7.03.14 Hepatitis C Viremic Organs for Transplantation to Non-Viremic Patients			
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Policy Statement

The transplantation of Hepatitis C virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The American Society of Transplantation Consensus Conference on the use of hepatitis C virus (HCV) viremic donors in solid organ transplantation concluded that the transplantation of organs from HCV viremic donors into HCV non-viremic recipients should be conducted only under monitored institutional review board (IRB)-approved protocols and studies. (See Supplemental Information)

Coding

The following CPT codes may be used for this transplant:

Kidney Transplant codes

- 50300-50365
- 50547

Pancreas Transplant codes

- 48550-48554

Small Bowel Transplant codes

- 44120-44121
- 44132-44136
- 44715-44721

Liver Transplant codes

- 47133-47147

Lung Transplant codes

- 32850-32856

Heart Lung Transplant codes

- 33930-33935

Heart Transplant codes

- 33940-33945

The following HCPCS codes may be used for this transplant:

Small Bowel Transplant code

- S2053

Multivisceral Organ Transplant codes

- S2054-S2055

Lung Transplant codes

- S2060-S2061

Pancreas Kidney Transplant code

- S2065

Description

In patients with end-stage organ failure, donor organ shortage is a growing concern and there is increasing consideration of use of increased infectious risk, as well as otherwise medically marginal, donors. Hepatitis C virus (HCV)-infected donor organs are typically discarded. The availability of direct-acting antiviral agents (DAA) has made it possible to effectively treat most HCV-infected patients including those who develop acute hepatitis infection after receiving an organ transplant from an HCV viremic donor.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Solid organ transplant represents donor and recipient surgical procedures and, as such, is not subject to regulation by the U.S. Food and Drug Administration (FDA).

Direct-Acting Antiviral Treatment
There are multiple drug combinations approved by the FDA for the treatment of chronic HCV infection. Drug regimen choice and duration of treatment are based on the HCV genotype as well as the degree of liver cirrhosis.

The FDA in 2016 approved a fixed-dose combination tablet containing sofosbuvir, a drug previously approved in 2013, and velpatasvir which was the first DAA to treat HCV genotypes 1-6. (Epclusa - Gilead Sciences)

In 2017, 2 pangenotypic products were approved by the FDA. A once-daily single tablet containing the nucleotide analog nonstructural protein NS5B polymerase inhibitor sofosbuvir, the HCV NS5A inhibitor velpatasvir, and pangenotypic HCV NS3/4A protease inhibitor voxilaprevir was approved to treat adults with chronic HCV genotypes 1-6 without cirrhosis or with mild cirrhosis. This product is also indicated in patients who have been previously treated with the DAA drug sofosbuvir or other drugs for HCV that inhibit NS5A. (Vosevi - Gilead Sciences)

The combination of glecaprevir and pibrentasvir was approved for the treatment of adults with chronic HCV infection across all genotypes 1-6 without cirrhosis or with compensated cirrhosis,

including patients with moderate to severe kidney disease and those who are on dialysis. The products are also approved for patients with HCV genotype 1 infection who have been previously treated with a regimen containing an NS5A inhibitor or an NS3/4A protease inhibitor but not both. (Mavyret - AbbVie)

There is no specific labeling of DAA treatment for post-exposure prophylaxis for persons exposed to HCV viremic blood or contaminated body fluids.

Rationale

Background

Long wait times for solid organ transplant and the high-risk of mortality while on the transplant waiting list for a kidney, thoracic organ, liver, and other solid organs have prompted an investigation into strategies to increase organ allocation and decrease discard rates of potentially viable donor organs. Although organs from hepatitis C virus (HCV)-infected donors have historically been transplanted only into recipients with preexisting HCV infection, direct-acting antiviral (DAA) HCV drugs achieve cure rates greater than 95% with well-tolerated side effects, thus enlarging the pool of organs for wait listed patients who might consider accepting HCV-infected organs.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Evaluation of published literature on solid organ transplantation issues related to donor and recipient discordance with respect to hepatitis C virus (HCV)-HIV, HCV-hepatitis B virus (HBV) or HCV-HIV-HBV co-infections as well as cytomegalovirus transmission or reactivation is beyond the scope of this policy.

Evaluation of the published literature related to choices and/or modification of post-transplant immunosuppression regimens including drug-drug interactions is also beyond the scope of this policy.

Kidney Transplantation

Clinical Context and Therapy Purpose

The purpose of a kidney transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage renal disease is to provide a treatment option that is an alternative to or an improvement on existing management.

Potential benefit of this approach is to reduce 1) waiting time to transplant, 2) waitlist-associated morbidity/mortality, and 3) the discard of otherwise healthy solid organs. Use of direct-acting antiviral (DAA) regimens to treat or prevent acute HCV infection in recipients of kidney transplant from HCV viremic donors is likely to prevent acute and chronic downstream sequelae of transplant acquired HCV infection.

The question addressed in this evidence review is: Does kidney transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage renal disease result in an improvement in net health outcomes?

The following PICO was used to select literature to inform this review.

Population
The relevant population of interest are individuals who are HCV non-viremic, on the waiting list for a kidney transplant and in whom the benefit of accepting a solid organ transplant from an HCV viremic donor may outweigh the harms in comparison to waiting for a solid organ from an HCV non-viremic donor.

Interventions
The therapy being considered is kidney transplant from an HCV viremic donor combined with DAA agents for HCV. Recipients would receive guideline-directed therapy for the treatment of acute HCV infection.

Comparators
The following therapies are currently being used to make decisions about kidney transplantation: continued disease management on a waiting list until an HCV non-viremic donor kidney is available for transplant.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, change in disease status, treatment-related mortality, treatment-related morbidity, morbid events, quality of life and resource utilization.

Specific outcomes include incidence of HCV viremia and sustained virological response (SVR) rates after use of DAA agents in the transplant recipient at 12 weeks (SVR12) after completion of HCV treatment, assessment of transplanted organ function, the incidence of organ rejection, graft survival, overall survival and time on waitlist.

There is also a potential for harm resulting from increased post-transplant complications associated with HCV allograft infection among those who fail to achieve an SVR with initial treatment with DAA and are at risk of developing acute HCV infection with fibrosing cholestatic hepatitis (FCH). HCV-associated FCH is a well-described complication in association with liver and kidney transplantation. In severe cases, the graft may be lost with a need for another transplant. There are multiple clinical scenarios including relapse of HCV infection in an HCV non-viremic donor organ and acute HCV infection with the transplantation of an HIV-viremic organ into an HCV non-viremic recipient. Additional precipitating factors that have been reported include the use of azathioprine and co-infection with HBV. The effect of highly effective DAA treatment has been hypothesized to decrease the likelihood of FCH.

Study Selection Criteria
Evidence reviews have used a best available evidence approach. Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Multiple prospective and retrospective cohort studies evaluating feasibility, efficacy and safety of transplant of kidneys from HCV viremic donors into HCV non-viremic recipients have been published. The study characteristics and results are summarized in Tables 1 and 2. These studies have used a range of different DAA regimens based on the contemporaneous availability and recommendations at the time of conduct of these studies.

Most prospectively conducted studies in which DAA were initiated early in the course of transplant or immediately post-transplant for a duration of 8 to 12 weeks report SVR12 rates approaching 100% and stable organ function during 1 year of follow-up.[1,2,3,4,] A majority of early studies[1,2,3,] used a 12-week course of grazoprevir/elbasvir, a non-pangenotypic DAA regimen. However, this regimen is no longer recommended by the American Association for the Study of Liver Diseases.[5,] Other studies have explored options for "ultra-short course" pangenotypic therapy[6,] or used a "standard-of-care" approach with 12-week treatment duration with therapy beginning weeks to months after transplant.[7,] However, "ultra-short course" therapy (2 to 4 days) was associated with treatment failures, including one patient who developed a highly resistant virus, whereas the delayed treatment approach has been associated with increased risks of cytomegalovirus and BK virus, and several cases of FCH.[7,8,6,] Current treatment recommendations include initiating treatment within the first month after liver transplant, preferably within the first week when the patient is clinically stable with a pangenotypic DAA regimen that includes daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) or sofosbuvir (400 mg)/velpatasvir (100 mg) for 8 weeks.

