Hepatitis C Positive Organs for Transplantation to Non-Viremic Patients

Policy Number: 7.03.14          Last Review: 8/1/2020
Origination: 8/2019             Next Review: 8/1/2021

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Hepatitis C Positive Organs for Transplantation to Non-Viremic Patients. This is considered investigational.

When Policy Topic is covered
n/a

When Policy Topic is not covered
The transplantation of HCV-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient combined with direct-acting antiviral treatment for HCV is considered investigational.

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

Description of Procedure or Service

<table>
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<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tr>
<td>Individuals: Who require a kidney transplant and are HCV non-viremic</td>
<td>Interventions of interest are: Kidney transplant from an HCV viremic donor combined with direct-acting antiviral agents</td>
<td>Comparators of interest are: Continued management on waiting list until an HCV non-viremic donor kidney is available</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Treatment-related mortality • Treatment-related morbidity • Morbid events • Quality of life • Resource utilization</td>
</tr>
<tr>
<td>Individuals:</td>
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<td>Relevant outcomes include:</td>
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</tbody>
</table>


## Populations

### Who require a lung transplant and are HCV non-viremic

**Interventions**
- Interest are: Lung transplant from an HCV viremic donor combined with direct-acting antiviral agents

**Comparators**
- Interest are: Continued management on waiting list until an HCV non-viremic donor lung is available

**Outcomes**
- Overall survival
- Disease-specific survival
- Change in disease status
- Treatment-related mortality
- Treatment-related morbidity
- Morbid events
  - Quality of life
  - Resource utilization

### Individuals:
- Who require a heart transplant and are HCV non-viremic

**Interventions of interest are:**
- Heart transplant from an HCV viremic donor combined with direct-acting antiviral agents

**Comparators of interest are:**
- Continued management on waiting list until an HCV non-viremic donor heart is available

**Relevant outcomes include:**
- Overall survival
- Disease-specific survival
- Change in disease status
- Treatment-related mortality
- Treatment-related morbidity
- Morbid events
  - Quality of life
  - Resource utilization

### Individuals:
- Who require a liver transplant and are HCV non-viremic

**Interventions of interest are:**
- Liver transplant from an HCV viremic donor combined with direct-acting antiviral agents

**Comparators of interest are:**
- Continued management on waiting list until an HCV non-viremic donor liver is available

**Relevant outcomes include:**
- Overall survival
- Disease-specific survival
- Change in disease status
- Treatment-related mortality
- Treatment-related morbidity
- Morbid events
  - Quality of life
  - Resource utilization

### Individuals:
- Who require other type of solid organ transplant are HCV non-viremic

**Interventions of interest are:**
- Other solid organ transplant from an HCV viremic donor combined with direct-acting antiviral agents

**Comparators of interest are:**
- Continued management on waiting list until an HCV non-viremic donor solid organ is available

**Relevant outcomes include:**
- Overall survival
- Disease-specific survival
- Change in disease status
- Treatment-related mortality
- Treatment-related morbidity
- Morbid events
  - Quality of life
  - Resource utilization

## Summary

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 hepatitis C-infected patients including those who develop acute hepatitis infection after receiving an organ transplant from a hepatitis C viremic donor.

For individuals who are HCV non-viremic who have end-stage renal disease and are candidates for a kidney transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing dialysis or other appropriate treatment and remaining on the transplant wait-list consists of preliminary results of two open-label nonrandomized trials (THINKER and EXPANDER). The primary outcomes were sustained virologic response (SVR) and graft function and survival. Major adverse events attributable to the selected HCV DAA regimen was also assessed. To date, the experience of 30 participants has been reported in the literature. Participants generally had comparable demographic characteristics. The studies differed in whether or not donor kidneys were genotyped in advance of

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**Populations**

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<thead>
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**Individuals:**
- Who require a heart transplant and are HCV non-viremic

**Interventions of interest are:**
- Heart transplant from an HCV viremic donor combined with direct-acting antiviral agents

**Comparators of interest are:**
- Continued management on waiting list until an HCV non-viremic donor heart is available

**Relevant outcomes include:**
- Overall survival |
- Disease-specific survival |
- Change in disease status |
- Treatment-related mortality |
- Treatment-related morbidity |
- Morbid events |
|   - Quality of life |
|   - Resource utilization |

**Individuals:**
- Who require a liver transplant and are HCV non-viremic

**Interventions of interest are:**
- Liver transplant from an HCV viremic donor combined with direct-acting antiviral agents

**Comparators of interest are:**
- Continued management on waiting list until an HCV non-viremic donor liver is available

**Relevant outcomes include:**
- Overall survival |
- Disease-specific survival |
- Change in disease status |
- Treatment-related mortality |
- Treatment-related morbidity |
- Morbid events |
|   - Quality of life |
|   - Resource utilization |

**Individuals:**
- Who require other type of solid organ transplant are HCV non-viremic

**Interventions of interest are:**
- Other solid organ transplant from an HCV viremic donor combined with direct-acting antiviral agents

**Comparators of interest are:**
- Continued management on waiting list until an HCV non-viremic donor solid organ is available

