meet identified needs.

The goal of the QI/UM Program is to ensure the excellent provision and delivery of high quality medical and behavioral health care, pharmaceutical, and other health care services and quality health plan services for our members. The QI/UM Program focuses on monitoring and evaluating the quality and appropriateness of care provided by the Highmark Health Options health care provider network, as well as the effectiveness and efficiency of systems and processes that support the health care delivery system. The QI/UM Program is assessed on an annual basis to determine the status of all activities, identify opportunities that meet the QI/UM Program objectives, and develop a work plan.

As a participating provider, Highmark Health Options asks that you cooperate with QI activities to improve the quality of care and services members receive. This may include the collection and evaluation of data, participation in various QI initiatives and programs, and allowing the plan to use and share your performance data.

Implementation and evaluation of the QI/UM Program is embedded into Highmark Health Options daily operations. The QI/UM Program has available and uses appropriate internal information, systems, practitioners and community resources to monitor and evaluate use of health care services, continuous improvement process and implementation of positive change.

The Scope of the Program includes, but is not limited to:

- Enrollment
- Members' Rights and Responsibilities
- Network Accessibility and Availability, including those related to Special Needs
- Network Credentialing/Recredentialing
- Medical Record Standards
- Claims Administration
- Clinical Outcomes

## *HHO Quality Improvement Program cont.*

- Patient Safety
- Preventive Health, Disease Management and Long-Term Services and Support (LTSS)
- Continuous Quality Improvement using Total Quality Management Principles
- Member and Provider Satisfaction
- Health Education

To request a copy of the complete Highmark Health Options Quality Improvement Program, Work Plan, or Annual Evaluation, please contact the Highmark Health Options Provider Services Department at 1-844-325-6251.

## CAHPS SATISFACTION SCORES ARE IN!

Earlier this year, a satisfaction survey was sent to members called the Consumer Assessment of Healthcare Providers and Systems (CAHPS). Our members were selected at random and asked to provide feedback about their health care experience. We use this feedback to improve the health care experience for all of our members.

Adults in our plan report being most satisfied with how well doctors communicated with them (92.3%), their ability to get needed care (87.4%), and our customer service (86.0%). We are very proud of these ratings, but also realize there is still opportunity for improvement.

Surveys also went out to the families of members under the age of 18 years so we could gather feedback on services provided to children in our health plan. This group is also satisfied with how well doctors communicated with them (93.4%), as well as reporting satisfaction with their child's personal doctor (92.9%). While we are proud of these ratings, we recognize that there are still opportunities to provide a better experience for our members.

We continue to work with members and doctors to provide exceptional care and services. We act on member feedback in the CAHPS surveys to improve the health care experience for both you and your patient. We welcome suggestions you may have on improving the patient experience. **Improving the quality of health care is a team effort!**

## REPORTABLE CONDITIONS

The State of Delaware requires Providers to report certain diseases, infections, conditions and outbreaks such as, but not limited to, chicken pox, lead poisoning, Lyme disease and mumps<sup>1</sup>. A full listing of notifiable diseases can be found at <http://dhss.delaware.gov/dph/dpc/rptdisease.html>, along with how to report and identify rapidly reportable conditions that require immediate contact to the Delaware Division of Public Health.

<sup>1</sup>Delaware Administrative Code 16 DE Admin Code 4202 Control of Communicable and Other Disease Conditions Section 2.0

## CONTINUITY OF COORDINATION AND CARE

The seamless sharing of information between healthcare providers, such as between primary care physicians (PCPs) and specialists, presents many challenges to the continuity of care and treatment of our members. Highmark Health Options membership includes some of the most vulnerable individuals who may suffer from severe or chronic illnesses. Enhanced communication among and between all those who participate in providing care to a patient is imperative in ensuring that all decisions about the patient's care are informed and contribute to the patient's overall well-being. Continuity of care issues can result in suboptimal outcomes, increased costs, and medical errors.

It is to the benefit of both the patient and healthcare professional to communicate any reports, therapies, medications, and concerns identified by providers across treatment settings. Please contact your Provider Relations Representative with questions about how you can help improve patient care between settings.

## MEMBER RIGHTS AND RESPONSIBILITIES

Our members have certain rights and responsibilities that are a vital part of membership with Highmark Health Options. These rights and responsibilities are included in the member handbook and are reviewed annually in the Health Options member newsletter.