Table 1. Summary of Key Trials: Study Characteristics - Transplantation of Hepatitis C Virus Viremic Kidney

Study	Study Type	Country	Dates	Participants	Treatment	Follow Up
Goldberg et al (2017) [1,] **Reese et al (2018)[2,] THINKER-1 and -2 (NCT02743897)**	Prospective Cohort	United States (Single site at University of Pennsylvania)	2016-ongoing	• N=20 (N=10 in THINKER-1 and N=10 in THINKER-2) • Participant criteria targeted patients who were anticipated to have prolonged waiting times for kidney transplants from HCV non-viremic donor and sought to exclude patients with conditions that would substantially elevate risks for liver disease, death, or	• 12 weeks GZR/ELB without NS5a RASs • 16 weeks GZR/ELB-RBV with NS5a RASs • DAA initiated when recipients tested positive for HCV viremia (generally 1 to 3 days post-transplant)	6 months to 1 year

Study	Study Type	Country	Dates	Participants	Treatment	Follow Up
				• allograft failure after transplant • Donor genotype 1 HCV		
Durand et al (2018)[3] EXPANDER-1 (NCT02781649)	Prospective Cohort	United States (Single site at John Hopkins)	2016-2018	• N=10 • Kidney transplant candidates on the deceased donor transplant waiting list • Donor genotype 1,2 or 3 HCV	• Genotype 1a without NS5a RASs, 1b, or 4: 12 weeks GZR/ELB • Genotype 1a with NS5a RASs: 16 weeks GZR/ELB/RBV • Genotype 2 or 3: 12 weeks of GZR/ELB/SOF • Genotype not determined: 12 weeks GZR/ELB • DAA initiated immediately before transplant	12 weeks
Sise et al (2020)[4] MYTHIC (NCT03781726)	Prospective Cohort	United States (multicenter, 7 sites)	2019-2020	• N=30 • Kidney transplant candidates on the deceased donor transplant waiting list with anticipated wait time >2 years • Donor genotype 1a, 2 or 4 HCV	• GLE/PIB for 8 weeks • DAA initiated 2 to 5 days post-transplant	20 weeks
Gupta et al (2020)[6] DAPPeR (NCT03249194)	Prospective Cohort	United States (single site at Virginia Commonwealth University)	2017-2018	• N=50 • Kidney transplant candidates on the deceased donor transplant waiting list with anticipated wait time >2 years • Donor genotype 1a, 2 or 3 HCV	• Group 1 (n=10): 2 doses of SOF/VEL (first dose no sooner than 6 hours prior to transplant; second on day 1 of transplant) • Group 2 (n=40): 4 doses of SOF/VEL (first dose no sooner than 6 hours prior to transplant; subsequent dose on day 1,	Median 8 months

Study	Study Type	Country	Dates	Participants	Treatment	Follow Up
					2 and 3 of transplant) • Development of HCV viremic status at any time posttransplant triggered a full course of DAA therapy as follows • Group 1: Genotype 1 12 weeks of ELB/GZR • Group 2A: SOF/VEL ± RBV for 12 weeks funded by Gilead • Group 2B: DAA therapy as per investigator choice and covered by insurance	
Franco et al (2019)[9].	Prospective Cohort	Spain (3 sites)	2017	• N=4 • Kidney transplant candidates on the deceased donor transplant waiting list • Donor genotype 1a and 1b	• GLE/PIB for 8 weeks • DAA initiated 6 hours before transplant	6 months
Kapila et al (2020)[8].	Retrospective Cohort	United States (multicenter, 5 sites)	2018	• N=77 (Kidney=64) • Kidney transplant candidates on the deceased donor transplant waiting list	• Patients underwent HCV NAT and genotype testing 3 to 5 days post-transplant • DAA regimen and duration at the discretion of the hepatologist and consisted of LED/SOF, GLE/PIB, VEL/SOF • DAA initiated at a median of 72 days after transplant	Unclear (range from 16 to 55 weeks based on extrapolation from a graph)

Study	Study Type	Country	Dates	Participants	Treatment	Follow Up
Feld et al (2020)[10], NCT04017338	Prospective Cohort	Canada (single site at Toronto General Hospital)	2019	• N=30 (Kidney=10) • Transplant candidates on the deceased donor transplant waiting list	• GLE/PIB (single dose 6 to 12 hours before transplant and once a day for 7 days after surgery i.e., 8 doses in total) • Ezetimibe (single dose prior to transplant)	12 weeks
Molnar et al (2019)[7]	Retrospective Cohort	United States (Single site at Methodist University Hospital, Memphis)	2018	• N=53 • 53 out of 73 kidney transplants from HCV NAT positive and/or antibody positive kidney included in analysis • Donor genotype 1a, 1b, 2 or 3 HCV	• GLE/PIB, SOF/VEL, or SOF/LED for at least 12 weeks • DAA initiated at a median of 76 days after transplant	Median 302 days
Friebus-Kardash et al (2019)[11]	Retrospective Cohort	Germany (single center)	2016-2017	• N=7 • 7 out of 143 (4.9%) kidney transplants from 5 deceased HCV viremic donors identified retrospectively • Donor genotype 1 and 3a	• SOF/LED or SOF/VEL for 8 to 12 weeks • DAA initiated within a median of 7 days after transplant	1 year

DAA; direct acting antiviral agents; ELB; elbasvir; GLE; glecaprevir; GZR; grazoprevir; HCV: hepatitis-C virus; LED: ledipasvir; NAT: nucleic acid test; NS5a RASs: Nonstructural protein 5A resistance associated substitution; PIB: pibrentasvir; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir

Table 2. Summary of Key Trials Study Results - Transplantation of Hepatitis C Virus Viremic Kidney

Study	Outcomes Related to HCV Cure	Graft Function Related Outcomes	Safety and Other Miscellaneous Outcomes
Goldberg et al (2017) [1], THINKER-1 (NCT02743897)	SVR12: 100% (10/10)	*6-month outcomes (n=10), median (IQR)* Serum creatinine: 1.1 mg/dL (0.8 to 1.3) eGFR: 62.8 mL/min/1.73 m^2 (51.8 to 83.1)	• None reported
Reese et al (2018)[2], THINKER-2 (NCT02743897)	SVR12: 100% (20/20)	*6-month outcomes (n=20), median (IQR)* Serum creatinine: 1.2	• 1 serious adverse event (proteinuria adjudicated as being possibly related to

Study	Outcomes Related to HCV Cure	Graft Function Related Outcomes	Safety and Other Miscellaneous Outcomes
		mg/dL (1.0 to 1.3) eGFR: 67.5 mL/min/1.73 m^2 (57.8 to 85.7) *12-month outcomes (n=10), median (IQR)* Serum creatinine: 1.1 mg/dL (1.0 to 1.3) eGFR: 72.8 mL/min/1.73 m^2 (58.6 to 74.4)	HCV and with substantial improvement after treatment) • Self-reported physical quality of life improved from pretransplant levels, and mental quality of life was similar to pretransplant levels
Durand et al (2018) [3]. EXPANDER-1 (NCT02781649)	SVR12: 100% (10/10)	*12-week outcomes (n=10), median (IQR)* Serum creatinine: 1.05 mg/dL (0.9 to 2.0) eGFR: 63.5 mL/min/1.73 m^2 (47.8 to 69.9).	• Median wait time from study entry to transplantation was 1 month • 5 recipients never had a detectable level of plasma HCV RNA with pre-exposure prophylaxis • No treatment-related adverse events occurred
Sise et al (2020)[4].MYTHIC (NCT03781726)	SVR12: 100% (30/30)	*6-month outcomes (n=20), median (IQR)* Serum creatinine: 1.2 mg/dL eGFR: 57 mL/min/1.73 m^2	• Median time between consent and transplantation was 6.3 weeks • One recipient died of complications of sepsis 4 months after achieving SVR • No severe adverse events reported deemed likely related to HCV infection or treatment • 3 patients developed acute cellular rejection • 3 developed polyomavirus viremia that resolved after reduction of immunosuppression
Gupta et al (2020)[6].DAPPeR (NCT03249194)	SVR12: 98% (48/50)	After a median follow-up of 8 months posttransplant, overall patient and allograft survivals: 98% respectively (with one each of graft loss and one death)	• HCV transmission rates: 30%, 13% and 4% in group 1,2 and 3 respectively; overall 12% • Overall acute rejection rate was 4% (2/50)
Franco et al (2019)[9].	SVR12: 100% (4/4)	Stable functioning graft at the end of the follow-up period of 6 months. Mean or median values of graft function were not reported.	• No adverse events associated with DAA treatment were recorded
Kapila et al (2020)[8].	SVR12: 71% (41/58) 10 had undetectable viral loads but are not eligible for SVR12, and 7 remain on treatment	Delayed graft function in one patient One patient died with complicated post-transplant course; did not receive DAA even though viral load was high; patient died at an outside hospital, and the cause of death is unknown.	• No significant adverse events from DAA treatment

Study	Outcomes Related to HCV Cure	Graft Function Related Outcomes	Safety and Other Miscellaneous Outcomes
Feld et al (2020)[10.] NCT04017338	SVR12: 100% (10/10)	No episodes of acute rejection reported. Graft survival 100% at last follow-up. Median eGFR at 12 weeks: 74 mL/min/1.73 m² (IQR 65 to 92)	• Safety events stratified by organ were not reported
Molnar et al (2019)[7.]	SVR12: 100% (53/53)	*Mean eGFR (±SD):* End of treatment: 67±21 mL/min/1.73 m² 12-week posttreatment: 67±17 mL/min/1.73 m² Loss of graft: None	• Median time between transplant and treatment initiation was 76 days • One patient developed fibrosing cholestatic hepatitis with complete resolution • Four recipients developed acute rejection
Friebus-Kardash et al (2019)[11.]	SVR12: 100% (7/7)	None exhibited delayed allograft function and no rejection episodes observed during DAA treatment or during follow-up for as long as 1 year after transplant. Mean or median values of graft function were not reported.	• No severe adverse effects reported

DAA; direct acting antiviral agents; eGFR; estimated glomerular filtration rate; HCV: hepatitis-C virus; IQR: inter-quartile range; RNA: ribonucleic acid, SD: standard deviation; SVR12: sustained virologic response at week 12

Tables 3 and 4 display notable limitations identified in each study. The studies were in general well conducted and reported. The major limitations are small sample size, studies were mostly conducted at single centers at academic institutions, limited duration of follow-up for graft survival and function, and lack of comparative analysis with historical controls. Randomized controlled trials in this context are neither feasible or required. The published studies enrolled a limited number of subjects since they intended to examine the feasibility of transplanting kidneys from HCV viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible, multicenter trials with standardized protocols, and rigorous adjudication of outcomes and adverse events, are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers.

