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Policy Evaluation: Hepatitis C: Direct-Acting Antivirals

Research Questions:

- How has utilization of direct-acting antivirals (DAAs) changed over time as disease severity restrictions have been removed from the prior authorization (PA) criteria?
- Has there been an increase over time in the percentage of DAAs prescribed by primary care providers?
- Have patient characteristics and liver disease complications of those treated with DAAs changed over time with the opening up of treatment criteria?
- How many patients with chronic hepatitis C and concomitant alcohol and/or substance use disorder have been treated with a DAA?
- How many patients have been retreated with a DAA?

Conclusions:

- Per member per month (PMPM) utilization of the DAAs has increased over time (**Figure 1**) and significant changes to the PA criteria in 2018 and 2019 resulted in an immediate increase in DAA utilization followed by stabilization.
- There was a clear shift of prescribing from specialty providers toward primary care providers after March 1, 2019. Approximately 62% of new DAA regimens were prescribed by primary care providers in the study group (March 2019-January 2020) compared to 47.3% in the control group (March 2019-February 2019).
- Revisions to the PA criteria in 2019 allowed for an increased percentage of DAA claims for patients with the absence of severe liver disease. There was a decrease in percentage of patients with comorbid compensated cirrhosis from 33.8% to 15.5% after revisions to the PA criteria. The percentage of those with comorbid decompensated cirrhosis was also reduced from 14.1% to 7.6% in the same time period.
- After policy changes in 2019, more patients with substance use disorder (SUD) were treated with a DAA, 34.2% in the control group received a DAA compared to 49.7% in the study group.
- Retreatment rates with DAAs continued to be low (<2%) in all patients receiving DAAs.

Recommendations:

- Maintain current PA policy for DAAs and continue to monitor trends in utilization, changes in patient characteristics and barriers to patient access to treatment.

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Background:

Hepatitis C virus (HCV) infection is the most common blood born infection in the United States and has contributed substantially to hepatic related morbidity and mortality.[1] The true prevalence of chronic HCV infections is unknown due to the dynamic nature of the disease, but it is estimated that 2.4 million people in the United States were actively infected with HCV between 2013 and 2016.[1] Exact prevalence is difficult to determine because approximately 50% of people with HCV infection may be unaware of their diagnosis and another 15-20% will spontaneously clear acute HCV infection. In the United States, chronic HCV infection is the leading cause of cirrhosis, liver failure, hepatocellular carcinoma (HCC), and liver transplants.[2] Chronic HCV is also the leading cause of death for blood born infections, surpassing human immunodeficiency virus (HIV) in 2007 with approximately 10-fold greater incidence of death compared to hepatitis B virus (HBV) related deaths.[3] The goals of treatment for HCV include prevention of these long-term complications of liver disease, eradication of HCV, and reduce transmission of HCV to others.[4]

For those without advanced liver disease, there has been an effort to increase prescribing by primary care providers. One large meta-analysis indicated that having primary care providers involved with managing HCV treatment led to similar and, in some cases, increased SVR rates and follow up.[5] Providing more access to HCV treatment via primary care providers has the potential to improve HCV related outcomes and reduce transmission in high-risk populations. Those at highest risk for transmitting and acquiring HCV infection are people who inject drugs.[1] This increased risk indicates the need to improve treatment availability for those with substance use disorder (SUD). A large meta-analysis conducted in 2018 indicated that those who inject drugs and those receiving medication assisted therapy (MAT) for SUD did not have significantly reduced SVR rates.[6]

Treatment for HCV has progressed significantly over the past decade. Only 55-60% of patients were able to achieve SVR with regimens prior to DAAs, and many patients experienced significant rates of adverse reactions to treatment. The development of second generation DAAs provided treatment options without the use of interferon or ribavirin that have fewer and more tolerable adverse effects. DAAs have the added benefit of being very effective in treating HCV, resulting in SVR for over 90% of patients in clinical trials. Additionally, duration of therapy has been shortened to 8-12 weeks in most patients with a number of regimens approved for treatment of all HCV genotypes. However, these medications come with a significant financial burden and definitive, long-term outcomes have yet to be established.