**Relevant outcomes include:**
- Overall survival |
- Disease-specific survival |
- Change in disease status |
- Treatment-related mortality |
- Treatment-related morbidity |
- Morbid events |
|   - Quality of life |
|   - Resource utilization |
transplantation. Appropriate DAA regimens were chosen to match genotype or pangenotypic was used. There were differences in the timing of administration of the DAA regimen, but all participants were followed to ascertain the need for extension of the original regimen or addition of another drug. All recipients showed evidence of HCV nucleic acid positivity and viral loads were determined in some instances. All recipients had SVR by the completion of the appropriate DAA regimen with the longest follow-up out to 12 months in 10 participants. There were no reports of allograft rejection or renal function abnormalities. Transient elevations in liver transaminases were reported but not in all participants. Assessment of quality of life by standard patient-reported measures in the first ten participants of the THINKER cohort indicated that quality of life was initially diminished in the early postoperative period. At 12 months, the physical component score of the RAND-36 questionnaire improved beyond baseline but the mental component score returned to baseline. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are HCV non-viremic who have end-stage pulmonary disease and are candidates for lung transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of preliminary results of a single open-label nonrandomized trial of 36 HCV viremic lung transplants treated with 4 weeks of pangenotypic DAAs. The primary outcomes were SVR and graft function and survival. SVR at 12 weeks and graft survival at 6 months was available for 28 participants and both rates were 100%. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are HCV non-viremic who have end-stage cardiac disease and are candidates for heart transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of 2 single-arm, open-label nonrandomized trials that total 17 HCV viremic heart genotype 1 transplants. The primary outcomes were SVR and graft function and survival. Trial protocols differed in the timing of administration and duration of DAA with elbasvir/grazoprevir. All recipients achieved an SVR including when the extension of treatment was required. Each trial reported a death; one unrelated to DAA or HCV infection and the other due to antibody mediated graft rejection in a patient who had a positive cross-match. Several case reports have published outcomes for four adults and three infants less than one year of age. The results for the pediatric cases were derived from the national transplant registry and only included graft and overall survival. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are HCV non-viremic who have end-stage liver disease and are candidates for liver transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of a report from a single-site prospectively evaluating 55 recipients of HCV Ab+/NAT- donors compared to 57 recipients of HCV Ab-/NAT- donors. Graft function and loss were comparable
between groups, as was mortality by one year of follow-up. Seroconversion was
detected by NAT in five of the HCV Ab+/NAT- recipients. Four were successfully
treated with an appropriate HCV antiviral therapy and subsequent SVR. A fifth
recipient died before treatment of non-HCV related causes. Several case reports
have published outcomes for a total of 12 adults who received HCV viremic liver
transplants. A notable finding in the reports is that the majority of recipients had
prior HCV infection and had successfully achieved an SVR using genotype-specific
DAA when reinfection was identified. The evidence is insufficient to determine the
effects of the technology on health outcomes.

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 last five years in the published literature. The evidence is
insufficient to determine the effects of the technology on health outcomes.

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 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 waitlisted patients who might consider accepting HCV-infected
organs.

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 (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, two 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 through 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 blood or contaminated body fluids.

**Rationale**

This evidence review was created in May 2019 with a search of the PubMed database performed through February 28, 2020.

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.

RCTs of transplantation of a hepatitis C virus (HCV) viremic solid organ into an HCV non-viremic donor that would exclude the use of direct-acting antiviral (DAA) in a comparator arm would not meet the requirement of clinical equipoise.
Evaluation of published literature on transplantation issues related to HCV-HIV, HCV-HBV or HCV-HIV-HBV co-infections as well as cytomegalovirus transmission or reactivation is beyond the scope of this policy.

There is considerable literature on transplantation of high-risk solid organ donors HCV-infected recipients in the pre-DAA treatment era. This literature is not evaluated in the report except for the consideration of liver transplantation.

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.

Study limitations tables have not been prepared because all of the publications reviewed are acknowledged as either pilot studies, ongoing trials with preliminary results or case reports. Statistical analyses were limited or nonexistent under these circumstances.

**Kidney Transplantation**

**Clinical Context and Therapy Purpose**
The purpose of transplanting a kidney from an HCV viremic donor to an HCV non-viremic recipient is to reduce waiting time to transplant and waitlist-associated morbidity and mortality and to reduce the discard of otherwise healthy solid organs. The purpose of using DAAs to treat HCV non-viremic recipients who may become viremic upon receiving a solid organ transplant from HCV viremic donors is to treat or prevent acute HCV infection and thereby prevent associated acute and chronic downstream sequelae of transplant acquired HCV infection.

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.

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.

**Patients**
The relevant population of interest is 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-negative 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. Solid organ transplant is
provided in a tertiary inpatient setting staffed and equipped to perform the surgical procedure and postsurgical intensive care. Treatment of HCV non-viremic recipients would be managed by infectious disease specialists, transplant surgeons, and nephrologists.

**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, and change in disease status, treatment-related mortality and treatment-related morbidity.

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 after completion of HCV treatment, assessment of transplanted organ function, the incidence of organ rejection, graft survival, OS 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 DAAs 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-negative donor organ and acute HCV infection with the transplantation of an HIV-viremic organ into an HCV-negative 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.

Most of the information on outcomes associated with the use of an HCV positive donor kidney transplant has been in HCV positive recipients in the pre-DAA era. A decrement in survival has been demonstrated compared to receiving an HCV-negative graft. However, there remains an OS advantage over remaining on dialysis. The use of a high-risk donor also reduces the kidney transplant waiting time. (Kucirka)

**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
Goldberg et al (2017) reported preliminary results of the Transplanting Hepatitis C Kidneys into Negative Kidney Recipients (THINKER) trial; an open-label, single-arm trial that transplanted ten patients without HCV with kidneys from HCV-infected donors with positive HCV nucleic acid test (NAT) at the time of transplant. All donors were genotyped prior to transplantation and donated kidneys were restricted to genotype 1 infection and the use of elbasvir-grazoprevir for treatment. All recipients developed viremia within 3 days post-transplant and were then immediately treated with DAA genotype and continued for 12 weeks. All patients had a negative HCV RNA by day 30 of therapy and 100% achieved a durable cure of HCV infection. Elbasvir-grazoprevir, which is approved for patients with any level of baseline kidney function, was well tolerated in the immediate post-transplant period. One patient, who had a prior diagnosis of IgA nephropathy, developed focal segmental glomerulosclerosis in the transplanted kidney that was possibly related to DAA therapy.

Reese et al (2018) reported longer follow-up (12 months) of the original THINKER study participants as well as 6-month outcome data for an additional 10 participants. Additional details on participant inclusion criteria were available in this publication; participants were seronegative for HIV, HCV RNA, and hepatitis B surface antigen and had no acceptable living kidney donor. No substantial evidence of liver disease was detected via FibroScan (Echosens) imaging or hepatic serologic testing. Evaluation by a hepatologist and/or a transplant surgeon had to show no overt contraindication for liver transplant in the unlikely event of acute liver failure after HCV transmission during a kidney transplant.