Table 3. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Goldberg et al (2017) [1.] THINKER-1 (NCT02743897)					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Reese et al (2018)[2.] THINKER-2 (NCT02743897)					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Durand et al (2018) [3.] EXPANDER-1 (NCT02781649)					1. Not sufficient duration for benefit 2. Not sufficient duration for harms

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Sise et al (2020)[4]. MYTHIC (NCT03781726)					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Gupta et al (2020)[6].DAPPeR (NCT03249194)					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Franco et al (2019)[9].					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Kapila et al (2020)[8].					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Feld et al (2020)[10]. NCT04017338					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Molnar et al (2019)[7].					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Friebus-Kardash et al (2019)[11].					1. Not sufficient duration for benefit 2. Not sufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Goldberg et al (2017) [1]. THINKER-1 (NCT02743897)	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Reese et al (2018)[2]. THINKER-2 (NCT02743897)	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome				

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
	4. Inadequate control for selection bias	assessed by treating physician				
Durand et al (2018)[3]. EXPANDER-1 (NCT02781649)	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Sise et al (2020)[4].MYTHIC (NCT03781726)	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Gupta et al (2020)[6].DAPPeR (NCT03249194)	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Franco et al (2019)[9].	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician	1. Not registered			
Kapila et al (2020)[8].	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician	1. Not registered			
Feld et al (2020)[10]. NCT04017338	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Molnar et al (2019)[7].	1. Participants not randomly allocated 2. Allocation not concealed	1. Not blinded to treatment assignment 2. Not blinded	1. Not registered			

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
	3. Allocation concealment unclear 4. Inadequate control for selection bias	outcome assessment 3. Outcome assessed by treating physician				
Friebus-Kardash et al (2019)[11]	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician	1. Not registered			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Kidney Transplantation

For individuals who require a kidney transplant and are HCV non-viremic and receive a kidney transplant from an HCV viremic donor combined with DAA, the evidence consists of multiple single-arm prospective and retrospective studies. These studies reported outcomes for a total of 252 recipients who received a kidney transplant from an HCV viremic donor. Most prospectively conducted studies in which DAA were initiated early in the course of transplant or immediately post-transplant for a duration of 8 to 12 weeks report SVR12 rates approaching 100% and stable organ function during 1 year of follow-up. There is considerable heterogeneity between the studies in terms of whether or not donor kidneys were genotyped in advance of transplantation, whether use of DAA regimens chosen to match genotype or pangenotypic were used, and differences in the timing and duration of the DAA regimen. Use of ultra-short course therapy (2 to 4 days) was associated with treatment failures whereas the delayed treatment approach has been associated with increased risks of cytomegalovirus and BK virus, and several cases of FCH. Current treatment recommendations include initiating treatment within the first month after liver transplant, preferably within the first week when the patient is clinically stable with a pangenotypic DAA regimen that includes a daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) or sofosbuvir (400 mg)/velpatasvir (100 mg) for 8 weeks. The published studies enrolled a limited number of subjects since they intended to examine the feasibility of transplanting kidneys from HCV viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible; multicenter trials with standardized protocols, and rigorous adjudication of outcomes and adverse events are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers.

Lung Transplantation

Clinical Context and Therapy Purpose

The purpose of lung transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage pulmonary disease is to provide a treatment option that is an alternative to or an improvement on existing management.

Potential benefit of this approach is to reduce 1) waiting time to transplant, 2) waitlist-associated morbidity/mortality and 3) the discard of otherwise healthy solid organs. Use of DAA regimens to treat or prevent acute HCV infection in recipients of lung transplant from HCV viremic donors is likely to prevent acute and chronic downstream sequelae of transplant acquired HCV infection.

The question addressed in this evidence review is: Does lung transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage pulmonary disease result in an improvement in net health outcomes?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are HCV non-viremic, on the waiting list for a lung transplant and in whom the benefit of accepting a solid organ transplant from an HCV viremic donor may outweigh the harms in comparison to waiting for a solid organ from an HCV non-viremic donor.

Interventions

The therapy being considered is lung transplant from an HCV viremic donor combined with DAA agents for HCV. Recipients would receive guideline-directed therapy for the treatment of acute HCV infection.

Comparators

The following therapies are currently being used to make decisions about lung transplantation: continued disease management on a waiting list until an HCV non-viremic donor lung is available for transplant.

Outcomes

The general outcomes of interest are overall survival, disease-specific survival, change in disease status, treatment-related mortality, treatment-related morbidity, morbid events, quality of life and resource utilization.

Study Selection Criteria

Evidence reviews have used a best available evidence approach. Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

The key characteristics and results of the 3 studies are summarized in Tables 5 and 6.

Woolley et al (2019) reported the results of a prospective single arm study involving transplantation of HCV viremic hearts and lungs from donors to adults without HCV infection.[12,] DAA with sofosbuvir/velpatasvir was administered preemptively immediately after organ transplant for 4 weeks. The DAA regimen provided pangenotypic coverage and is not

associated with immunosuppressive drug interactions. The 4-week duration of DAA was used based on the investigator assumption that the HCV viral load transmission would be low at the time of transplantation. An additional exploratory 6-month post hoc analysis was done of transplantation outcomes from a population of 56 trial participants for whom HCV non-viremic donor organs became available. These participants had higher listing Organ Procurement and Transplantation Network status. Acute cellular rejection occurred more frequently in lung transplant recipients of HCV viremic donors, but the duration of follow-up is insufficient to determine the effect on long-term graft survival.

Cypel et al (2020) reported the results of a prospective single arm study in which 22 recipients on a lung transplant waiting list without significant liver disease received lungs from HCV-viremic donors.[13] This study also evaluated a novel approach of minimizing viral load *ex vivo* before transplantation, with the intent of preventing donor-recipient transmission by attempting to inactivate the HCV during the period of organ preservation before transplantation. Eleven of the 22 HCV viremic donor lungs were treated with ultraviolet C plus ex-vivo lung perfusion and the other 11 were treated with ex-vivo lung perfusion only. All patients received 12 weeks of oral sofosbuvir 400 mg/velpatasvir 100 mg starting at least 2 weeks after transplantation. The primary endpoint was a composite of survival and HCV-free status at 6 months after transplantation in all patients who received HCV viremic lungs. Patient outcomes such as survival, time in hospital, and incidence of acute rejection were compared between those receiving HCV viremic lungs and all patients who received HCV non-viremic lung transplants during the study period. The primary endpoint was achieved in 19 (86%) of 22 patients in the HCV viremic group. Six-month survival was 95% in recipients receiving lungs from HCV viremic donors versus 94% in recipients receiving lungs from HCV non-viremic donors (external control). However, the duration of follow-up is insufficient to determine the effect on long-term graft survival. Two patients presented with HCV relapse within 3 months after sofosbuvir/velpatasvir completion and required retreatment.

Feld et al (2020) reported the results of a prospective single arm study in which 30 recipients on a solid organ transplant waiting list received transplants (13 lung, 10 kidney, 6 heart, and 1 kidney-pancreas) from 18 HCV-infected donors.[10]. All 13 (100%) lung transplant recipients met the primary endpoint of undetectable HCV RNA at 12 weeks post-transplant, and were HCV RNA-negative at last follow-up (median, 36 weeks post-transplant; IQR, 25 to 47).