The Oregon Drug Use Review/Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, cost, consideration for the number of patients waiting for treatment, little provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options become available, real world experience increases, and the community standard evolves, the P&T Committee has expanded treatment in a step-wise fashion to patients with less severe disease (**Table 1**). Current drug policies in place approve treatment for patients with HCV regardless of disease severity.

The goal of this policy update is to determine how the most recent prior authorization changes outlined in **Table 1** have effected utilization of the DAAs and characteristics of patients receiving therapy.

Table 1: Changes to PA criteria

Implementation Date	Prior to 2018	January 2018	January 2019	March 2019
Metavir Score Limitations	Fibroscan ® or FibroSure ® with advanced fibrosis or cirrhosis **(F3 or F4**) OR APRI score > 1.5 or FIB-4 > 3.25 OR F2 (or APRI > 1.0) with HIV coinfection under treatment of specialist	**Confirmed F2** OR HIV co-infection OR extrahepatic manifestations of HCV infection AND if F3 or F4 required to be prescribed by specialist (< F2 no specialist needed)	**No changes**	**No fibrosis** or disease severity requirements. Prescribed by or in consultation with a specialist only for those with cirrhosis.
Alcohol and Substance Use disorder limitations	Patients required to be evaluated for alcohol and substance use disorder and was required to be enrolled in a treatment program or under care of an addiction specialist for approval	Patient actively abusing alcohol OR diagnosed with substance use disorder OR prescriber is aware of IV drug use THEN the patient must be enrolled in treatment program or under care of an addiction specialist for approval	Alcohol use and substance use disorder limitations removed from PA criteria	No changes

Table 2: Direct Acting Antiviral Regimens for Treatment of Chronic Hepatitis C Infection

Drug Brand Name	Generic Name	Approved genotypes	Decompensated Cirrhosis	Mechanism of Action	Duration**	FDA Approval
Epclusa ®	Sofosbuvir/velpatasvir	HCV GT 1-6	GT 1-6 with RBV	NS5B inhibitor/NS5A inhibitor	12 weeks	June 2016
Harvoni ®	Ledipasvir/sofosbuvir	HCV GT 1, 4, 5, or 6	GT 1 with RBV	NS5A inhibitor/NS5B inhibitor	8-12 weeks	October 2014
Mavyret ®	Glecaprevir/pibrentasvir	HCV GT 1-6	Contraindicated	NS3/4A protease inhibitor/NS5B inhibitor	8-16 weeks	August 2017
Vosevi ®	Sofosbuvir/velpatasvir/voxilaprevir	HCV GT 1-6 TE	Contraindicated	NS5B inhibitor/NS5A inhibitor/NS3 protease inhibitor	12 weeks	July 2017
Zepatier ®	Elbasvir/grazoprevir	HCV GT 1 or 4	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor	12-16 weeks	January 2016

Abbreviations: TE = treatment experience; RBV = ribavirin; NS = nonstructural proteins; HCV = hepatitis C virus infection; GT = genotype
****Duration typically 8-12 weeks for treatment naïve patients without decompensated cirrhosis. Duration of therapy extended for certain DAA-treatment experienced individuals and those with decompensated cirrhosis.**

