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How Does Treating Chronic Hepatitis C Affect Individuals in Need of Organ Transplants in the United Kingdom?

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ABSTRACT

Objectives: To estimate the impact of cures for chronic hepatitis C (CHC) infection on organ donation in the United Kingdom. Curing CHC infection reduces the need for liver transplants and enables cured individuals to donate organs of all types.

Methods: We adapted a double-queuing model of organ allocation to estimate the effects of CHC infection cures on liver, lung, heart, and kidney transplants in the United Kingdom. We assumed that cured individuals would donate organs at similar rates as the general population and no longer require liver transplants because of CHC infection. We estimated how curing CHC infection influences waitlist lengths for each organ and the annual net present value to society on the basis of quality-adjusted life-years gained through additional transplants under opt-in and opt-out organ donation policies.

Results: Curing CHC generates the most value for patients on the liver waitlist, because it increases the number of transplantable livers *and* reduces the need for transplants. Under the current opt-in policy, liver waitlist length falls by 24%, generating £34.3 million of annual net present value. Growth in the number of uninfected lungs, hearts, and kidneys generates an additional £19.2 million annually, with £18.7 million from kidneys. Implementing the opt-out policy, liver waitlist length would decrease by 75%, implying that treating CHC eliminates one-third of the excess liver waitlist due to an opt-in policy.

Conclusions: Treating CHC has large positive spillovers to uninfected individuals by reducing the need for liver transplants and allowing cured individuals to donate organs. These spillovers have not been included in traditional value assessments of CHC treatment.

Keywords: cure, economic value, hepatitis C, organ donation, organ transplant.

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Introduction

Chronic hepatitis C (CHC) is an infectious disease causing inflammation of the liver, which typically spreads through blood-to-blood contact.[1,2] CHC is associated with several extrahepatic complications, including kidney disease, depression, cardiovascular disease, and type II diabetes.[3] In the United Kingdom, CHC prevalence is approximately 240 000 people,[4] with high-risk groups including individuals with current or past injection drug use, and minority ethnic populations. Injection drug use remains the most prevalent form of transmission, accounting for about 85% of hepatitis C infections in the United Kingdom.[5]

People with hepatitis C virus (HCV) often do not exhibit symptoms until they are already experiencing complications such as liver cirrhosis, liver failure, or liver cancer.[1] In recent years, novel direct-acting antivirals (DAAs) have transformed CHC treatment. With sustained virologic response (SVR) rates of 95% or more, DAAs are more effective than the previous standard of care, which had lower SVR rates (40%-50%) and high toxicity.[6–10] *SVR* is defined as the absence of detectable hepatitis C ribonucleic acid at

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6 months or more after treatment cessation, at which point CHC is considered cured. In addition, DAAs are now the World Health Organization's preferred treatment for CHC[11] because compared with the previous standard of care, DAAs' all-oral regimens, shorter treatment durations, and reduced side effects make them easier to administer in community settings, where it is easiest to reach the CHC-infected.[11,12] DAAs are now being administered throughout the United Kingdom, following national recommendations.[12]

Previous studies have examined the effect of DAAs on clinical and economic outcomes among people with CHC, both within and outside the United Kingdom.[13,14] Nevertheless, CHC treatment with DAAs may also have spillover benefits for uninfected individuals. In particular, curing CHC may benefit people on organ waitlists.

The United Kingdom, like many countries, faces a shortage of donated organs. Among patients on the organ transplant waitlist, on average, 3 people die every day in the United Kingdom.[15] Waiting times can be long; between 2016 and 2017, the average waiting time was 864 days for a kidney, 255 days for lungs, 138 days for a liver, and 1280 days for a nonurgent heart transplant.[16] One in 6 waitlist patients become too ill to receive a heart, lung, or liver, and they are suspended from the waitlist.[17] Not all potential organ donors become actual organ donors, which contributes to the organ shortage.[16]

Historically, donation by hepatitis C–positive individuals has been very rare,[18] although this could change in the future.[19] Nevertheless, individuals treated and cured of CHC have the potential to become organ donors, helping to alleviate some of the organ shortage.