Table 5. Summary of Key Trials: Study Characteristics Transplantation of Hepatitis C Virus-Infected Lung

Study	Study Type	Country	Dates	Participants	Treatment	Follow Up
Wooley et al (2019)[12] DONATE HCV (NCT03086044)	Prospective Cohort	United States (Single site at Brigham and Women's Hospital)	2017-2018	• N=44 (Lung=36) • Heart or lung transplant candidates on waiting list • Donor genotype for entire cohort: HCV 1 (61%), HCV 2 (17%), HCV 3 (17%), and indeterminate (5%)	• 4 weeks SOF/VEL • DAA initiated within post transplant	6 months
Cypel et al (2020)[13] (NCT03112044)	Prospective Cohort	Canada (Single site at Toronto General Hospital)	2017-2018	• N=22 • Lung transplant candidates on the deceased donor transplant waiting list	• 11 of 22 subjects received EVLP plus UVC perfusate irradiation prior to transplant • 12 weeks SOF/VEL to all patients	6 months

Study	Study Type	Country	Dates	Participants	Treatment	Follow Up
				• Donor genotype 1,2 or 3 HCV	• DAA initiated 2 weeks post-transplant (median of 21 days after transplantation; IQR, 16.76 to 24.75)	
Feld et al (2020)[10]. NCT04017338	Prospective Cohort	Canada (single site at Toronto General Hospital)	2019	• N=30 (Lung=13) • Transplant candidates on the deceased donor transplant waiting list	• EVLP plus UVC perfusate irradiation prior to transplant • GLE/PIB (single dose 6 to 12 hours before transplant and once a day for 7 days after surgery i.e., 8 doses in total) • Ezetimibe (single dose prior to transplant)	12 weeks

DAA; direct acting antiviral agents; EVLP: ex-vivo lung perfusion; GLE; glecaprevir; HCV: hepatitis-C virus; IQR: inter-quartile range; PIB: pibrentasvir; SOF: sofosbuvir; UVC: ultraviolet C

Table 6. Summary of Key Trials Study Results Transplantation of Hepatitis C Virus-Infected Lung

Study	Outcomes Related to HCV Cure	Graft Function Related Outcomes	Safety and Other Miscellaneous Outcomes
Wooley et al (2019)[12]. DONATE HCV (NCT03086044)	SVR12: 100% (28/28) Note: Of 44 subjects enrolled, data from first 35 subjects (28 lung and 7 heart) enrolled who had completed 6 months of follow-up was reported.	Acute cellular rejection for which treatment was indicated: 54% (15/28) Graft survival at 1 month: 100% (28/28) Graft survival at 6 month: 100% (28/28) Overall survival at 6 month: 100% (28/28)	• Liver-function >3 times ULN <30 days post-transplant: 7% (2/28) • Liver-function >3 times ULN ≥30 days post-transplant: 7% (2/28)
Cypel et al (2020)[13]. (NCT03112044)	SVR12: 100% (20/20) Note: 20 out of 22 developed HCV infection	Acute rejection A1 or higher: 50% (11/22) Primary endpoint of survival and HCV-free status at 6 months: 86% (19/22)	• EVLP plus UVC versus EVLP alone o Median viral load: 167 IU/mL [IQR, 20 to 12,000] vs 4390 IU/mL [IQR, 170 to 112,000] at day 7; p=.048 o Prevention of HCV transmission: 18% (2 of 11) vs none • 10% failure rate including one patient developing fibrosing cholestatic hepatitis proven by biopsy

Study	Outcomes Related to HCV Cure	Graft Function Related Outcomes	Safety and Other Miscellaneous Outcomes
Feld et al (2020)[10], NCT04017338	SVR12: 100% (13/13)	Acute rejection: 23% (3/13) Two recipients died due to causes unrelated to study drug treatment (sepsis at 49 days and subarachnoid hemorrhage at 109 days post-transplant) Median FEV1 at 12 weeks: 76% of predicted (IQR, 57 to 78)	• Safety events stratified by organ were not reported

EVLP: ex-vivo lung perfusion; FEV1: forced expiratory volume; HCV: hepatitis-C virus; IQR: inter-quartile range; IU: international units; SVR12: sustained virologic response at week 12; ULN: upper limit of normal; UVC: ultraviolet C

The purpose of limitation tables (see Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence. The studies were in general well conducted and reported. The major limitations are small sample size, studies were mostly conducted at single centers at academic institutions and limited duration of follow-up for graft survival and function. The published studies enrolled a limited number of subjects since they intended to examine the feasibility of transplanting lungs from HCV viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible; multicenter trials with standardized protocols and rigorous adjudication of outcomes and adverse events are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Wooley (2019)[12],(NCT03086044) DONATE HCV					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Cypel (2020)[13], (NCT03112044)					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Feld et al 2020[10], (NCT04017338)					1. Not sufficient duration for benefit 2. Not sufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Wooley (2019)[12.](NCT03086044) DONATE HCV	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician		6. Not intent to treat analysis (interim data for 35 of 44 subjects enrolled reported)		
Cypel (2020)[13.] (NCT03112044)	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Feld et al 2020[10.] (NCT04017338)	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Lung Transplantation

For individuals who require a lung transplant and are HCV non-viremic and receive a lung transplant from an HCV-viremic donor combined with direct- acting antiviral agents, the evidence consists of 3 single-arm prospective studies. The 3 studies reported outcomes for a total of 61 recipients who received a lung transplant from an HCV-viremic donor. While the studies by

Wooley et al (2019) and Cypel et al (20202) used a pangenotypic DAA regimen consisting of sofosbuvir plus velpatasvir, the duration and initiation of treatment was markedly different. In Wooley et al (2019), treatment duration was 4 weeks initiated immediately after transplant while in Cypel et al (2020), treatment duration was 12 weeks initiated 2-weeks after transplant. Feld et al (2020) also used a pangenotypic DAA treatment of glecaprevir plus pibrentasvir for a total duration of 8 days in association with single dose ezetemibe as well as ex-vivo lung perfusion plus ultraviolet-C radiation delivered to the circulating perfusate as an additional measure to lower HCV viral load. All three studies reported SVR12 rates of 100%. Reported rate of graft survival at 6 months available for 28 participants in the first study was 100%. The primary endpoint of survival and HCV-free status at 6 months after transplantation was 86% in the second study. Two patients presented with HCV relapse within 3 months after sofosbuvir plus velpatasvir completion and required retreatment in the second study. Acute rejection requiring treatment was reported in 23% of recipients in the third study. While the 3 published studies enrolled a limited number of subjects as they intended to examine the feasibility of transplanting lungs from HCV-viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible; multicenter trials with standardized protocols, and rigorous adjudication of outcomes and adverse events are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers.

Heart Transplantation

Clinical Context and Therapy Purpose

The purpose of a heart transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage cardiac disease is to provide a treatment option that is an alternative to or an improvement on existing management.

Potential benefit of this approach is to reduce 1) waiting time to transplant, 2) waitlist-associated morbidity/mortality and 3) the discard of otherwise healthy solid organs. Use of DAA regimens to treat or prevent acute HCV infection in recipients of heart transplant from HCV viremic donors is likely to prevent acute and chronic downstream sequelae of transplant acquired HCV infection.

The question addressed in this evidence review is: Does heart transplant from an HCV- viremic donor to an HCV non-viremic recipient who has end-stage cardiac disease result in an improvement in net health outcomes?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are HCV non-viremic, on the waiting list for a heart transplant and in whom the benefit of accepting a solid organ transplant from an HCV viremic donor may outweigh the harms in comparison to waiting for a solid organ from an HCV non-viremic donor.

Interventions

The therapy being considered is heart transplant from an HCV viremic donor combined with DAA agents for HCV. Recipients would receive guideline-directed therapy for the treatment of acute HCV infection.

Comparators

The following therapies are currently being used to make decisions about heart transplantation: continued disease management on a waiting list until an HCV non-viremic donor heart is available for transplant.

Outcomes

The general outcomes of interest are overall survival, disease-specific survival, change in disease status, treatment-related mortality, treatment-related morbidity, morbid events, quality of life and resource utilization.

Study Selection Criteria

Evidence reviews have used a best available evidence approach. Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

The key characteristics and results of 4 studies are summarized in Tables 9 and 10.

McLean et al (2019) reported the results of a prospective single arm study in which 10 recipients on a heart transplant waiting list without significant liver disease received hearts from HCV genotype 1 viremic donor hearts.[14.] Nine of 10 recipients achieved SVR12 after a 12-week course of daily elbasvir/grazoprevir therapy when results were positive for HCV viremia post-transplant. The 10th recipient experienced antibody-mediated rejection and multi-organ failure and died on day 79. No serious adverse events occurred from HCV transmission or treatment. Bethea et al (2019) reported the results of a prospective single arm study in which 20 recipients on a heart transplant waiting list received HCV viremic donor hearts.[15.] All 20 recipients achieved SVR12 after receiving a single pre-emptive dose of glecaprevir/pibrentasvir before transport to the operating room followed by an 8-week course of glecaprevir/pibrentasvir after transplantation. Patient and allograft survival were 100% at a median follow-up of 10.7 months. The reports by Woolley et al (2019)[12.] and Feld et al (2020)[10.] were described in the previous section since these study cohorts included a variety of solid-organ transplants. Both studies reported SVR12 rates of 100%.