The Highmark Health Options Member Rights and Responsibilities are available online for our network providers to help maintain awareness and support your relationship with your Highmark Health Options members.

You'll find the Member Rights and Responsibilities in Chapter 2, Unit 2, of the *Highmark Health Options Provider Manual*. The *Provider Manual* is available on the Highmark Health Options website under **Providers > Provider Manual**. A hard copy of the Member Rights and Responsibilities is available upon request by calling your Provider Relations representative.

## MEDICATIONS TO REQUIRE PRIOR MEDICAL AUTHORIZATION

A subset of medications require a pre-service authorization for medications obtained through the medical benefit. This prior authorization process applies to all Highmark Health Options members. Medical necessity criteria for each medication listed below is outlined in the specific medication policies available online. To access Highmark Health Options medication policies, please visit: <https://www.highmarkhealthoptions.com/Provider/Medication-Information/Medication-Prior-Authorization-Criteria>. Failure to obtain authorization will result in a claim denial.

### Procedure Codes Requiring Authorization

#### AUTHORIZATION REQUIRED AS OF 9/2/2019

Procedure Code	Description	Procedure Code	Description
J0584	Crysvita (Burosumab-twza)	Q2042	Kymriah (Tisagenlecleucel)
J0180	Fabrazyme (Agalsidase Beta)	J9217	Lupron (Leuprolide acetate)
Q5108	Fulphila (Pegfilgrastim-jmdb)	Q5107	Mvasi (Bevacizumab-awwb)
J1559	Hizentra (Immune Globulin)	Q5110	Nivestym (Filgrastim-aafi)
J1575	Hyqvia (Immune Globulin/ Hyaluronidase)	Q5104	Renflexis (Infliximab-abda)
Q5103	Inflectra (Infliximab-dyyb)	Q2041	Yescarta (Axicabtagene Ciloleucel)
Q5109	Ixifi (Infliximab-qbtx)		

#### AUTHORIZATION REQUIRED AS OF 11/4/2019

Procedure Code	Description	Procedure Code	Description
J3262	Actemra (Tocilizumab)	J0222	Onpattro (Patisiran)
J0881	Aranesp (non-ESRD) (Darbepoetin Alfa)	Q5112	Ontruzant (trastuzumab-dttb)
J0882	Aranesp (ESRD) (Darbepoetin Alfa)	J0129	Orencia (Abatacept)
J9039	Blinicyto (Blinatumomab)	J0885	Procrit (non-ESRD) (Epoetin Alfa)

<b>J0717</b>	<b>Cimzia (Certolizumab Pegol)</b>	<b>Q4081</b>	<b>Procrit (ESRD on dialysis) (Epoetin Alfa)</b>
<b>J0185</b>	CInvanti (Burosumab-twza)	<b>J1301</b>	Radicava (Edaravone)
<b>J9171</b>	Docetaxel	<b>J3285</b>	Remodulin (Treprostinil)
<b>J9269</b>	Elzonris (Tagraxofusp-erzs)	<b>Q5105</b>	Retacrit (ESRD on dialysis) (Epoetin Alfa-epbx)
<b>J1453</b>	Emend (Aprepitant)	<b>Q5106</b>	Retacrit (non-ESRD) (Epoetin Alfa-epbx)
<b>J3380</b>	Entyvio (Vedolizumab)	<b>J9311</b>	Rituxan Hycela (Rituximab/Hyaluronidase)
<b>J0885</b>	Epogen (non-ESRD) (Epoetin Alfa)	<b>J1602</b>	Simponi Aria (Golimumab)
<b>Q4081</b>	Epogen (ESRD on dialysis) (Epoetin Alfa)	<b>J3357</b>	Stelara subQ (Ustekinumab)
<b>J9019</b>	Erwinaze (Asparaginase Erwinia Chrysanthemi)	<b>J3358</b>	Stelara IV (Ustekinumab)
<b>J9307</b>	Folotylin (Pralatrexate)	<b>Q9991</b>	Sublocade, less than or equal to 100 mg (Buprenorphine ER)
<b>J9210</b>	Gamifant (Emapalumab-lzsg)	<b>Q9992</b>	Sublocade, greater than 100 mg (Buprenorphine ER)
<b>J9179</b>	Halaven (Eribulin Mesylate)	<b>J7325</b>	Synvisc/Synvisc One (Hylan Polymers A and B)
<b>J9356</b>	Herceptin Hylecta (Trastuzumab/hyaluronidase-oysk)	<b>J0593</b>	Takhzyro (Lanadelumab-flyo)
<b>Q5113</b>	Herzuma (Trastuzumab)	<b>J9022</b>	Tecentriq (Atezolizumab)
<b>J9173</b>	Imfinzi (Durvalumab)	<b>J3490*</b>	Tegsedi (Inotersen)
<b>J0202</b>	Lemtrada (Alemtuzumab)	<b>J1746</b>	Trogarzo (Ibalizumab-uiyk)
<b>J9119</b>	Libtayo (Cemiplimab-rwlc)	<b>Q5115</b>	Truxima (Rituximab-abbs)