Treating CHC reduces the need for liver transplant, because CHC is a common indication for liver transplant.[16] A previous study has estimated the impact of CHC treatment on liver transplant outcomes in the United States.[20] This research focused on 1 channel of causality: fewer liver transplants for HCV-infected patients would free up organs for those with other forms of liver failure. Nevertheless, curing CHC would also increase the supply of usable, uninfected organs by eliminating HCV from potential donors who are currently infected. Little is known about how this might impact the waitlist for livers and other organs not directly affected by CHC. In this study, we estimated how universally screening for and treating CHC and allowing cured individuals to donate organs would affect transplant outcomes in the United Kingdom, compared with the current policy in which treatment rates are low (in part because of underdiagnosis)[12] and donation by HCV-positive individuals is rare.[18]

We expected 2 effects of universally treating CHC—first, it should reduce the demand for livers and, second, it should increase the supply of all donated organs. In this study, we specifically considered livers, hearts, lungs, and kidneys. To estimate the effects of such a policy change on the number of patients receiving transplants, we used a double-matching queue model developed by Boxma et al.[21] We parameterized and adapted this model to fit organ donation and transplant patterns in the United Kingdom to estimate the impact of universally treating people with CHC and allowing them to donate organs. Our main study outcomes were the number of additional organ transplants that would occur, the associated quality-adjusted life-years (QALYs) gained, and the economic value of the QALY gains. We interpreted our results in the context of opt-in and opt-out policies for organ donation. Although opt-out has the potential to significantly increase organ donation, in many countries, individuals must opt-in to become an organ donor.[22]

Currently, throughout the United Kingdom (except Wales), people must sign up to become an organ donor or explicitly make their wishes known. England and Scotland are considering adopting an opt-out policy, in which people are presumed to have consented to donate organs, unless they opt-out.[23,24] Therefore, interpreting our results under an opt-out policy scenario is relevant to a comprehensive policy discussion.

Methods

We adapted a double-queuing model developed by Boxma et al[21] to estimate the effects of treating HCV-infected individuals and allowing them to donate organs on the UK organ transplant system. Specifically, we considered effects on liver, heart, lung, and kidney transplant waitlists. The Boxma model (Figure 1) captures the dynamics between the demand for organs (ie, patients requiring an organ transplant) and the supply of organs (ie, organs from donors available for transplantation). Boxma et al define the efficiency of the organ transplantation system in steady state in terms of the following performance metrics:

1. The rate of organ outdating, which is the rate at which organs are discarded because there is no demand for them before they perish.
2. The rate of registrant removals or deaths, which is the rate at which patients on the waitlist leave without a transplant because of death or becoming too ill. Removals and deaths are attributed to patients waiting too long for a needed organ transplant.
3. The average number of organs in the organ bank at any given time.
4. The average number of patients on the waitlist at any given time.
5. The long-run fraction of time in which the organ bank is empty.

These performance metrics are the model outputs.[25] The model inputs that determine the values of the performance metrics are as follows:

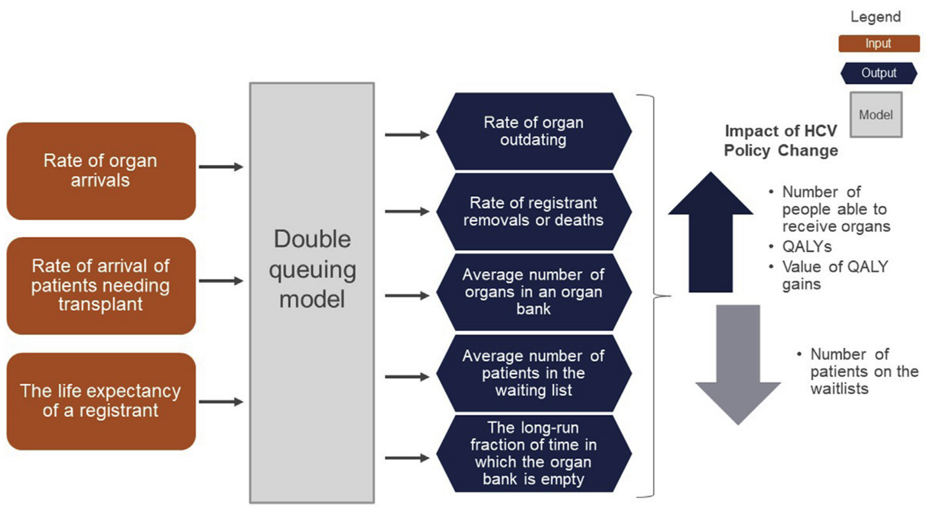
1. The arrival rate of donated organs.
2. The arrival rate of patients needing a transplant.
3. The life expectancy of a waitlist registrant: the number of months a patient on the waitlist can wait for an organ before their health deteriorates to the point of death or being removed from the waitlist.