Five patients in the 20-participant cohort experienced transient aminotransferase levels.

Quality of life assessment was reported for the first cohort of participants via in-person administration of the RAND-36 questionnaire at enrollment and post-transplant weeks 4, 16, 24, and 52. The Physical Component Summary and Mental Component Summary scores were calculated from the 8 RAND-36 domains and normalized to population standards, with higher scores indicating better quality of life. Normalized mean Physical Component Summary scores decreased at 4 weeks and then increased steadily to above pretransplant levels (the mean improvement in Physical Component Summary score from consent to 12 months after transplant was 6.7 [p = 0.012]). Normalized mean Mental Component Summary scores also decreased at 4 weeks and subsequently returned to baseline and remained stable by 12 months (p = 0.47).

Durand et al (2018) reported on the Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV Negative Recipients (EXPANDER) Trial, an open-label nonrandomized study of 10 recipients of HCV-infected kidneys who received HCV
treatment at the time of transplant. EXPANDER did not restrict transplantation to donors infected with HCV genotype 1 and therefore used elbasvir-grazoprevir supplemented with sofosbuvir for 12 weeks for recipients of kidneys infected with genotype 2 or 3. One participant developed transient asymptomatic transaminase levels greater than 5 times the upper limit of normal which resolved by day 14 without intervention.

The key characteristics and results of these studies are summarized in Tables 1 and 2.

**Table 1. Summary of Key Trials: Study Characteristics Transplantation of HCV-Infected Kidney**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Treatment</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg (2017) 1, (NCT02 743897) THINKER-1</td>
<td>Pilot Prospective Interventional</td>
<td>United States Single site</td>
<td>2016-ongoing</td>
<td>10 HCV non-viremic listed for kidney transplant</td>
<td>HCV genotype1-viremic donor kidney + 12 weeks of GZR-EBR</td>
<td>NA</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Reese (2018) 2, (NCT02 743897) THINKER-1; THINKER-2</td>
<td>Pilot Prospective Interventional</td>
<td>United States Single site United States Single site</td>
<td>2016-ongoing</td>
<td>10 HCV non-viremic listed for kidney transplant Additional 10 HCV non-viremic listed for kidney transplant</td>
<td>HCV genotype1-viremic donor kidney + 12 weeks of GZR-EBR HCV genotype1-viremic donor kidney + 12 weeks of GZR-EBR</td>
<td>NA</td>
<td>12 month 6 months</td>
</tr>
</tbody>
</table>
Table 2. Summary of Key Trials Study Results Transplantation of HCV-Infected Kidney

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Outcome</th>
<th>Primary Safety Outcome</th>
<th>Secondary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg (2017)</td>
<td>N(%)</td>
<td></td>
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</tr>
<tr>
<td>THINKER</td>
<td>10 (100%)¹</td>
<td>0²</td>
<td>1 recipient with FSGS³</td>
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<td></td>
<td>At 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reese (2018)</td>
<td>10(100%)¹</td>
<td>0²</td>
<td>0³</td>
</tr>
<tr>
<td>THINKER-1 THINKER-2</td>
<td>At 12 months</td>
<td>0²</td>
<td>0³</td>
</tr>
<tr>
<td></td>
<td>10(100%)²</td>
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<td></td>
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<td>Durand (2018)</td>
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<td>0³</td>
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<tr>
<td>EXPANDER-1</td>
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¹ Post-treatment sustained virologic response (SVR). The primary analysis based on a calculation of SVR rates (number of subjects with SVR-12; negative HCV RNA 12 weeks after completing HCV therapy) / (number of subjects treated with HCV therapy post-kidney transplantation)
² Major adverse events attributable to HCV therapy (GZR-EBR and SOF if required) in post-kidney transplant patients.
³ Allograft rejection
⁴ Renal function indices: serum creatinine level (Cr) and glomerular filtration rate (GFR)

Cr: creatinine; EXPANDER-1: Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-negative Recipients; FSGS: focal segmental glomerulosclerosis; GFR: glomerular filtration rate; IQR: interquartile range; THINKER: Transplanting Hepatitis C Kidneys into Negative Kidney Recipients

Section Summary: Kidney Transplantation

For individuals who are HCV non-viremic who have end-stage renal disease and are candidates for a kidney transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing dialysis or other appropriate treatment and remaining on the transplant wait-list consists of preliminary results of two open-label nonrandomized trials (THINKER and EXPANDER). Relevant outcomes were SVR and graft function and survival. Major adverse events attributable to the selected HCV DAA regimen was also assessed. To date, the experience of 30 participants has been reported in the literature. Participants generally had comparable demographic characteristics. The studies differed in
whether or not donor kidneys were genotyped in advance of transplantation. Appropriate DAA regimens were chosen to match genotype or pangenotypic was used. There were differences in the timing of administration of the DAA regimen, but all participants were followed to ascertain the need for extension of the original regimen or addition of another drug. All recipients showed evidence of HCV nucleic acid positivity and viral loads were determined in some instances. All recipients had SVR by the completion of the appropriate DAA regimen with the longest follow-up out to 12 months in 10 participants. There were no reports of allograft rejection or renal function abnormalities. Transient elevations in liver transaminases were reported but not in all participants. Assessment of quality of life by standard patient-reported measures in the first ten participants of the THINKER cohort indicated that quality of life was initially diminished in the early postoperative period. At 12 months, the physical component score of the RAND-36 questionnaire improved beyond baseline but the mental component score returned to baseline. The evidence is insufficient to determine the effects of the technology on health outcomes.

Lung Transplantation

Clinical Context and Therapy Purpose
The purpose of transplanting a lung from an HCV viremic donor to an HCV non-viremic recipient is to reduce waiting time to transplant and waitlist-associated morbidity and mortality and to reduce the discard of otherwise healthy solid organs. The purpose of using DAAs to treat HCV non-viremic recipients who may become viremic upon receiving a solid organ transplant from HCV viremic donors is to treat or prevent acute HCV infection and thereby prevent associated acute and chronic downstream sequelae of transplant acquired HCV infection.