Table 9. Summary of Key Trials: Study Characteristics Transplantation of Hepatitis C Virus-Infected Heart

Study	Study Type	Country	Dates	Participants	Treatment	Follow Up
McLean et al (2019)[14.] USHER (NCT03146741)	Prospective Cohort	US (Single Site at University of Pennsylvania Hospital)	2017-2018	• N= 20 (10 transplanted at time of publication) • Adult candidates who were anticipated to have prolonged wait times for an HCV non-viremic transplant • Genotype 1a	• 12 weeks GZR/ELB without NS5a RASs • 16 weeks GZR/ELB/RBV with NS5a RASs • DAA initiated 3 days after transplant	12 months
Bethea et al (2019)[15.] (NCT03208244)	Prospective Cohort	United States (Single site at Massachusetts General Hospital)	2017-2018	• N=20 • Heart transplant candidates on waiting list • Genotype 1a, 1b, 3	• 8 weeks GLE/PIB • Single dose prior to transplant followed by 8 weeks of treatment	52 weeks
Wooley et al (2019)[12.] DONATE HCV (NCT03086044)	Prospective Cohort	United States (Single site at Brigham and Women's Hospital)	2017-2018	• N=44 (Heart=8) • Heart or lung transplant candidates on waiting list	• 4 weeks SOF/VEL • DAA initiated within few	6 months

Study	Study Type	Country	Dates	Participants	Treatment	Follow Up
				• Donor genotype for entire cohort: HCV 1 (61%), HCV 2 (17%), HCV 3 (17%), and indeterminate (5%)	hours post-transplant	
Feld et al (2020)[10.] NCT04017338	Prospective Cohort	Canada (single site at Toronto General Hospital)	2019	• N=30 (Heart=6) • Transplant candidates on the deceased donor transplant waiting list • Genotype 1a, 1b, 2, 3	• GLE/PIB (single dose 6 to 12 hours before transplant and once a day for 7 days after surgery i.e., 8 doses in total) • Ezetimibe (single dose prior to transplant)	12 weeks

DAA; direct acting antiviral agents; ELB; elbasvir; GLE; glecaprevir; GZR; grazoprevir; HCV: hepatitis-C virus; NS5a RASs: Nonstructural protein 5A resistance associated substitution; PIB: pibrentasvir; SOF: sofosbuvir; VEL: velpatasvir

Table 10. Summary of Key Trials Study Results Transplantation of Hepatitis C Virus-Infected Heart

Study	Outcomes Related to HCV Cure	Graft Function Related Outcomes	Safety and Other Miscellaneous Outcomes
McLean et al (2019)[14.] USHER (NCT03146741)	SVR12: 90% (9/10)	Grade 2R acute cellular rejection: 20% (2/10) One patient had a cross-match, experienced antibody-mediated rejection and multi-organ failure, and died on day 79.	• 2 patients developed acute kidney injury with 1 requiring months of dialysis before recovering sufficient kidney function to stop renal replacement therapy
Bethea et al (2019)[15.] (NCT03208244)	SVR12: 100% (20/20) Note: 20 out of 22 developed HCV infection	Patient and allograft survival: 100% at a median follow-up of 10.7 months (range, 6.5 to 18.0)	• No DAA drug reactions or interactions necessitated a lapse or cessation of DAA or immunosuppressive therapy, and no treatment-related or HCV-attributable adverse events were reported.
Wooley et al (2019)[12.] DONATE HCV (NCT03086044)	SVR12: 100% (8/8)	Acute cellular rejection for which treatment was indicated: 43% (3/8) Graft survival at 1 month: 100% (8/8) Graft survival at 6 month: 100% (8/8) Overall survival at 6 month: 100% (8/8) One recipients died 8 months post-transplant from cause unrelated to HCV infection	• Liver-function >3 times ULN <30 days post-transplant: 43% (3/8) • Liver-function >3 times ULN ≥30 days post-transplant: None

Study	Outcomes Related to HCV Cure	Graft Function Related Outcomes	Safety and Other Miscellaneous Outcomes
Feld et al (2020)[10], NCT04017338	SVR12: 100% (6/6)	Acute rejection: 67% (4/6) Median left ventricular ejection fraction at 12-week follow-up: 58% (IQR 56 to 60) Median 6-minute walk distance at 12-week follow-up: 480 m (IQR, 403 to 538)	• Safety events stratified by organ were not reported

DAA; direct acting antiviral agents; HCV: hepatitis-C virus; IQR: inter-quartile range; SVR12: sustained virologic response at week 12; ULN: upper limit of normal

Tables 11 and 12 display notable limitations identified in each study. The studies were in general well conducted and reported. The major limitations are small sample size, studies were mostly conducted at single centers at academic institutions and limited duration of follow-up for graft survival and function. The published studies enrolled a limited number of subjects since they intended to examine the feasibility of transplanting hearts from HCV viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible; multicenter trials with standardized protocols, and rigorous adjudication of outcomes and adverse events are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
McLean et al (2019)[14], USHER (NCT03146741)					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Bethea et al (2019)[15], (NCT03208244)					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Wooley et al (2019)[12], DONATE HCV (NCT03086044)					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Feld et al (2020)[10], NCT04017338					1. Not sufficient duration for benefit 2. Not sufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
McLean et al (2019)[14], USHER (NCT03146741)	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Bethea et al (2019)[15], (NCT03208244)	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Wooley et al (2019)[12], DONATE HCV (NCT03086044)	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Feld et al (2020)[10], NCT04017338	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Heart Transplantation
For individuals who require a heart transplant and are HCV non-viremic and receive a heart transplant from an HCV viremic donor combined with DAA, the evidence consists of 4 single-arm prospective studies. These 4 studies reported outcomes for a total of 44 recipients who received a heart transplant from an HCV viremic donor. The timing, duration and specific DAA regimens used in the 4 published studies were different. Except for the first study published by McLean et al (2019) that used a non-pangenotypic DAA regimen of grazoprevir/elbasvir, the remaining 3 studies used a pan-genotypic DAA regimen of sofosbuvir/velpatasvir or glecaprevir/pibrentasvir. SVR12 rates were 100% in the 3 studies that used a pangenotypic DAA regimen while it was 90% in the study that used a non-pangenotypic DAA regimen. The 4 published studies enrolled a limited number of subjects since they intended to examine the feasibility of transplanting hearts from HCV viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible; multicenter trials with standardized protocols and rigorous adjudication of outcomes and adverse events are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers.

Liver Transplantation
Clinical Context and Therapy Purpose
The purpose of a liver transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage liver disease is to provide a treatment option that is an alternative to or an improvement on existing management.

Potential benefit of this approach is to reduce 1) waiting time to transplant, 2) waitlist-associated morbidity/mortality and 3) the discard of otherwise healthy solid organs. Use of DAA regimens to treat or prevent acute HCV infection in recipients of liver transplant from HCV viremic donors is likely to prevent acute and chronic downstream sequelae of transplant acquired HCV infection.

The question addressed in this evidence review is: Does liver transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage liver disease result in an improvement in net health outcomes?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who are HCV non-viremic, on the waiting list for a liver transplant and in whom the benefit of accepting a solid organ transplant from an HCV viremic donor may outweigh the harms in comparison to waiting for a solid organ from an HCV non-viremic donor.

Interventions
The therapy being considered is a liver transplant from an HCV viremic donor combined with DAA agents for HCV. Recipients would receive guideline-directed therapy for the treatment of acute HCV infection.

Comparators
The following therapies are currently being used to make decisions about liver transplantation: continued disease management on a waiting list until an HCV non-viremic donor liver is available for transplant.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, change in disease status, treatment-related mortality, treatment-related morbidity, morbid events, quality of life and resource utilization.

HCV-associated FCH is a well-described complication in association with liver and kidney transplantation. In severe cases, the graft may be lost with a need for another transplant. There are multiple clinical scenarios including relapse of HCV infection in an HCV non-viremic donor organ and acute HCV infection with the transplantation of an HCV viremic organ into an HCV non-viremic recipient. Additional precipitating factors that have been reported include the use of azathioprine and co-infection with hepatitis B. The effect of highly effective DAA treatment has been hypothesized to decrease the likelihood of FCH.

Study Selection Criteria
Evidence reviews have used a best available evidence approach. Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Bethea et al (2020) reported the results of a prospective single arm study in which 9 recipients on a liver transplant waiting list received livers from HCV viremic donors followed by a 12-week course of oral glecaprevir/pibrentasvir within 5 days of transplant.[16.] Nine of 9 (100%) recipients achieved SVR12. One recipient developed acute cellular rejection, which was substantiated by biopsy findings on postoperative day 50, which was successfully managed with increased baseline immunosuppression. All patients were alive at a median of 46 weeks (range, 20 to 76 weeks).

Kwong et al (2018)[17.] and Sobotka et al (2021)[18.] reported the findings of retrospective studies that included outcomes of a combined total of 25 recipients who received livers from HCV viremic donors. In both studies, DAA treatment was not initiated immediately post-transplant and there was considerable heterogeneity in the specific DAA used. Reported SVR12 rates were 100% (25/25). Cotter et al (2019)[19.] reported the findings of a retrospective analysis from a transplant registry. Rates of 1- and 3-year graft survival were similar among recipients who received a liver transplant from HCV viremic donors versus those who received organs from HCV non-viremic donors.