To make the model analytically tractable, we applied simplifying assumptions about the model inputs' distributions. Specifically, we assumed that organs and patients each arrive at the double queue according to independent Poisson distributions, and that registrants' life expectancy is exponentially distributed. Further details can be found in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.09.2923.

Data Sources

Three model performance metrics were assumed given observed facts about organ donation in the United Kingdom, whereas the other performance metrics and the model inputs were obtained from government data and the literature. Specifically, the rate at which organs perish because of lack of a recipient

Figure 1. The model schematic. The Boxma double-queuing model captures the dynamics between the demand for organs (ie, patients requiring a transplant of an organ) and the supply of organs (ie, organs from donors available for transplantation). Inputs are fed into the model, producing the performance metrics (outputs), which measures the efficacy of the organ transplant system. We used the change in the number of patients on the waitlist from the Boxma model to calculate the change in QALYs and economic value of the QALYs gained due to additional transplants.



HCV indicates hepatitis C virus; QALY, quality-adjusted life-year.

was assumed to be 0 under current policy. This is consistent with the persistence of waitlists for our studied organs in the United Kingdom.[16,26–28] That is, because there have consistently been more patients on UK organ waitlists than organs available for transplant, organs rarely perish for lack of a potential transplant recipient. The model assumes all organs are assigned to a recipient immediately upon donation, leaving no organs waiting in the organ bank. Similarly, we assumed that the organ bank is empty 100% of the time, because organs are immediately distributed to the patients in the queue. The rate of registrant removals or deaths, average number of waiting patients, rate of organ arrivals, arrival rate of patients needing transplants, and registrant life expectancy were derived from the National Health Service (NHS) Blood and Transplant 2016/2017 activity report, which provides comprehensive data on the UK transplant system. The amount of time an organ could last between donation and transplant before perishing (cold ischemia time) was obtained from the academic literature.[29–32] Given the persistence of waitlists for our studied organs in the United Kingdom,[16,26–28] we assumed that under current policy all organs are transplanted within the cold ischemia time.

Estimation Strategy

Model inputs were recovered using a calibration procedure. Inputs were allowed to vary slightly from their observed literature-based values to match the performance metrics produced by the model with those observed in the NHS activity report. The exception was for the kidney, in which the registrants' life expectancy was allowed to vary by more than 100% of what we estimated, on the basis of NHS data, so that the estimated number of patients on the kidney waitlist would more closely match that observed in the NHS data. We prioritized the accuracy of the estimated number of patients on the waitlists because this output directly affected our calculations of the QALYs gained and economic value of the simulated policy change. In addition, although the performance metrics, rate of organ arrivals, and arrival rate of patients needing transplants were clearly observable in the NHS data, the life expectancy of a waitlist registrant could be approximated only through censoring and selection bias. (Censoring occurs because it is unclear how long a transplant recipient would have survived without the transplant. Selection bias affects life expectancy estimates if the sickest patients receive transplants first.) Therefore, we found it reasonable to allow for larger differences between observed and fitted values for registrant life expectancy compared with the other inputs and outputs.