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.

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.

Patients
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-negative 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. Solid organ transplant is
provided in a tertiary inpatient setting staffed and equipped to perform the surgical procedure and postsurgical intensive care. Treatment of HCV non-viremic recipients would be managed by infectious disease specialists, transplant surgeons, and pulmonologists.

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, and change in disease status, treatment-related mortality and treatment-related morbidity.

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
Woolley et al (2019) conducted a trial involving transplantation of HCV viremic hearts and lungs from donors to adults without HCV infection and reported the results on 44 patients. Donors were not selected on the basis of HCV genotype and DAA with sofosbuvir-velpatasvir was administered preemptively immediately after organ transplant and continuing for four weeks. The DAA regimen provided pangenotypic coverage and is not associated with immunosuppressive drug interactions. The four-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. Relevant outcomes were SVR at 12 weeks (16 weeks after transplantation) and 6-month graft survival. The key characteristics and results of the study are summarized in Tables 3 and 4. An additional exploratory 6-month post hoc analysis was done of transplantation outcomes from a population of 56 trial participants for whom HCV negative 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 positive donors, but the duration of follow-up is insufficient to determine the effect on long-term graft survival.

The significance of the eclipse period and the sensitivity of available NAT for HCV was assessed by Watson et al (2017). A single-center retrospective review of a
prospectively collected database for lung transplant recipients including HCV Banat- donors sought to ascertain the rate of seroconversion. Between 1/1/17 and 8/9/17, a total of 64 HCV Ab- recipients underwent lung transplantation. The recipients of 13 (20%) HCV Banat- donors underwent protocol NAT at 2 and 12 months and all were NAT- at the time of publication. One recipient developed reactive HCV Ab at six months post-transplant with follow-up HCV RNA undetectable.

Table 3. Summary of Key Trials: Study Characteristics Transplantation of HCV-Infected Heart and Lung

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wooley (2019)</td>
<td>Pilot Prospective Interventional</td>
<td>United States Single site</td>
<td>2017-ongoing</td>
<td>53 HCV non-viremic listed for heart or lung transplant</td>
<td>53 HCV positive donors</td>
<td>44 HCV NAT positive (36 lung and 8 heart) + 4 weeks of SOF - VEL</td>
<td>NA</td>
</tr>
</tbody>
</table>


Table 4. Summary of Key Trials Study Results Transplantation of HCV-Infected Heart and Lung

<table>
<thead>
<tr>
<th>Study</th>
<th>Total participants N=35</th>
<th>Lung transplant recipients N=28</th>
<th>Heart transplant recipients N=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wooley (2019)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV Ab +: 1 week</td>
<td>27(77)</td>
<td>17(49)</td>
<td></td>
</tr>
<tr>
<td>HCV Ab+: 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR 12 weeks</td>
<td>35 (100)</td>
<td>35 (100)</td>
<td></td>
</tr>
<tr>
<td>SVR 24 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute cellular rejection requiring treatment</td>
<td>15(54)</td>
<td>3(43)</td>
<td></td>
</tr>
<tr>
<td>Graft survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>28(100)</td>
<td>28(100)</td>
<td>7(100)</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAAs</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HCV infection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DAA: direct-acting antiviral; HCV Ab+: hepatitis C antibody positive; SVR: sustained virologic response.
Section Summary: Lung Transplantation
For individuals who are HCV non-viremic who have end-stage pulmonary disease and are candidates for lung transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of preliminary results of a single open-label nonrandomized trial of 36 HCV viremic lung transplants treated with 4 weeks of pangenotypic DAAs. Relevant outcomes were SVR and graft function and survival. SVR at 12 weeks and graft survival at 6 months was available for 28 participants and both rates were 100%. The evidence is insufficient to determine the effects of the technology on health outcomes.

Heart Transplantation

Clinical Context and Therapy Purpose
The purpose of transplanting a heart from an HCV viremic donor to an HCV non-viremic recipient is to reduce waiting time to transplant and waitlist-associated morbidity and mortality and to reduce the discard of otherwise healthy solid organs. The purpose of using DAAs to treat HCV non-viremic recipients who may become viremic upon receiving a solid organ transplant from HCV viremic donors is to treat or prevent acute HCV infection and thereby prevent associated acute and chronic downstream sequelae of transplant acquired HCV infection.

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.

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.

Patients
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 negative 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. Solid organ transplant is provided in a tertiary inpatient setting staffed and equipped to perform the surgical procedure and postsurgical intensive care. Treatment of HCV non-viremic recipients would be managed by infectious disease specialists, cardiothoracic surgeons, and cardiologists.
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, and change in disease status, treatment-related mortality and treatment-related morbidity.

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 report by Woolley et al (2019) described above and summarized in Tables 3 and 4, included 8 heart transplant recipients; 7 of whom survived to assess relevant outcomes of SVR at 12 weeks and graft survival at 6 months. Both rates were 100%. The eighth recipient died of bacterial sepsis that was not judged to be related to either DAAs or acute HCV infection.

McLean et al (2019) reported a pilot trial, USing Hepatitis c positive hearts for negative Recipients (USHER), that was intended to determine the safety and efficacy of transplanting 10 hearts from HCV-viremic donors into HCV negative patients followed by treatment with elbasvir/grazoprevir treatment upon detection of HCV viremia (NCT03146741; sponsor: Merck). The cobas HCV Test, for use on the 6800/8800 Systems (Roche Diagnostics Systems, Inc.) with an analytic sensitivity of approximately 15 IU/mL of plasma was used for HCV viral load surveillance in recipients. The investigators report that they did not use an "on-call" to the operating room treatment protocol for the following reasons; post-transplant treatment on day three increased the likelihood that patients were clinically stable at the time of treatment initiation with a reduced likelihood of treatment interruption for transplant complications; to better reflect a real-world scenario where DAA therapy might not be available at the time of transplantation due to hospital formulary policies; and to provide data on the HCV transmission rates via transplantation. Key study characteristics and results are summarized in Tables 5 and 6.
Table 5. Summary of Nonrandomized Trial Study Characteristics-Heart Transplant

<table>
<thead>
<tr>
<th>Study</th>
<th>Study.Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Follow.Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLean (2019) &amp; (NCT03146741) USHER</td>
<td>Pilot Single Arm Interventional</td>
<td>United States Single site</td>
<td>2017-2018</td>
<td>20 adult HCV negative patients enrolled 10 transplanted at time of publication</td>
<td>Genotype 1 HCV viremic donors + EBR-GZR treatment upon detection of HCV viremia</td>
<td>6-12 months</td>
</tr>
</tbody>
</table>

EBR-GZR = elbasvir-grazoprevi; HCV: hepatitis C virus; USHER: USing Hepatitis c positive hearts for negative Recipients.