Table 13. Summary of Key Trials: Study Characteristics Transplantation of Hepatitis C Virus-Infected Liver

Study	Study Type	Country	Dates	Participants	Treatment	Follow Up
Bethea et al (2020)[16.] NCT03208127	Prospective Cohort	United States (Single site at Massachusetts General Hospital)	2017-2018	• N= 9 • Adult candidates registered for liver transplant	• 12 weeks GLE/PIB • DAA initiated within 5 days after transplant • Mean time to DAA initiation was 1.7 days post-transplant	46 weeks
Kwong et al (2018)[17.]	Retrospective Cohort	United States (Single site at	2017-2018	• N=10	• DAA regimen heterogenous	52 weeks

Study	Study Type	Country	Dates	Participants	Treatment	Follow Up
		Stanford University)		• Adult liver transplant recipients with donor-derived HCV infection • Transplant offered to candidates with a high estimated risk of waitlist dropout while awaiting liver transplantation • HCV genotype 1, 2 and 3	o SOF/DCV± RBV (n=1) o SOF/LDV±RBV (n=3) o SOF/VEL±RBV (n=6) o Treatment duration 12 to 24 weeks • Single dose prior to transplant followed by 8 weeks of treatment	
Cotter et al (2019)[19,]	Registry Study	United States (Scientific Registry of Transplant Recipients)	2008-2018	• Adults who underwent a primary, single-organ, deceased donor liver transplant • As per NAT status o Negative donor-negative recipient (n=11,270) o Negative donor-positive recipient (n=748) o Positive donor-negative recipient (n=87) o Positive donor-positive recipient (n=73)	• Not reported	2 years
Sobotka et al (2021)[18,]	Retrospective Cohort	United States (single site at Ohio State University Wexner Medical Center)	2017-2020	• N=20 • Transplant candidates on the deceased donor transplant waiting list • HCV genotype 1a (n=10), 2 (n=1), 3 (n=8) and 1a/3 (n=1)	• SOF/VEL (n=17) • GLE/PIB (n=2) • LED/SOF/RBV (n=1) • Mean time to DAA initiation was 38 days post-transplant • Duration of treatment not reported	Unclear

DAA; direct acting antiviral agents; DCV: Daclatasvir; GLE; glecaprevir; HCV: hepatitis-C virus; LED: ledipasvir; NAT: nucleic acid test; PIB: pibrentasvir; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir

Table 14. Summary of Key Trials Study Results Transplantation of Hepatitis C Virus-Infected Liver

Study	Outcomes Related to HCV Cure	Graft Function Related Outcomes	Safety and Other Miscellaneous Outcomes
Bethea (2020)[16.] NCT03208127	SVR12: 100% (9/9)	Acute cellular rejection: 11% (1/9) Survival rate: 100% (median of 46 weeks follow-up; range, 20 to 76 weeks) All participants continue to exhibit broadly preserved allograft function, as assessed by serial liver function test and international normalized ratio readings	• No treatment-related or HCV-attributable adverse events reported
Kwong (2018)[17.]	SVR12: 100% (10/10)	ACR/AMR: 30% (3/10) Graft loss or death: None (median follow-up of 380 days, IQR, 263 to 434) post-transplant	• No significant adverse events directly related to HCV reported
Cotter (2019)[19.]	Not reported	1-year graft survival based on NAT status • Negative donor-negative recipient: 93% • Negative donor-positive recipient: 93% • Positive donor-negative recipient: 93% • Positive donor-positive recipient: 94% 3-year graft survival based on NAT status • Negative donor-negative recipient: 88% • Negative donor-positive recipient: 88% • Positive donor-negative recipient: 86% • Positive donor-positive recipient: 90%	• Safety events not reported
Sobotka (2021)[18.]	SVR: 100% (15/15)	Unclear	• Safety events not reported

ACR: Acellular rejection; AMR: antibody-mediated rejection; HCV: hepatitis-C virus; NAT: nucleic acid test; SVR12: sustained virologic response at week 12

Tables 15 and 16 display notable limitations identified in each study. The studies were in general well conducted and reported. The major limitations are small sample size, studies were mostly conducted at single centers at academic institutions and limited duration of follow-up for graft survival and function. While the published studies enrolled a limited number of subjects as they intended to examine the feasibility of transplanting hearts from HCV-viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible, multicenter trials with standardized protocols, and rigorous adjudication of outcomes and adverse events, are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers. Reported registry studies suffer from selection bias as well lack of adjustments of prognostic variables between groups.

Table 15. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Bethea et al (2020)[16.] NCT03208127					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Kwong et al (2018)[17.]					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Cotter et al (2019)[19.]					1. Not sufficient duration for benefit 2. Not sufficient duration for harms
Sobotka et al (2021)[18.]		1. Not clearly defined (duration of DAA treatment not specified)			1. Not sufficient duration for benefit 2. Not sufficient duration for harms

DAA; direct acting antiviral agents.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 16. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Bethea et al (2020)[16.] NCT03208127	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Kwong et al (2018)[17.]	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Cotter et al (2019)[19.]	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Sobotka et al (2021)[18.]	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician		6. Not intent to treat analysis (data for 15 of 20 subjects reported)		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Liver Transplantation

For individuals who require a liver transplant and are HCV non-viremic and receive a liver transplant from an HCV viremic donor combined with DAA, the evidence consists of 1 prospective and 3 retrospective cohort studies. The timing, duration and specific DAA regimens used in the published studies were different. The single prospective study that enrolled 9 recipients who received livers from HCV viremic donors were treated with a 12-week course of pangenotypic DAA within 5 days of transplant and reported SVR12 rates of 100%. The 2 retrospective studies reported findings from a combined total of 25 recipients who received livers from HCV viremic donors but were not treated with DAA immediately post-transplant, reported 100% SVR12 rates. Additionally, a retrospective analysis from a transplant registry reported similar 1- and 3-year graft survival among recipients who received a liver transplant from HCV viremic donors versus those who received from HCV non-viremic donors. These studies enrolled a limited number of subjects since they intended to examine the feasibility of transplanting livers from HCV viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible; multicenter trials with standardized protocols, and rigorous adjudication of outcomes and adverse events are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers.

Other Solid Organ Transplantation
Clinical Context and Therapy Purpose
The purpose of other solid organ transplants (e.g., small bowel or pancreas) from an HCV viremic donor to an HCV non-viremic recipient who has end-stage organ disease is to provide a treatment option that is an alternative to or an improvement on existing management.

Potential benefit of this approach is to reduce 1) waiting time to transplant, 2) waitlist-associated morbidity/mortality and 3) the discard of otherwise healthy solid organs. Use of DAA to treat or prevent acute HCV infection in recipients of solid organ transplant from HCV viremic donors is likely to prevent acute and chronic downstream sequelae of transplant-acquired HCV infection.

The question addressed in this evidence review is: Does other solid organ transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage organ disease result in an improvement in net health outcomes?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who are HCV non-viremic, on the waiting list for a solid organ transplant such as a small bowel or pancreas transplant and in whom the benefit of accepting a solid organ transplant from an HCV viremic donor may outweigh the harms in comparison to waiting for a solid organ from an HCV negative donor.

Interventions
The therapy being considered is a solid organ transplant from an HCV viremic donor combined with DAA agents for HCV. Recipients would receive guideline-directed therapy for the treatment of acute HCV infection.

Comparators
The following therapies are currently being used to make decisions about solid organ transplantation: continued disease management on a waiting list until an HCV non-viremic donor organ is available for transplant.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, change in disease status, treatment-related mortality, treatment-related morbidity, morbid events, quality of life and resource utilization.

Study Selection Criteria
Evidence reviews have used a best available evidence approach. Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
No prospective studies were identified that reported on planned transplantation of HCV viremic solid organs such as small bowel or pancreas into HCV non-viremic recipients.

Section Summary: Other Solid Organ Transplantation
For individuals who are HCV non-viremic who have end-stage organ disease and are candidates for a solid organ transplant such as for small bowel or pancreas, evidence for the

use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list has not been reported in the published literature.