The performance metrics produced by the recovered parameters served as the "base-case" values. We then made assumptions on how inputs would vary on the basis of the policy change, and estimated the model again to understand how the long-run performance metrics would change as a result. In particular, we simulated the effects of universally treating HCV-infected individuals and allowing them to donate organs in the following way: (1) the rate of organ arrivals would increase proportionally to the prevalence of HCV-positive individuals who are not coinfected with HIV (~0.035%[4,33–35]) and (2) the arrival rate of patients needing a liver transplant would reduce proportionally by the fraction of patients who currently join the waitlist because of CHC (5%).[36] Note that this specification implicitly assumes that all HCV-infected individuals will be treated, and that all treated individuals will be cured, given that newly released DAAs have cure rates of up to 100% in clinical trials.[37] This is intended to show the potential spillovers of such a scenario to organ waitlist registrants. To the extent that individuals with CHC lack access to treatment or have difficulty adhering to it, the effects of the policy change would be muted. We also assumed that individuals with CHC would donate organs at similar rates to the general population.

Table 1. Number of patients in UK queues for organ transplant under the policy change of treating CHC and allowing cured individuals to donate in an opt-in organ donation system.

Organ	Real-world values[16]	Estimated number of individuals in the queue under various scenarios		Percent reduction in the queue under the policy change
		Base case (current policy)	Policy change (treat CHC and allow donation)	
Liver	552	544	413	24
Lung	368	366	365	0
Heart	270	270	268	1
Kidney	8095	7407	7280	2

CHC indicates chronic hepatitis C.

Table 2. Impact of treating CHC on the number of people able to receive organs, QALYs gained, and the net present value of the policy change compared with the base-case scenario (current policy).

Organ	Number of additional patients receiving organs per year	QALYs gained due to additional transplants	Annual net present value of policy change (£)
Liver	132	1 144	34 334 351
Lung	1	7	202 209
Heart	2	10	290 346
Kidney	127	623	18 688 324
All	262	1 784	53 515 230

Note. Following the National Institute for Health and Care Excellence convention, a discount rate of 3.5% was applied, and a value of £30 000 per QALY was assumed.
CHC indicates chronic hepatitis C; QALY, quality-adjusted life-year.

On the basis of this specification, we were able to estimate the change in the size of each organ waitlist because of the policy change in a given year. From the literature, we obtained estimates of QALYs that would be gained through the additional transplants that occurred.[38,39] The annual net present value (NPV) of the policy change was calculated as follows:

$$\text{Net present value} = \Delta\text{Queue} \times * \text{QALYs} \times * \text{£}30,000,$$

where ΔQueue denotes the change in the size of the patient queue after the policy change and QALYs denote the additional QALYs a patient gains on receiving a transplant, compared with waiting for an organ but not receiving one.

Future QALY gains were discounted at a 3.5% rate and each QALY was valued at £30 000, as per National Institute for Health and Care Excellence conventions.

Opt-Out Policy Scenario

Although our base-case results considered the effects of treating CHC-infected individuals in the United Kingdom (except in Wales) under current opt-in policy, we also simulated a hypothetical movement to opt-out organ donation throughout the United Kingdom, both alone and combined with treating CHC. Specifically, we assumed that the UK-wide organ donation consent rate would rise from 63% to 76.2%, given the observed increase in consent when Wales moved to opt-out.[16,27]

Results

Liver

We estimated that the UK liver waitlist contains 544 individuals under current policy (base case) versus 552 reported in NHS data (Table 1). Treating all individuals with CHC in the United Kingdom and allowing cured individuals to donate organs would generate the most social value for patients on the liver transplant waitlist compared with those on other organ waitlists. In the long-term under current opt-in policy, we estimated that HCV elimination would reduce the liver waitlist size by 24%, with an additional 132 patients receiving liver transplants annually. By freeing up livers for transplant to uninfected individuals, this policy change would translate to 1144 QALYs gained and an NPV of £34.3 million every year for uninfected registrants (Table 2).