Table 6. Summary of Nonrandomized Trial Study Results- Heart Transplant

<table>
<thead>
<tr>
<th>Study</th>
<th>Viral load Day 3</th>
<th>Viral load undetectable week 4 EBR-GZR SVR 12 weeks</th>
<th>NS5A resistance in genotype 1a</th>
<th>Grade 2R ACR</th>
<th>Severe AMR resulting in death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACR: acute cellular rejection; 2R: moderate rejection; AMR: antibody mediated rejection; EBR-GZR = elbasvir-grazoprevir; SVR: sustained virologic response;

One EBR-GZR treatment was empirically extended to 16 weeks with the addition of oral ribavirin in 1 heart recipient based on the non-responder viral load status of a kidney recipient from the same donor. Ribavirin was discontinued secondary to anemia.

Case reports and series are summarized in Tables 7 and 8. Gottlieb et al (2017) reported a single case of an HCV Ab- adult female patient with biventricular heart failure, Organ Procurement and Transplantation Network status 1A and who was not a candidate for the bridge to transplant mechanical ventricular assist. An HCV Ab and NAT+ donor heart was transplanted. An unanticipated post-transplant management issue was reported given that there was an insufficient donor sample to perform HCV genotyping. The recipient developed an HCV viral load sufficient to perform genotyping by day 13 after transplant. At that time, DAA with sofosbuvir-velpatasvir was initiated. HCV genotype 3a was identified and the patient completed 12 weeks of DAA treatment with last dose on post-transplant day 96. HCV viral titers were negative by post-transplant day 23 and remained negative.

Radzi (2019) provided the only identified experience with pediatric heart transplantation of HCV-antibody positive patients by inquiry of the United Network for Organ Sharing, the U.S. private nonprofit organization that administers the
Organ Procurement and Transplantation Network. Post-transplant survival was the only outcome available for three infants who received an HCV Ab+ donor heart.

Table 7. Summary of Key Case Reports and Series Characteristics - Heart Transplant

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participants</th>
<th>Treatment.Delivery</th>
<th>Follow.Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottlieb (2017)</td>
<td>United States</td>
<td>Patient 1 HCV-seronegative female</td>
<td>HCV NAT-positive donor + SOF-VEL 12 weeks</td>
<td>1 year</td>
</tr>
<tr>
<td>Jawad (2018)</td>
<td>Germany</td>
<td>Patient 1 HCV-seronegative male</td>
<td>HCV seropositive donor Year 4: SOF+DCV</td>
<td>5 years</td>
</tr>
<tr>
<td>Moayedi (2018)</td>
<td>United States</td>
<td>Patient 1 HCV-seronegative male Patient 2 HCV-seronegative Female with LVAD</td>
<td>HCV NAT-positive donor + SOF-VEL 12 weeks initiated at 2 weeks post-transplant</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Radzi (2019)</td>
<td>United States</td>
<td>3 HCV-seronegative infants &lt; 1 year of age with CHD</td>
<td>HCV seropositive donor</td>
<td>0.38 to 5.91 years</td>
</tr>
</tbody>
</table>

CHD: congenital heart disease; DCV: daclatasvir; HCV: hepatitis C virus; LVAD: left ventricular assist device; NAT: nucleic acid testing; SOF: sofosbuvir; VEL: velpatasvir.

Table 8. Summary of Key Case Reports and Series Results - Heart Transplant

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Outcome 1 SVR</th>
<th>Outcome 2 Graft survival</th>
<th>Outcome 3¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottlieb (2017)</td>
<td>HCV NAT-positive donor + SOF-VEL 12 weeks</td>
<td>Sustained at 1 year</td>
<td>No rejection episodes</td>
<td>No renal or hepatic AEs No hospitalization</td>
</tr>
<tr>
<td>Jawad (2018)</td>
<td>HCV seropositive donor Year 4: SOF+DCV</td>
<td>Sustained at 6 months</td>
<td>No rejection episodes</td>
<td>Progression of CAV Preservation of LVEF (60%)</td>
</tr>
<tr>
<td>Moayedi (2018)</td>
<td>HCV NAT-positive donor + SOF-VEL 12 weeks initiated at 2 weeks post-transplant</td>
<td>SVR at 12 weeks in patients 1 and 2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Radzi (2019)</td>
<td>HCV seropositive donor</td>
<td>No HCV treatment reported</td>
<td>2 alive at 5.91 and 1.91 years 1 dead at.38 years</td>
<td>NR</td>
</tr>
</tbody>
</table>
Section Summary: Heart Transplantation
For individuals who are HCV non-viremic who have end-stage cardiac disease and are candidates for heart transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of preliminary results of 2 single-arm, open-label nonrandomized trials that total 17 HCV viremic heart genotype 1 transplants. Relevant outcomes were SVR and graft function and survival. Trial protocols differed in the timing of administration and duration of DAA with elbasvir/grazoprevir. All recipients achieved an SVR including when the extension of treatment was required. Each trial reported a death; one unrelated to DAA or HCV infection and the other due to antibody mediated graft rejection in a patient who had a positive cross-match. Several case reports have published outcomes for four adults and three infants less than one year of age. The results for the pediatric cases were derived from the national transplant registry and only included graft and overall survival. The evidence is insufficient to determine the effects of the technology on health outcomes.