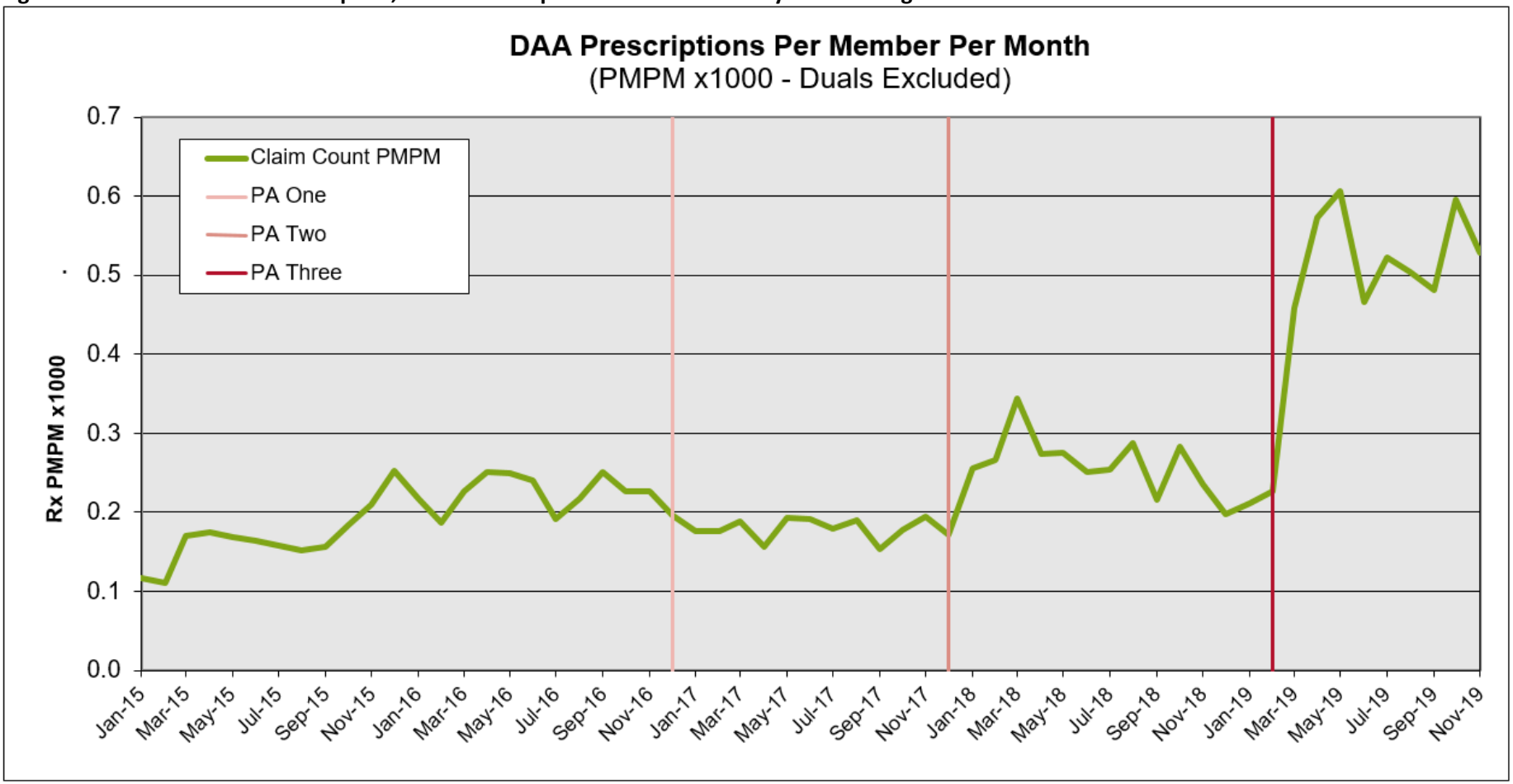
Methods:
Overall utilization was evaluated over time by charting all paid CCO and FFS pharmacy claims for any DAA listed in **Table 2** from January 2015 through November 2019 (**Figure 1)**. In order to look at utilization in more detail and evaluate the effects of removing all disease severity and abstinence prior authorization restrictions in March 2019, a pre and post-observational cohort was identified of patients newly started on DAA therapy. Patients with a paid FFS or CCO pharmacy claim for any DAA in **Table 2** from March 2018 through February 2019 (one year prior to the policy change) were defined as the control group, patients with claims from March 1, 2019 to January 31, 2020 were defined as the study group. Patients were included if they were newly started on a DAA, where new start is defined as no DAA in the year prior the earliest DAA claim in the respective period. Patients were excluded if they had less than 75% eligibility in the year prior to their index event (the date of the new start). Patients with Medicare Part D coverage as indicated by benefit packages of BMM, BMD, MND or MED were also excluded.