Summary of Evidence

For individuals who require a kidney transplant and are HCV non-viremic and receive a kidney transplant from an HCV viremic donor combined with DAA, the evidence consists of multiple single-arm prospective and retrospective studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related mortality, treatment-related morbidity, morbid events, quality of life and resource utilization. These studies reported outcomes for a total of 252 recipients who received a kidney transplant from an HCV viremic donor. Most prospectively conducted studies in which DAA were initiated early in the course of transplant or immediately post-transplant for a duration of 8 to 12 weeks report SVR12 rates approaching 100% and stable organ function during 1 year of follow-up. There is considerable heterogeneity between the studies in whether donor kidneys were genotyped in advance of transplantation, use of DAA pangenotypic or specific regimens chosen to match genotype were used, and differences in the timing and duration of the DAA regimen. Use of ultra-short course therapy (2 to 4 days) was associated with treatment failures whereas the delayed treatment approach has been associated with increased risks of cytomegalovirus and BK virus, and several cases of FCH. Current treatment recommendations include initiating treatment within the first month after kidney transplant, preferably within the first week when the patient is clinically stable with a pangenotypic DAA regimen that includes daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) or sofosbuvir (400 mg)/velpatasvir (100 mg) for 8 weeks. While the published studies enrolled a limited number of subjects as they intended to examine the feasibility of transplanting kidneys from HCV viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible; multicenter trials with standardized protocols, and rigorous adjudication of outcomes and adverse events are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who require a lung transplant and are HCV non-viremic and receive a lung transplant from an HCV viremic donor combined with DAA, the evidence consists of 3 single-arm prospective studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related mortality, treatment-related morbidity, morbid events, quality of life and resource utilization. The 3 studies reported outcomes for a total of 61 recipients who received a lung transplant from an HCV viremic donor. While the studies by Wooley et al (2019) and Cypel et al (2020) used a pangenotypic DAA regimen consisting of sofosbuvir/velpatasvir, the duration and initiation of treatment were markedly different. In Wooley et al (2019), treatment duration was 4 weeks initiated immediately after transplant while in Cypel et al (2020), treatment duration was 12 weeks initiated 2 weeks after transplant. Feld et al (2020) also used a pangenotypic DAA treatment of glecaprevir/pibrentasvir for a total duration of 8 days along with single dose ezetemibe as well as use of ex-vivo lung perfusion plus ultraviolet-C radiation delivered to the circulating perfusate as an additional measure to lower HCV viral load. All 3 studies reported SVR12 rates of 100%. Reported rate of graft survival at 6 months available for 28 participants in the first study was 100%. The primary endpoint of survival and HCV-free status at 6 months after transplantation was 86% in the second study. Two patients presented with HCV relapse within 3 months after sofosbuvir/velpatasvir completion and required retreatment in the second study. Acute rejection requiring treatment was reported in 23% of recipients in the third study. The 3 published studies enrolled a limited number of subjects since they intended to examine the feasibility of transplanting lungs from HCV viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible; multicenter trials with standardized protocols, and rigorous adjudication of outcomes and adverse events are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who require a heart transplant and are HCV non-viremic and receive a heart transplant from an HCV viremic donor combined with DAA, the evidence consists of 4 single-arm prospective studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related mortality, treatment-related morbidity, morbid events, quality of life and resource utilization. These 4 studies reported outcomes for a total of 44 recipients who received a heart transplant from an HCV viremic donor. The timing, duration and specific DAA regimens used in the 4 published studies were different. Except for the first study published by McLean et al (2019) that used a non-pangenotypic DAA regimen of grazoprevir/elbasvir, the remaining 3 studies used a pan-genotypic DAA regimen of sofosbuvir/velpatasvir or glecaprevir/pibrentasvir. SVR12 rates were 100% in the 3 studies that used a pangenotypic DAA regimen while it was 90% in the study that used a non-pangenotypic DAA regimen. The 4 published studies enrolled a limited number of subjects as they intended to examine the feasibility of transplanting hearts from HCV viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible; multicenter trials with standardized protocols, and rigorous adjudication of outcomes and adverse events are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who require a liver transplant and are HCV non-viremic and receive a liver transplant from an HCV viremic donor combined with DAA, the evidence consists of 1 prospective and 3 retrospective cohort studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related mortality, treatment-related morbidity, morbid events, quality of life and resource utilization. The timing, duration and specific DAA regimens used in the published studies were different. The single prospective study that enrolled 9 recipients who received livers from HCV viremic donors were treated with a 12-week course of pangenotypic DAA within 5 days of transplant and reported SVR12 rates of 100%. The 2 retrospective studies reported findings from a combined total of 25 recipients who received livers from HCV viremic donors but not treated with DAA immediately post-transplant reported 100% SVR12 rates. Additionally, a retrospective analysis from a transplant registry reported similar 1- and 3-year graft survival among recipients who received liver transplant from HCV viremic donors versus those who received organs from HCV non-viremic donors. These studies enrolled a limited number of subjects as they intended to examine the feasibility of transplanting liver from HCV viremic donors into HCV non-viremic recipients and are informative in concluding that such a strategy is feasible; multicenter trials with standardized protocols, and rigorous adjudication of outcomes and adverse events are needed to confirm these promising results and demonstrate their generalizability to settings outside of academic centers. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are HCV non-viremic who have end-stage organ disease and are candidates for a solid organ transplant such as for small bowel or pancreas, evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list has not been reported in the published literature. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related mortality, treatment-related morbidity, morbid events, quality of life and resource utilization. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given

to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

The American Society of Transplantation

The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients.[20] Key findings and recommendations are summarized in Table 17.

Table 17. American Society of Transplantation Consensus Conference - Use of Hepatitis C Virus Viremic Donors

Content Area	Key Point
Definition of HCV positive	HCV viremic reflecting a positive NAT should be adopted
Data interpretation	HCV antibody status alone limits interpretation of outcomes of transplantation of HCV "positive" organs
Transmission and Treatment	Highest risk for unexpected HCV transmission is associated with organ donation from a person who injected drugs within the eclipse or pre-viremic period
OPTN policy	No current policies prevent transplantation of HCV-viremic organs into HCV non-viremic recipients
Ethical considerations	Transplantation of HCV-viremic organs into HCV non-viremic recipients should be conducted under site specific IRB approved protocols with multi-step informed consent.

HCV: hepatitis-C virus; NAT: nucleic acid test; OPTN: Organ Procurement and Transplantation Network

American Association for the Study of Liver Diseases

The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America have published online HCV guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. The recommendation for treatment of HCV-uninfected transplant recipients receiving organs from HCV viremic donors are summarized in Table 18. These guidelines were last updated on January 21, 2021.

Table 18. American Association for the Study of Liver Diseases Recommendations When Considering Use of Hepatitis C Virus Viremic Donor Organs in Hepatitis C Virus Uninfected Recipients[5]

Recommendation When Considering Use of HCV Viremic Donor Organs in HCV Uninfected Recipients	Rating
Informed consent should include the following elements: • Risk of transmission from an HCV viremic donor (and with a PHS-defined increased risk donor, the potential risks for other viral infections) • Risk of liver disease if HCV treatment is not available or treatment is unsuccessful • Risk of graft failure • Risk of extrahepatic complications, such as HCV-associated renal disease • Risk of HCV transmission to partner • Benefits, specifically reduced waiting time and possibly lower waiting list mortality • Other unknown long-term consequences (hepatic and extrahepatic) of HCV exposure (even if cure is attained)	I, C
Transplant programs should have a programmatic strategy to: • Document informed consent • Assure access to HCV treatment and retreatment(s), as necessary • Ensure long-term follow-up of recipients (beyond SVR12)	I, C
Recommendation Regarding Timing of DAA Therapy for HCV Negative Recipients of HCV Viremic Liver Transplant	
Early[a] treatment with a pangenotypic DAA regimen is recommended when the patient is clinically stable.	II, B
Recommendations[b] for Treatment of HCV Uninfected Recipients of Liver Grafts from HCV Viremic Donors	
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c] for 12 weeks	I, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks	I, C
Recommendation Regarding Timing of DAA Therapy for HCV Negative Recipients of HCV Viremic Non-Liver Solid Organ Transplant	

Recommendation When Considering Use of HCV Viremic Donor Organs in HCV Uninfected Recipients	Rating
Prophylactic[d]/preemptive[e] treatment with a pangenotypic DAA regimen is recommended	II, B
Recommendations[b] for Treatment of HCV Uninfected Recipients of Non-Liver Organs from HCV Viremic Donors	
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c] for 12 weeks	I, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks	I, C

DAA: direct acting antiviral; HCV: hepatitis C virus; SVR12: sustained virologic response; PHS: United States Public Health Service

[a] Early treatment refers to starting within the first month after liver transplant, preferably within the first week when the patient is clinically stable.

[b] Listed by evidence level and alphabetically. Other considerations in selection of the DAA regimen:

- Presence of liver dysfunction (e.g., elevated bilirubin) as protease inhibitors should be avoided
- Specific drugs that are contraindicated or not recommended with specific DAA agents, including but not limited to:
  - High-dose antacid therapy (e.g., twice daily proton pump inhibitor)
  - Amiodarone (contraindicated with sofosbuvir-inclusive regimens; see prescribing information)
  - Specific statins (e.g., atorvastatin)
- Consideration of immunosuppressive drugs and DAA interactions

[c] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Refer to the prescribing information.

[d] Prior to HCV RNA results, typically immediately pre-transplant or day 0 post-transplant

[e] Day 0 to within the first week post-transplant, typically as soon as the patient is deemed clinically stable

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 19.