Liver Transplantation

Clinical Context and Therapy Purpose
The purpose of transplanting a liver from an HCV viremic donor to an HCV non-viremic recipient is to reduce waiting time to transplant and waitlist-associated morbidity and mortality and to reduce the discard of otherwise healthy solid organs. The purpose of using DAAs to treat HCV non-viremic recipients who may become viremic upon receiving a solid organ transplant from HCV viremic donors is to treat or prevent acute HCV infection and thereby prevent associated acute and chronic downstream sequelae of transplant acquired HCV infection.

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.

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.

Patients
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 negative 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. Solid organ transplant is provided in a tertiary inpatient setting staffed and equipped to perform the surgical procedure and postsurgical intensive care. Treatment of HCV non-viremic recipients would be managed by infectious disease specialists, transplant surgeons, and hepatologists.

**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, and change in disease status, treatment-related mortality and treatment-related morbidity. 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 negative donor organ and acute HCV infection with the transplantation of an HIV-viremic organ into an HCV negative 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**
Luckett et al (2019) reported a prospective review of all HCV nonviremic liver transplant patients who had received HCV Ab+/NAT- donor organs during a 1 year period. The recipients were compared to a group from the same center who had received a U.S. Public Health Service increased-risk HCV Ab-/NAT- donor liver. The only baseline difference was in the MELD score at the time of transplantation indicating a higher status on the transplant list for those who received the HCV Ab
and NAT- organs. The study explored the potential for viremia to be observed in the HCV Ab+ and NAT- population of 53 patients; 2 patients in the original population of 55 died before HCV testing was carried out. A positive HCV NAT was found in five recipients; four of whom underwent HCV anti-viral treatment with subsequent SVR. The fifth recipient died of unrelated causes. This finding raised the possibility of a false-negative NAT in the donor but with low probability due to the high sensitivity of currently available NAT testing. The authors discussed the possibility of a reservoir of occult HCV infection of the liver; however, no tissue was available for analysis in either donors or recipients. The key characteristics and results of this study are summarized in Table 9 and 10.

Table 9. Summary of Key Observational Comparative Study Characteristics - Liver Transplant

<table>
<thead>
<tr>
<th>Study</th>
<th>Study.Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Group.1</th>
<th>Group.2</th>
<th>Follow.Up</th>
</tr>
</thead>
</table>

HCV Ab+: hepatitis C antibody positive; HCV AB-: hepatitis C antibody negative; NAT-: nucleic acid test negative

Table 10. Summary of Key Observational Comparative Study Results - Liver Transplant

<table>
<thead>
<tr>
<th>Study</th>
<th>HCV Ab+ / NAT- Recipient n=55</th>
<th>HCV Ab- / NAT- Recipient n=57</th>
</tr>
</thead>
<tbody>
<tr>
<td>recipients</td>
<td>43 (78)</td>
<td>57 (100)</td>
</tr>
<tr>
<td>Donor HCV NAT performed in eclipse period, n (%)</td>
<td>51 (93)</td>
<td>56 (98)</td>
</tr>
<tr>
<td>HCV viremia detected in recipient n (%)</td>
<td>5 (9.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Graft loss, n/N (%) 3 months 1 year Overall</td>
<td>2/55 (3.6) 5/37 (13.5) 8/55 (14.5)</td>
<td>3/57 (5.3) 4/42 (9.5) 7/57 (12.3)</td>
</tr>
<tr>
<td>Mortality, n/N (%) 3 months 1 year Overall</td>
<td>2/55 (3.6) 4/36 (11.1) 7/54 (13.0)</td>
<td>3/57 (5.3) 4/42 (9.5) 6/56 (10.7)</td>
</tr>
</tbody>
</table>

HCV Ab+: hepatitis C antibody positive; HCV AB-: hepatitis C antibody negative; NAT-: nucleic acid test negative; PHS: U.S. Public Health Service.

A total of 12 patients have been identified in case reports and case series who were transplanted with HIV Ab + or NAT+ liver donors. The majority of the patients had prior HCV infection, were treatment experienced and HCV NAT- at the time of transplantation. All patients were found to be NAT+ after transplantation and received DAA at a wide range of time periods after identification of seroconversion. DAA treatment was provided on the basis of genotype with an
appropriate drug combination and duration consistent with the products available at the time. Additional details of key characteristics and results of the case reports are summarized in Table 11 and Table 12.

Table 11. Summary of Key Case Report and Series Characteristics - Liver Transplant

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participants</th>
<th>Treatment Delivery</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saberi (2018)¹¹</td>
<td>United States</td>
<td>57 year old female, HCV genotype 1a post- HCV DAA SVR with Child-Turcotte-Pugh class A cirrhosis</td>
<td>HCV Ab negative/NAT positive donor + 24 weeks LDV/SOF initiated at postoperative day 25</td>
<td>2 years</td>
</tr>
<tr>
<td>Campos-Varela (2018)</td>
<td>United States/Spain</td>
<td>64 year old male, HCV genotype 1b, post-interferon based regimen and HCC treated with TACE</td>
<td>HCV Ab positive donor</td>
<td>1 year</td>
</tr>
<tr>
<td>Kwong (2018)¹¹</td>
<td>United States</td>
<td>10 adult HCV NAT negative patients Prior HCV treated with DAA (70%)</td>
<td>HCV NAT + liver donor + DAA based on genotype</td>
<td>17 months</td>
</tr>
</tbody>
</table>

Ab: antibody; DAA: direct-acting antiviral; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; LDV: ledipasvir; NAT: nucleic acid test; SOF: sofosbuvir; SVR: sustained virologic response; TACE: transcatheter arterial chemoembolization