Baseline characteristics of age, gender, and race were assessed at the index event (IE). Patients were also categorized by IE prescriber type and if they were treatment experienced. Prescriber classifications were collected to determine what percentage of those prescribing DAAs were specialists compared to primary care providers before and after removing PA restrictions. The breakdown of each provider classification and how they were categorized is outlined in **Appendix 2**. Retreatment was defined as those with a second DAA course starting at least 12 weeks after the end of their initial DAA treatment. End of the initial treatment is defined as the first gap of greater than 2 weeks between subsequent DAA claims. Additionally, patients with substance use disorder, alcohol use disorder and liver disease complications were identified based on the diagnosis codes listed in **Appendix 3**.

Lastly, to describe changes in the proportion of patients with a diagnosis of HCV over time, the proportion all eligible patients in the Oregon Health Plan (OHP) during the pre- and post- periods with a diagnosis of hepatitis C since 2011 were collected (**Table 6**). The ICD-10 codes used to capture the diagnoses are included in **Appendix 3**. The percentage of these patients treated at any time since 2011 with a DAA is also included in **Table 6**.

Results:
Figure 1 represents the utilization of DAAs per member per month (PMPM x 1000) from January 1, 2015 to November 30, 2019 in the Oregon Health Plan (OHP). DAA utilization increased after policy changes were implemented in January 2018 and March 2019. The most recent data was collected over 8 months after the PA revisions were implemented in March 2019. Of note, DAA claims peaked in May 2019 when PA criteria were modified to permit increased access to hepatitis C treatment. Since March 2019, DAA utilization has stabilized after the initial increase at approximately 0.5 to 0.6 claims PMPM x 1000. There was also a slight increase in DAA claims with revision of the PA restrictions in 2018, from 0.17 claims PMPM x 1000 in December 2017 to 0.25 claims PMPM x 1000 in January of 2018. This trend also stabilized.

Figure 1. Trend of DAA utilization per 1,000 members per month from January 2015 through November 2019



Demographics of FFS and CCO members in the control and study group are presented in **Table 3**. A total of 1,014 patients had claims for a DAA from March 2018 to February 2019 and 2,057 patients had claims for a DAA between March 2019 and February 2020. Race and gender distributions were similar between the two groups. There was a trend towards increased utilization in younger patients (those aged 18 to 34) after the 2019 PA criteria revisions as DAA claims increased from 8.1% in the control group to 18.6% in the study group. However, claims for patients aged 55 years and greater decreased from 51.2% in the control group to 37.7% in the study group. Rates of treatment between those aged 35-54 years were similar before and after the changes to the PA criteria, at a rate of 40.6% and 43.5%, respectively.

Table 3. Demographics of patients receiving DAA treatment

	March 2018-February 2019		March 2019-January 2020	
Total Treated with DAA	**N=1,014**		**N=2,057**	
Average Age (min-max)	52 (12-69)		48 (6-72)	
< 18 (%)	1	0.1%	3	0.1%
18-34 (%)	82	8.1%	383	18.6%
35-54 (%)	412	40.6%	895	43.5%
>=55 (%)	519	51.2%	776	37.7%
Female	451	44.5%	937	45.6%
Race				
White	595	58.7%	1,185	57.6%
Black	33	3.3%	53	2.6%
Asian	11	1.1%	20	1.1%
Other	69	6.8%	156	7.6%
Unknown	306	30.2%	643	31.3%

Table 4 describes the comorbidities associated with patients starting a new DAA regimen in the control and study groups. Of the 1,014 treated in the control group, 33.8% had compensated cirrhosis and 14.1% had decompensated cirrhosis. In contrast, of the 2,057 patients that were treated in the study group, only 15.4% had associated compensated cirrhosis and 7.9% had associated decompensated cirrhosis. There was an increase in utilization for those with SUD from 34.2% in the control group to 51.4% in the study group. The rates of coexisting alcohol use disorder were similar in both the control and study group at 22.1% and 23.5%, respectively. PA revisions did not lead to an apparent difference in patients that also had a diagnosis of hepatocellular carcinoma between the control or study groups. There was also a low percentage of those retreated with a DAA in both the study group (0.5%) and the control group (1.6%).