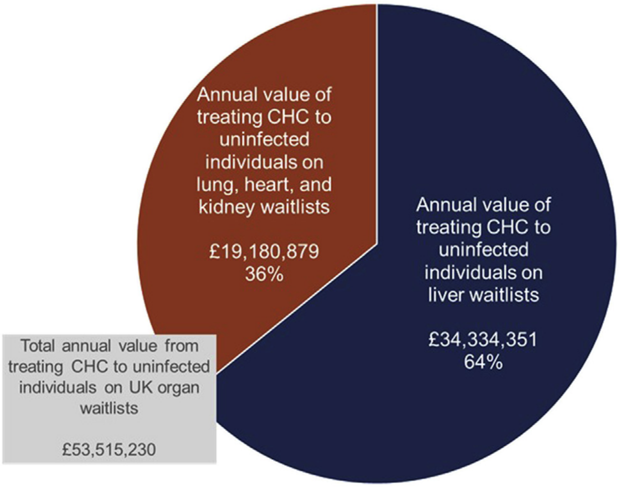
The value of treating CHC for individuals on the UK liver waitlist would stem from 2 sources. First, the policy change would increase the supply of livers, because people cured of CHC could potentially become liver donors. Second, treating CHC would reduce the demand for liver transplants, because CHC is a common indication for liver transplantation in the United Kingdom.[36] In the long run, curing CHC would preclude the need for future liver transplants due to HCV and reduce the waitlist size, increasing the chances for others to receive a needed transplant.

Lung, Heart, and Kidney

Our estimation of the Boxma model fit the observed UK waitlist for heart exactly (270), was correct within 2 patients for lung (366 estimated vs 368 actual), and was an underestimation for kidney (7407 estimated vs 8095 actual; Table 1). Apart from positive effects for patients on the liver waitlist, we found that treating CHC and allowing cured individuals to donate organs would have considerable positive spillover effects for patients on other organ waitlists. We estimated that under the current opt-in policy, 1 additional patient would receive a lung transplant, 2 additional patients would receive heart transplants, and 127 additional patients would receive kidney transplants annually with HCV elimination. These amounted to an annual gain of 7 QALYs for lung, 10 for heart, and 623 for kidney, for an annual NPV of approximately £202 000 for lung, £290 000 for heart, and £18.7 million for kidney (Table 2).

Summing the NPV gains across all studied organs, we found a total annual NPV of £53.5 million (Figure 2). Of this, the liver accounted for most of the gains, at £34.3 million (64%), whereas lung, heart, and kidney together accounted for £19.2 million (36%). The disproportionate share of liver is unsurprising because HCV primarily affects the liver; therefore, treating CHC would both decrease the demand for livers and potentially increase the supply. Among the other organs considered (lung, heart, and kidney), the largest impacts were seen for patients on the kidney waitlist, with more modest effects for patients on the lung and heart waitlists. This is likely because the kidney transplant waitlist is the largest in the United Kingdom and does not exclusively depend on

Figure 2. Value of positive spillovers from treating CHC to uninfected individuals on UK organ waitlists. Following the National Institute for Health and Care Excellence convention, a discount rate of 3.5% was applied and a value of £30 000 per QALY was assumed. CHC treatment policies simulated under an opt-in organ donation system.



CHC indicates chronic hepatitis C; QALY, quality-adjusted life-year.

cadaveric donations. In 2017, approximately 8095 patients were on the kidney waitlist, whereas 368 waited for a lung and 270 for a heart.[16]

Opt-Out Policy Scenario

We also estimated the effects of an opt-out policy for organ donation alone, and in combination with treating CHC and allowing cured individuals to donate. Our results (Table 3) revealed that an opt-out policy could reduce the number of patients on the waitlist by 75%, 23%, 36%, and 97% for liver, lung, heart, and kidney, respectively, for a total annual value of £1.19 billion relative to the base case. CHC cures reduce waitlists for livers by nearly one-third the amount of a nationwide opt-out policy. Combining CHC cures with an opt-out policy would have larger effects than either policy alone, with a total social value of £1.23 billion relative to the base case.