Table 12. Summary of Key Case Series Results - Liver Transplant

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Outcome 1 SVR</th>
<th>Outcome 2 Graft survival</th>
<th>Outcome 3 AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saberi (2018)¹¹</td>
<td>HCV Ab negative/NAT positive donor + 24 weeks LDV/SOF initiated at postoperative day 25</td>
<td>Achieved at 8 weeks Maintained at 2 years</td>
<td>Functioning graft</td>
<td>NR</td>
</tr>
<tr>
<td>Campos-Varela (2018)</td>
<td>HCV Ab positive donor</td>
<td>Achieved at 12 weeks post-interferon containing DAA regimen when genotype 3 was identified</td>
<td>Functioning graft</td>
<td>None identified</td>
</tr>
<tr>
<td>Kwong (2018)¹¹</td>
<td>HCV NAT+ liver donor + DAA based on genotype (n) Genotype!A: (4) 1B: (1) 2B: (1) 3: (4) Days to treatment range (11-84)</td>
<td>All 10 achieved SVR after 12-24 weeks of genotype specific DAA</td>
<td>1 ACR+AMR 1 ACR 1 AMR Successfully treated</td>
<td>1 ribavirin intolerance</td>
</tr>
</tbody>
</table>

Ab: antibody; ACR: acute cellular rejection; AMR: antibody-mediated rejection; DAA: direct-acting antiviral; HCV: hepatitis C virus; LDV: ledipasvir; NAT: nucleic acid; NR: not reported; SOF: sofosbuvir; SVR: sustained virologic response;
Section Summary: Liver Transplantation
For individuals who are HCV non-viremic who have end-stage liver disease and are candidates for liver transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of a report from a single-site prospectively evaluating 55 recipients of HCV Ab+/NAT- donors compared to 57 recipients of HCV Ab-/NAT- donors. Graft function and loss were comparable between groups, as was mortality by one year of follow-up. Seroconversion was detected by NAT in five of the HCV Ab+/NAT- recipients. Four were successfully treated with an appropriate HCV antiviral therapy and subsequent SVR. A fifth recipient died before treatment of non-HCV related causes. Several case reports have published outcomes for a total of 12 adults who received HCV viremic liver transplants. A notable finding in the reports is that the majority of recipients had prior HCV infection and had successfully achieved an SVR using genotype-specific DAA when reinfection was identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

Other Solid Organ Transplantation

Clinical Context and Therapy Purpose
The purpose of transplanting other solid organs (eg small bowel or pancreas) from an HCV viremic donor to an HCV non-viremic recipient is to reduce waiting time to transplant and waitlist-associated morbidity and mortality and to reduce the discard of otherwise healthy solid organs. The purpose of using DAAs to treat HCV non-viremic recipients who may become viremic upon receiving a solid organ transplant from HCV viremic donors is to treat or prevent acute HCV infection and thereby prevent associated acute and chronic downstream sequelae of transplant acquired HCV infection.

The purpose of other solid organ transplants 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.

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.

**Patients**
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. Solid organ transplant is provided in a tertiary inpatient setting staffed and equipped to perform the surgical procedure and postsurgical intensive care. Treatment of HCV non-viremic recipients would be managed by infectious disease specialists, transplant surgeons, and hepatologists.

**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, and change in disease status, treatment-related mortality and treatment-related morbidity.

**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 publications were identified in the last five years that reported on planned transplantation of HCV -viremic solid organs such as small bowel or pancreas into HCV non-viremic recipients. One earlier publication of outcomes for 16 simultaneous pancreas-kidney transplant recipients from HCV positive donors patients identified in the United Network for Organ Sharing database (2000-2011) reported 4 kidney allograft losses and 6 pancreas allograft losses without a known direct relationship to HCV.15.

**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 last five years in the published literature. The evidence is insufficient to determine the effects of the technology on health outcomes.
Summary of Evidence

For individuals who are HCV non-viremic who have end-stage renal disease and are candidates for a kidney transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing dialysis or other appropriate treatment and remaining on the transplant wait-list consists of preliminary results of two open-label nonrandomized trials (THINKER and EXPANDER). Relevant outcomes were sustained virologic response (SVR) and graft function and survival. Major adverse events attributable to the selected HCV DAA regimen was also assessed. To date, the experience of 30 participants has been reported in the literature. Participants generally had comparable demographic characteristics. The studies differed in whether or not donor kidneys were genotyped in advance of transplantation. Appropriate DAA regimens were chosen to match genotype or pangenotypic was used. There were differences in the timing of administration of the DAA regimen, but all participants were followed to ascertain the need for extension of the original regimen or addition of another drug. All recipients showed evidence of HCV nucleic acid positivity and viral loads were determined in some instances. All recipients had SVR by the completion of the appropriate DAA regimen with the longest follow-up out to 12 months in 10 participants. There were no reports of allograft rejection or renal function abnormalities. Transient elevations in liver transaminases were reported but not in all participants. Assessment of quality of life by standard patient-reported measures in the first ten participants of the THINKER cohort indicated that quality of life was initially diminished in the early postoperative period. At 12 months, the physical component score of the RAND-36 questionnaire improved beyond baseline but the mental component score returned to baseline. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are HCV non-viremic who have end-stage pulmonary disease and are candidates for lung transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of preliminary results of a single open-label nonrandomized trial of 36 HCV viremic lung transplants treated with 4 weeks of pangenotypic DAAs. Relevant outcomes were SVR and graft function and survival. SVR at 12 weeks and graft survival at 6 months was available for 28 participants and both rates were 100%. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are HCV non-viremic who have end-stage cardiac disease and are candidates for heart transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of preliminary results of 2 single-arm, open-label nonrandomized trials that total 17 HCV viremic heart genotype 1 transplants. Relevant outcomes were SVR and graft function and survival. Trial protocols differed in the timing of administration and duration of DAA with elbasvir/grazoprevir. All recipients achieved an SVR including when the extension of treatment was required. Each trial reported a death; one unrelated to DAA or HCV infection and the other due to antibody mediated graft rejection in a patient who had a positive cross-match. Several case reports have published outcomes for
four adults and three infants less than one year of age. The results for the pediatric cases were derived from the national transplant registry and only included graft and overall survival. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are HCV non-viremic who have end-stage liver disease and are candidates for liver transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of a report from a single-site prospectively evaluating 55 recipients of HCV Ab+/NAT- donors compared to 57 recipients of HCV Ab-/NAT- donors. Graft function and loss were comparable between groups, as was mortality by one year of follow-up. Seroconversion was detected by NAT in five of the HCV Ab+/NAT- recipients. Four were successfully treated with an appropriate HCV antiviral therapy and subsequent SVR. A fifth recipient died before treatment of non-HCV related causes. Several case reports have published outcomes for a total of 12 adults who received HCV viremic liver transplants. A notable finding in the reports is that the majority of recipients had prior HCV infection and had successfully achieved an SVR using genotype-specific DAA when reinfection was identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 last five years in the published literature. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements
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. Key findings and recommendations are summarized in Table 13.