Table 4. Comorbidities and complications of patients receiving DAA treatment

	March 2018-February 2019		March 2019-January 2020	
Total Treated with DAA	1,014		2,057	
Chronic Viral Hepatitis C	1,009	99.5%	2,042	99.3%
Compensated Cirrhosis	343	33.8%	316	15.4%
Decompensated Cirrhosis	143	14.1%	162	7.9%
Hepatocellular Carcinoma	18	1.8%	21	1.0%
Liver Transplant	2	0.2%	1	0.1%
Substance Use Disorder	347	34.2%	1,058	51.4%
Alcohol Use Disorder	224	22.1%	484	23.5%
Patients Retreated with DAA	16	1.6%	16	0.8%

Provider trends are highlighted in **Table 5.** A higher percentage of primary care providers prescribed DAAs after the PA was updated in March 2019. Approximately 63.7% of new DAA regimens were prescribed by primary care providers in the study group compared to 47.3% in the control group. Full details about prescriber classifications are outlined in **Appendix 2.**

Table 5. Prescriber Classifications

	March 2018-February 2019		March 2019-January 2020	
Total Treated with DAA	**1,014**		**2,057**	
Primary Care	**480**	**47.3%**	**1,312**	**63.7%**
Specialist	**534**	**52.7%**	**745**	**36.3%**

Table 6 presents the proportion of patients who possess a diagnosis of chronic hepatitis C infection within the entire eligible Oregon Medicaid population during the same two time periods using the analysis above. This table also reports the percentage of patients diagnosed with chronic hepatitis C infection who received new start DAA therapy. The percentage of patients diagnosed with chronic hepatitis C infection was similar between the two time periods at 2.5% in both groups. The percentage of those who received DAA increased from 10.7% to 20.4%.

Table 6. Proportion of Patients Diagnosed with Hepatitis C Enrolled and Treated with DAA

	March 2018-February 2019		March 2019-February 2020	
All Patients in Oregon Health Plan	989,304		985,827	
Patients with a diagnosis of hepatitis C	24,830	2.5%	24,789	2.5%
Patients Treated with DAAs	2,647	10.7%	5,065	20.4%

Discussion:
This report shows trends in utilization of DAAs following PA criteria revisions in March 2019. As of March 2019, treatment is covered for all patients with HCV, regardless of disease severity. Immediately following implementation, DAA utilization almost doubled from 0.23 claims PMPM x 1000 in February 2019 to 0.46 claims PMPM x 1000 the following month. Utilization continued to increase through May 2019, and then stabilized over subsequent months. DAA utilization has increased over time due to a number of potential factors including decreasing costs, increased provider familiarity, provider education and screening efforts. Additionally, policy changes in 2019 allowed treatment for those patients not eligible under the previous criteria due to fibrosis restrictions. Data from **Table 4** exhibits that healthier patients with fewer liver disease complications were treated with DAAs after March 2019. Additionally, there were more patients with a diagnosis of SUD treated with a DAA.

There was also increased prescribing by primary care providers. Since primary care providers are more accessible to patients, this likely contributed to the increase in overall claims for DAAs. This is highlighted in **Table 5** as the amount of DAA prescriptions from primary care providers rose from 47.3% to 63.7% after the PA policy was revised. This increase could be due to increased familiarity, more safety and efficacy data, and ongoing training efforts such as the Oregon ECHO program. Reduction in percentage of patients treated with decompensated cirrhosis is also likely a contributing factor as guidelines still recommend these patients be treated by hepatologists or infectious disease specialists.[7]