Table 19. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing-Kidney			
NCT03781726	Multi-center Study to Transplant Hepatitis-C Infected Kidneys (MYTHIC)	30	Dec 2021
NCT04515797	QUICKly Eradicate Hepatitis C in Patients Undergoing REnal Transplant With 4 Weeks of Glecaprevir/Pibrentasvir	80	Oct 2025
NCT03809533	The Use of Hepatitis C Positive Kidneys in Hepatitis C Negative Kidney Transplant Recipients	60	May 2024
NCT04575896	Kidney Transplants in Hepatitis C Negative Recipients With Hepatitis C Viremic Donors	10	Dec 2022
NCT04682509	A Single-center Pilot Study Evaluating a Preemptive Short Course of Glecaprevir/Pibrentasvir in Hepatitis C Positive to Negative Kidney Transplantation	20	Mar 2024
NCT02902120	HCV Treatment Immune Response With Grazoprevir/Elbasvir Before or After Renal Transplant	25	Dec 2020
NCT04075916	A Trial of Transplanting Hepatitis C Kidneys Into Hepatitis C-Negative Kidney Recipients	500	Dec 2025
NCT04605679	Hepatitis C Virus (HCV) Positive Kidney Grafts in HCV Negative Recipients	200	May 2023
NCT02743897	Transplanting Hepatitis C Kidneys Into Negative Kidney Recipients (THINKER)	53	Dec 2021
NCT03801707	Utilization of Hepatitis C Positive Kidneys in Negative Recipients (USE-Hep C)	25	Jan 2022

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing-Thoracic			
NCT03625687	Pan-genotypic Direct Acting Antiviral Therapy in Donor HCV-positive to Recipient HCV-negative Lung Transplant	25	Apr 2021
NCT03222531	Expanding the Pool in Orthotopic Heart Transplantation	20	Jul 2023
NCT03086044	Transplanting Hepatitis C Positive Thoracic Organs	100	Dec 2021
NCT03383419	Transplant of Redeemed Organs by Judicious Administration of New Direct-Acting Antivirals for Hepatitis-C Heart Recipients	20	Feb 2021
NCT04452578	Hepatitis C Virus (HVC) Positive Heart Grafts in HCV Negative Recipients	10	June 2023
NCT03377478	Expanding the Pool in Lung Transplantation	20	Feb 2026
NCT03724149	Transplanting Hepatitis C Lungs Into Negative Lung Recipients	10	Dec 2021
NCT04493385	The Hepatitis C Transplant Collaborative	500	Dec 2022
NCT04057001	Hepatitis C Positive Organ to Recipient Hepatitis C Negative Longitudinal Transplant Study	75	Jun 2024
NCT04017338	Transplantation Using Hepatitis C Positive Donors, A Safety Trial	40	Dec 2024
NCT04596475	Prevention of Transmission of Hepatitis C Virus (HCV) From HCV-Viremic Organ Donor	10	Mar 2022
NCT04508907	A Study to Evaluate Preemptive Therapy in Hepatitis C (HCV) Organ Transplant Recipients	20	Dec 2021
Ongoing-Liver			
NCT03819322	The Use of Hepatitis C Positive Livers in Hepatitis C Negative Liver Transplant Recipients	20	May 2024
NCT03650920	Hepatitis C Virus (HCV) Positive Liver Grafts in HCV Negative Recipients	100	Sep 2021
NCT03208127	DAA Treatment in Donor HCV-positive to Recipient HCV-negative Liver Transplant	50	Sep 2023
Unpublished-Lung			
NCT03523871	A Study of the Use of Hepatitis C Positive Donors for Hepatitis C Negative Lung Transplant Recipients With Post-transplant Treatment With Mavyret	20	Sep 2020
Unpublished-Kidney			
NCT02669966	Live Kidney Donors With Positive Anti-HCV Antibody, But Negative HCV PCR	2	Feb 2020
NCT02945150	Preemptive Treatment With Grazoprevir and Elbasvir for Donor HCV Positive to Recipient HCV Negative Kidney Transplant	8	Mar 2020
Unpublished-Heart			
NCT03382847	HCV Positive Heart Donors	25	April 2020

NCT: national clinical trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	32850	Donor pneumonectomy(s) (including cold preservation), from cadaver donor
	32851	Lung transplant, single; without cardiopulmonary bypass
	32852	Lung transplant, single; with cardiopulmonary bypass
	32853	Lung transplant, double (bilateral sequential or en bloc); without cardiopulmonary bypass
	32854	Lung transplant, double (bilateral sequential or en bloc); with cardiopulmonary bypass
	32855	Backbench standard preparation of cadaver donor lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare pulmonary venous/atrial cuff, pulmonary artery, and bronchus; unilateral
	32856	Backbench standard preparation of cadaver donor lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare pulmonary venous/atrial cuff, pulmonary artery, and bronchus; bilateral
	33930	Donor cardiectomy-pneumonectomy (including cold preservation)
	33933	Backbench standard preparation of cadaver donor heart/lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, and trachea for implantation
	33935	Heart-lung transplant with recipient cardiectomy-pneumonectomy
	33940	Donor cardiectomy (including cold preservation)
	33944	Backbench standard preparation of cadaver donor heart allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, pulmonary artery, and left atrium for implantation
	33945	Heart transplant, with or without recipient cardiectomy
	44120	Enterectomy, resection of small intestine; single resection and anastomosis
	44121	Enterectomy, resection of small intestine; each additional resection and anastomosis (List separately in addition to code for primary procedure)
	44132	Donor enterectomy (including cold preservation), open; from cadaver donor

Type	Code	Description
	44133	Donor enterectomy (including cold preservation), open; partial, from living donor
	44135	Intestinal allotransplantation; from cadaver donor
	44136	Intestinal allotransplantation; from living donor
	44715	Backbench standard preparation of cadaver or living donor intestine allograft prior to transplantation, including mobilization and fashioning of the superior mesenteric artery and vein
	44720	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; venous anastomosis, each
	44721	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; arterial anastomosis, each
	47133	Donor hepatectomy (including cold preservation), from cadaver donor
	47135	Liver allotransplantation, orthotopic, partial or whole, from cadaver or living donor, any age
	47140	Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
	47141	Donor hepatectomy (including cold preservation), from living donor; total left lobectomy (segments II, III and IV)
	47142	Donor hepatectomy (including cold preservation), from living donor; total right lobectomy (segments V, VI, VII and VIII)
	47143	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; without trisegment or lobe split
	47144	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with trisegment split of whole liver graft into 2 partial liver grafts (i.e., left lateral segment [segments II and III] and right trisegment [segments I and IV through VIII])
	47145	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with lobe split of whole liver graft into 2 partial liver grafts (i.e., left lobe [segments II, III, and IV] and right lobe [segments I and V through VIII])
	47146	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
	47147	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each
	48550	Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation
	48551	Backbench standard preparation of cadaver donor pancreas allograft prior to transplantation, including dissection of allograft from surrounding soft tissues, splenectomy, duodenotomy, ligation of bile duct, ligation of mesenteric vessels, and Y-graft arterial anastomoses from iliac artery to superior mesenteric artery and to splenic artery
	48552	Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each
	48554	Transplantation of pancreatic allograft

Type	Code	Description
	50300	Donor nephrectomy (including cold preservation); from cadaver donor, unilateral or bilateral
	50320	Donor nephrectomy (including cold preservation); open, from living donor
	50323	Backbench standard preparation of cadaver donor renal allograft prior to transplantation, including dissection and removal of perinephric fat, diaphragmatic and retroperitoneal attachments, excision of adrenal gland, and preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as necessary
	50325	Backbench standard preparation of living donor renal allograft (open or laparoscopic) prior to transplantation, including dissection and removal of perinephric fat and preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as necessary
	50327	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; venous anastomosis, each
	50328	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; arterial anastomosis, each
	50329	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; ureteral anastomosis, each
	50340	Recipient nephrectomy (separate procedure)
	50360	Renal allotransplantation, implantation of graft; without recipient nephrectomy
	50365	Renal allotransplantation, implantation of graft; with recipient nephrectomy
	50547	Laparoscopy, surgical; donor nephrectomy (including cold preservation), from living donor
HCPCS	S2053	Transplantation of small intestine and liver allografts
	S2054	Transplantation of multivisceral organs
	S2055	Harvesting of donor multivisceral organs, with preparation and maintenance of allografts; from cadaver donor
	S2060	Lobar lung transplantation
	S2061	Donor lobectomy (lung) for transplantation, living donor
	S2065	Simultaneous pancreas kidney transplantation

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
08/01/2019	BCBSA Medical Policy adoption
08/01/2020	Annual review. No change to policy statement. Policy guidelines and Literature review updated.
08/01/2021	Annual review. No change to policy statement. Policy guidelines and literature updated. Policy title changed from Hepatitis C Positive Organs for Transplantation to Non-Viremic Patients to current one.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield,

are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE **Red font: Verbiage removed**	**AFTER** **Blue font: Verbiage Changes/Additions**
Hepatitis C Positive Organs for Transplantation to Non-Viremic Patients 7.03.14 **Policy Statement:** The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.	**Hepatitis C Viremic Organs for Transplantation to Non-Viremic Patients 7.03.14** **Policy Statement:** The transplantation of Hepatitis C virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.