<b>J9313</b>	<b>Lumoxiti (Moxetumomab Pasudotox-tdfk)</b>	<b>Q5111</b>	<b>Udenyca (Pegfilgrastim-cbqv)</b>
<b>A9513</b>	Lutathera (Lutetium Lu 177 Dotatate)	<b>J1303</b>	Ultomiris (Ravulizumab-cwvz)
<b>J2503</b>	Macugen (Pegaptanib Octasodium)	<b>J3396</b>	Visudyne (Verteporfin)
<b>J1726</b>	Makena (Hydroxyprogesterone Caproate)	<b>J7179</b>	Vonvendi (Von Willebrand Factor Recombinant)
<b>J0887</b>	Mircera (ESRD on dialysis) (Methoxy Polyethylene Glycol-Epoetin Beta)	<b>A9606</b>	Xofigo (Radium Ra 223 Dichloride)
<b>J0888</b>	Mircera (non-ESRD) (Methoxy Polyethylene Glycol-Epoetin Beta)	<b>A9543</b>	Zevalin (Ibritumomab Tiuxetan)
<b>Q5114</b>	Ogivri (Trastuzumab-dkst)	<b>J9202</b>	Zoladex (Goserelin Acetate)
<b>J9266</b>	Oncaspar (Pegaspargase)	<b>J3490*</b>	Zulresso (Brexanolone)

\*This medication will be reviewed under the miscellaneous code J3490, J3590 or J9999 until a permanent code is assigned



## What if medication is not on the list?

- If the medication you are prescribing for your patient is not addressed on the Highmark Health Options Medication Prior Authorization Criteria website (<https://www.highmarkhealthoptions.com/Provider/Medication-Information/Medication-Prior-Authorization-Criteria>) that means it does not require a pre-service prior authorization. The process for obtaining this medication, which is not listed above, has not changed.
- If you intend to bill the medication on the medical benefit, you will administer the medication and submit the claim as you have in the past.

## Would you prefer to get the medication through pharmacy?

- This change only applies to the medical benefit. If the medication is to be billed at the pharmacy/ specialty pharmacy, you will continue to submit requests to Highmark Health Options Pharmacy Services. They can be reached at 1-844-325-6253.

## Submitting a Request

- The most efficient path of submitting a request (for one of the medications on the list above) is via Navinet. A form has been added to Navinet with autofill functionality to make completing and submitting your online request easier and faster.
- If you have questions regarding the authorization process and how to submit authorizations electronically via Navinet, please contact your Highmark Health Options Provider Relations Representative directly or Provider Services Department using the phone number 1-844-325-6251.

## Additional information

- Any decision to deny a prior authorization or to authorize a service is made by a licensed pharmacist based on individual member needs, characteristics of the local delivery system, and established clinical criteria.
- Authorization does not guarantee payment of claims. Medications listed above will be reimbursed by Highmark Health Options only if it is medically necessary, a covered service, and provided to an eligible member.
- Non covered benefits will not be paid unless special circumstances exists. Always review member benefits to determine covered & non-covered services.
- Current and previous provider notifications can be viewed at:  
<https://www.highmarkhealthoptions.com/provider/communications>