Data from this report also describes a shift in age of patients with claims for DAAs. There was a decrease in percentage of patients that would be included in the hepatitis C screening birth cohort (1945-1965), or those over 55 years old. The decreased percentage of patients in this age group could be due to successful prior treatment. This group was more likely to have met previous PA requirements due to liver disease severity secondary to being infected with hepatitis C for a longer period of time. However, the total number of patients in this age demographic was similar between the two groups indicating that the revisions to the PA criteria allowed more access for younger patients to be treated. This is most prominently seen in the age 18-34 demographic as percentage of claims increased in this age group from 8.1% in the control group to 18.6% in the study group. The increase in DAA claims for those under 55 years old is likely related to this population being less likely to have progressive fibrosis. The removal of restrictions regarding substance use disorder is also presumably a contributing factor to expanding access to DAAs in this age demographic. The removal of restrictions regarding substance use disorder is also presumably a contributing factor to expanding access to DAAs in this age demographic. According to the CDC, the opioid epidemic has had the largest impact on patients aged 25-54 years old.[8] Intravenous drug use associated with the opioid epidemic has exposed many patients in this age group to acquisition of hepatitis C infection.[7-9]

Similar to what has been seen in other policy evaluations, the impact of this policy change had a significant impact on utilization. The overall utility of DAAs has increased substantially and DAAs are being prescribed more by primary care providers as anticipated. This policy update has also expanded access to a higher percentage of patients with concomitant substance use disorder, which is particularly critical as this is a high risk population for acquisition and transmission of hepatitis C infection. Overall, the percentage of those with diagnosed hepatitis C infection receiving DAAs increased from 10.7% to 20.4%. Despite the increased awareness of available agents and push for more hepatitis C testing, the percentage of Oregon Medicaid patients diagnosed with hepatitis C infection was similar before and after revision of the PA in March 2019.

Limitations:
Claims data was used for collection and analysis making it difficult to obtain specifics regarding comorbidities, length of treatment, treatment success, and retreatment of patients with DAAs. It is difficult to fully assess what re-treatment rates will be since a full year's worth of data after initial treatment in the study group was not yet available at the time of data collection. Use of claims data also impacts the total amount of patients with diagnosis of hepatitis C as analysis relies on ICD-10 codes. It is unclear if patients that have successfully treated for hepatitis C had the diagnosis removed or if diagnoses codes were omitted for those who have not yet received a prescription for treatment. A more prolonged time frame may indicate a more profound difference between the two groups. Information about other potential consequences or benefits from changes in PA criteria, such as impact on HCC, liver transplant, or mortality due to hepatic complications could not be included due to inherent limitations in claims data.

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Appendix 1. Direct Acting Antivirals Included in Search

Drug Brand Name	Generic Name	Indication	Mechanism of Action
Epclusa ®	Sofosbuvir/velpatasvir	HCV GT 1-6	NS5B inhibitor/NS5A inhibitor
Harvoni ®	Ledipasvir/sofosbuvir	HCV GT 1, 4, 5, or 6	NS5A inhibitor/NS5B inhibitor
Mavyret ®	Glecaprevir/pibrentasvir	HCV GT 1-6	NS3/4A protease inhibitor/NS5B inhibitor
Vosevi ®	Sofosbuvir/velpatasvir/voxilaprevir	HCV GT 1-6 TE with NS5A inhibitor	NS5B inhibitor/NS5A inhibitor/NS3 protease inhibitor
Zepatier ®	Elbasvir/grazoprevir	HCV GT 1 or 4 with RBV in those with RBV TE	NS3/4A protease inhibitor/NS5A inhibitor
Epclusa ®	Sofosbuvir/velpatasvir	HCV GT 1-6	NS5B inhibitor/NS5A inhibitor
Harvoni ®	Ledipasvir/sofosbuvir	HCV GT 1, 4, 5, or 6	NS5A inhibitor/NS5B inhibitor
Olysio ®	Simeprevir	HCV GT1 with sofosbuvir	NS3/4A protease inhibitor
Sovaldi ®	Sofosbuvir	HCV GT 2 or 3 with ribavirin or HCV GT 1 or 4 with ribavirin and peginterferon alfa	NS5B polymerase inhibitor
Daklinza ®	Daclatasvir		NS5A inhinbitor
Copegus ®, Rebetol ®, Ribasphere ®	Ribavirin	HCV GT 1-4 with a DAA in circumstances listed above	Antiviral activity not fully understood. RBV increases the mutation frequency in genomes in several RNA viruses.