Table 13. American Society of Transplantation Consensus Conference - Use of Hepatitis C Virus Viremic Donors

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

**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**
A search of ClinicalTrials.gov in April 2019 identified some currently unpublished trials that might influence this review. (Table 14).

### Table 14. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT.No.</th>
<th>Trial.Name</th>
<th>Planned.Enrollment</th>
<th>Completion.Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02669966</td>
<td>Live Kidney Donors With Positive Anti-HCV Antibody, But Negative HCV PCR</td>
<td>2</td>
<td>Feb 2020</td>
</tr>
<tr>
<td>NCT02945150</td>
<td>Preemptive Treatment With Grazoprevir and Elbasvir for Donor HCV Positive to Recipient HCV Negative Kidney Transplant</td>
<td>8</td>
<td>Mar 2020</td>
</tr>
<tr>
<td>NCT02743897</td>
<td>Transplanting Hepatitis C Kidneys Into Negative Kidney Recipients (THINKER)</td>
<td>53</td>
<td>Dec 2021</td>
</tr>
<tr>
<td>NCT02781649</td>
<td>Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-negative Recipients (EXPANDER-1)</td>
<td>10</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>NCT03801707</td>
<td>Utilization of Hepatitis C Positive Kidneys in Negative Recipients (USE-Hep C)</td>
<td>25</td>
<td>Jan 2022</td>
</tr>
<tr>
<td>NCT03523871</td>
<td>A Study of the Use of Hepatitis C Positive Donors for Hepatitis C Negative Lung Transplant Recipients With Post-transplant Treatment With Mavyret</td>
<td>20</td>
<td>Sep 2020</td>
</tr>
<tr>
<td>NCT03625687</td>
<td>Pan-genotypic Direct Acting Antiviral Therapy in Donor HCV-positive to Recipient HCV-negative Lung Transplant</td>
<td>25</td>
<td>Apr 2021</td>
</tr>
<tr>
<td>NCT03222531</td>
<td>Expanding the Pool in Orthotopic Heart Transplantation</td>
<td>20</td>
<td>Jul 2023</td>
</tr>
<tr>
<td>NCT Number</td>
<td>Study Title</td>
<td>Participants</td>
<td>Start Date</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>NCT03382847</td>
<td>HCV Positive Heart Donors</td>
<td>25</td>
<td>Apr 2020</td>
</tr>
<tr>
<td>NCT03146741</td>
<td>Zepatier For Treatment Of Hepatitis C-Negative Patients Who Receive Heart Transplants From Hepatitis C-Positive Donors (HCV) (USHER)</td>
<td>20</td>
<td>Nov 2019</td>
</tr>
<tr>
<td>NCT03086044</td>
<td>Transplanting Hepatitis C Positive Thoracic Organs</td>
<td>100</td>
<td>Dec 2021</td>
</tr>
<tr>
<td>NCT03208244</td>
<td>DAA Treatment in Donor HCV-positive to Recipient HCV-negative Heart Transplant</td>
<td>30</td>
<td>Apr 2022</td>
</tr>
<tr>
<td>Unpublished-Lung</td>
<td>Lung Transplant HCV, Pilot Study</td>
<td>26</td>
<td>Apr 2021</td>
</tr>
<tr>
<td>Ongoing-Liver</td>
<td>DAA Treatment in Donor HCV-positive to Recipient HCV-negative Liver Transplant</td>
<td>50</td>
<td>Sep 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

REFERENCES


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>50300</td>
<td>Donor nephrectomy (including cold preservation); from cadaver donor, unilateral or bilateral</td>
</tr>
<tr>
<td>50320</td>
<td>Donor nephrectomy (including cold preservation); open, from living donor</td>
</tr>
<tr>
<td>50323</td>
<td>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</td>
</tr>
<tr>
<td>50325</td>
<td>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</td>
</tr>
<tr>
<td>50327</td>
<td>Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; venous anastomosis, each</td>
</tr>
<tr>
<td>50328</td>
<td>Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; arterial anastomosis, each</td>
</tr>
<tr>
<td>50329</td>
<td>Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; ureteral anastomosis, each</td>
</tr>
<tr>
<td>50340</td>
<td>Recipient nephrectomy (separate procedure)</td>
</tr>
<tr>
<td>50360</td>
<td>Renal allotransplantation, implantation of graft; without recipient nephrectomy</td>
</tr>
<tr>
<td>50365</td>
<td>Renal allotransplantation, implantation of graft; with recipient nephrectomy</td>
</tr>
<tr>
<td>50547</td>
<td>Laparoscopy, surgical; donor nephrectomy (including cold preservation), from living donor</td>
</tr>
<tr>
<td>48550</td>
<td>Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation</td>
</tr>
<tr>
<td>48551</td>
<td>Backbench standard preparation of cadaver donor pancreas</td>
</tr>
</tbody>
</table>
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

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

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 (ie, 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 (ie, 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

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

S2065 Simultaneous pancreas kidney transplantation

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

**ICD-10 Codes**

- **B17.1-** Acute Hepatitis C code range
- **B17.11**
- **B18.2** Chronic Viral hepatitis C
- **B19.2-** Unspecified Viral Hepatitis C code range
  **19.9**

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

- 8/1/19 New Policy. The transplantation of HCV-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient combined with direct-acting antiviral treatment for HCV is considered investigational.
- 8/1/20 No policy statement changes.

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