## PROVIDER NETWORK CONTACTS

### Provider Relations:

**Desiree Charest** - Sussex County  
 Provider Account Liaison  
*\*includes servicing of LTSS Providers*  
[Desiree.Charest@highmark.com](mailto:Desiree.Charest@highmark.com)  
 302-217-7991

**Cory Chisolm** - All Counties  
 Provider Account Liaison  
 Ancillary Strategy  
[Cory.Chisolm@highmark.com](mailto:Cory.Chisolm@highmark.com)  
 302-217-7960

**Nikki Cleary**- All Counties  
 Provider Account Liaison for Hospitals and  
 Ambulatory Surgery Centers  
[Nikki.Cleary@highmark.com](mailto:Nikki.Cleary@highmark.com)  
 302-502-4094

**Chandra Freeman** – Kent County and City of Newark  
 Provider Account Liaison  
*\*includes servicing of LTSS Providers*  
[Chandra.Freeman@highmark.com](mailto:Chandra.Freeman@highmark.com)  
 302-502-4067

**Desiree Charest (interim)** – New Castle County  
 Provider Account Liaison  
*\*includes servicing of LTSS Providers*  
[Desiree.Charest@highmark.com](mailto:Desiree.Charest@highmark.com)  
 302-217-7973

**Tracy Sprague**  
 Provider Account Liaison/Provider Complaints  
[Tracy.Sprague@highmark.com](mailto:Tracy.Sprague@highmark.com)  
 302-502-4120

**Paula Victoria**  
 Manager, Provider Relations, LTSS  
[Paula.Victoria@highmark.com](mailto:Paula.Victoria@highmark.com)  
 302-502-4083

### Provider Contracting:

**Melanie Anderson**  
 Director, Provider Networks & Contracting  
[Melanie.Anderson@highmark.com](mailto:Melanie.Anderson@highmark.com)  
 302-502-4072

**Elsa Honma**  
 Provider Contract Analyst, LTSS and Nursing Homes  
[Elsa.Honma@highmark.com](mailto:Elsa.Honma@highmark.com)  
 302-317-5967

**Kia Knox**  
 Senior Provider Contract Analyst  
[Kia.Knox@highmark.com](mailto:Kia.Knox@highmark.com)  
 302-502-4041

**Paula Brimmage**  
 Senior Provider Contract Analyst  
[Paula.Brimmage@highmark.com](mailto:Paula.Brimmage@highmark.com)  
 302-433-7709

**Terri Krysiak**  
 Provider Contract Analyst/PR Representative, Behavioral  
 Health  
[Terri.Krysiak@highmark.com](mailto:Terri.Krysiak@highmark.com)  
 302-502-4054

**Provider Complaints** (not claims related)  
 Email: [HHO-ProviderComplaints@highmark.com](mailto:HHO-ProviderComplaints@highmark.com)  
 Phone: 844-228-1364  
 Fax: 844-221-1569

## Important Addresses and Phone Numbers

### Addresses

Office Location	Highmark Health Options 800 Delaware Avenue Wilmington, DE 19801
Member Correspondence	Highmark Health Options – Member Mail P.O. Box 22188 Pittsburgh, PA 15222-0188
Provider Correspondence	Highmark Health Options – Provider Mail P.O. Box 22218 Pittsburgh, PA 15222-0188

### NaviNet

NaviNet Access 24/7	Click <a href="#">here</a> to enter the NaviNet Portal
---------------------	--

Department	Contact Number	Hours
Provider Services	1-844-325-6251	Mon. – Fri. 8 a.m. to 5 p.m.
Member Services	1-844-325-6251	Mon. – Fri. 8 a.m. to 8 p.m.
Member Services (DSHP Plus)	1-855-401-8251	Mon. – Fri. 8 a.m. to 8 p.m.
Authorizations	1-844-325-6251	Mon. – Fri. 8 a.m. to 5 p.m. (24/7 secure voicemail for inpatient admissions notification)
Care Management/Long Term Services and Supports (LTSS)	1-844-325-6251	Mon. – Fri. 8 a.m. to 5 p.m. (after hours support accessible through the Nurse Line)
Member Eligibility Check (IVR)	1-844-325-6161	24/7
Behavioral Health	1-844-325-6251	Mon. – Fri. 8 a.m. to 5 p.m.
Opioid Management Program	855-845-6213	Mon.- Fri. 8 a.m. to 5 p.m.