Abbreviations: TE = treatment experience; RBV = ribavirin; NS = nonstructural proteins; HCV = hepatitis C virus infection; GT = genotype

Appendix 2. DAAs Prescribed by Prescriber Classification

	Before Updated Prior Authorization (Control Group)		After Updated Prior Authorization Criteria (Study Group)	
	N	**(%)**	**N**	**(%)**
Primary Care Providers (Total)	**480**	**47.3%**	**1,312**	**63.7%**
NURSE PRACTITIONER - FAMILY	131	12.9%	263	12.8%
PHYSICIAN-FAMILY MEDICINE	96	9.5%	234	11.4%
PHYSICIAN ASSISTANT - MEDICAL	92	9.1%	291	14.1%
PHYSICIAN-INTERNAL MEDICINE	92	9.1%	291	14.1%
PHYSICIAN ASSISTANT	33	3.3%	110	5.3%
NURSE PRACTITIONER	25	2.5%	62	3.0%
STUDENT IN AN ORGANIZED HEALTH CARE EDUCATION/TRAINING PROGRAM	4	0.4%	30	1.5%
PHARMACIST	2	0.2%	6	0.3%
NATUROPATH	2	0.2%	13	0.6%
NURSE PRACTITIONER - ADULT HEALTH	3	0.3%	6	0.3%
PHYSICIAN-GENERAL PRACTICE	0	0.0%	6	0.3%
Specialty Providers (Total)	**534**	**52.7%**	**745**	**36.3%**
PHYSICIAN-INTERNAL MEDICINE-GASTROENTEROLOGY	293	28.9%	358	17.4%
PHYSICIAN-INTERNAL MEDICINE-INFECTIOUS DISEASE	166	16.4%	313	15.2%
PHYSICIAN-INTERNAL MEDICINE-HEPATOLOGY	23	2.3%	28	1.4%
SPECIALIST	22	2.2%	20	1.0%
PHARMACIST - CLINICIAN (PHC) / CLINICAL PHARMACY SPECIALIST	21	2.1%	2	0.1%
PHYSICIAN-EMERGENCY MEDICINE	7	0.7%	10	0.5%
PHYSICIAN ASSISTANT - SURGICAL	1	0.1%	3	0.1%
PHYSICIAN-PEDIATRICS-PEDIATRIC GASTROENTEROLOGY	1	0.1%	2	0.1%
PHYSICIAN-PEDIATRICS	0	0.0%	6	0.3%
PHYSICIAN-ANESTHESIOLOGY	0	0.0%	1	0.03%
PHYSICIAN-INTERNAL MEDICINE-HEMATOLOGY&ONCOLOGY	0	0.0%	1	0.03%
PHYSICIAN-SURGERY-UROLOGY	0	0.0%	1	0.03%

Appendix 3. Diagnosis Codes of Interest

Associated Diagnosis	ICD-10 Code
Chronic Hepatitis, Viral	
Chronic viral hepatitis C with or without hepatic coma and unspecified viral hepatitis C with or without hepatic coma	B1710, B1711, B182, B192x, Z2252
Cirrhosis	
Fibrosis and cirrhosis of the liver	K703x, K704x, K74x, K766
Compensated Cirrhosis	K7030, K740, K743, K744, K745, K7460, K7469
Decompensated Cirrhosis	G9340, G9341, G9349, I6783, I8500, I8501, I8510, I8511, K226, K228, K7210, K7290, K766, K767, R180, R188
Substance Use Disorder	
Opioid, sedative, hypnotic, anxiolytics, cocaine, stimulant, and other psychoactive substance related disorders	F11.x, F13.x, F14.x, F15.x, F19.x
Alcohol Use Disorder	
Alcohol abuse or dependence	F10.1x, F10.2x

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