Discussion

CHC is a common cause of liver and extrahepatic complications[3] and a leading indication for liver transplant.[36] Since the introduction of novel DAAs in 2014,[12] the treatment of CHC in the United Kingdom has evolved rapidly, with the prospect of a cure now attainable for the HCV-infected population. DAA regimens have greater efficacy, lower toxicity, and shorter treatment duration than the previous standard of care and reduce liver-related and extrahepatic morbidity and mortality, thus improving quality of life and life expectancy.[3,40] Moreover, DAAs have been deemed cost-effective in the United Kingdom and globally.[13,40–49]

In addition to cost effectiveness, other aspects of DAAs have been studied. Patient-reported outcomes such as quality of life and work productivity are less affected by DAA regimens, compared with the previous standard of care.[50] Van Nuys et al[51] valued the direct health gains from annually treating 7650 individuals with hepatitis C in England at £4.3 billion over 50 years, or roughly £23 000 of lifetime health gains per treated individual. For comparison, we found annual spillover gains worth £53.5 million, equivalent to roughly £223 per cured person per year. The annual spillover is modest because a cured individual has a low chance of donating an organ each year. Assuming a 20-year remaining life expectancy,[45] this translates to £3279 over the cured individual's lifetime; therefore, the spillovers amount to approximately 14% of the value of the direct health benefits in the analysis by Van Nuys et al.

Despite the well-documented effects of DAAs for people with CHC, these spillover benefits have received less attention. Our results are similar to those of Jena et al,[20] who found that systematic hepatitis C screening and treatment would spare 10 490 livers for transplant over 20 years in the United States, with almost 70% of these livers benefiting patients with non–CHC-induced liver failure. The increased availability of donor livers was estimated to lead to 52 700 additional life-years for uninfected patients and 22 800 life-years for patients with CHC, providing economic values of $7.9 billion and $3.5 billion, respectively. This translates to an additional 1.6 liver transplantations per 1 million US residents. The study by Jena et al focused only on the "demand" effect of reduced need for CHC-induced transplants. Incorporating the increased supply of uninfected livers, we estimate that curing CHC in the United Kingdom would result in an additional 2 liver transplants per 1 million UK residents. Results in the US and UK contexts are similar despite differences in study design; our study assumed 100% cure, whereas Jena et al[20] assumed 90% cure, and our study measured changes to the organ transplant system in the long run rather than over a 20-year period.

Table 3. Summary of benefits from opt-out policy only, and CHC cure + opt-out policies implemented together, relative to the base case.

Organ	Opt-out waitlist (% reduction)	Opt-out/CHC waitlist (% reduction)	QALYs gained under opt-out	QALYs gained under opt-out/CHC	NPV gains under opt-out (£)	NPV gains under opt-out/CHC (£)
Liver	137 (75)	39 (93)	3 549	4 403	106 479 664	132 079 617
Lung	282 (23)	280 (23)	385	394	11 564 359	11 809 032
Heart	174 (35)	172 (36)	553	565	16 604 860	16 956 178
Kidney	217 (97)	148 (98)	35 221	35 557	1 056 621 444	1 066 697 557
Total			39 709	40 918	1 191 270 327	1 227 542 385

Note. Under the opt-out/CHC scenario, CHC-infected individuals are universally screened for, treated, and allowed to donate organs, and the UK adopts an opt-out policy as well. Percent reductions in waitlists, QALYs gains, and NPV gains are in comparison with the base case (opt-in, except for Wales).
CHC indicates chronic hepatitis C; NPV, net present value; QALY, quality-adjusted life-year.

Although other studies have investigated the effects of treating CHC on liver waitlists,[20,52] this study is the first to examine the effects on organ waitlists beyond the liver. Specifically, we found that treating CHC and allowing cured individuals to donate would increase the availability of lungs, hearts, and kidneys for transplantation, accounting for 36% of the total value derived from the policy change, with the other 64% because of the liver. This estimated effect stems from an increased supply of donated hearts, lungs, and kidneys from individuals cured of CHC, rather than any assumptions about the extrahepatic manifestations of CHC before and after cure. CHC has been associated with higher prevalence of type 2 diabetes mellitus,[53–57] with CHC individuals being 11 times more likely to develop type 2 diabetes mellitus.[58] Furthermore, CHC is linked to various heart diseases[59–63] and several other extrahepatic manifestations.[64] Although it is possible that curing CHC could reduce the demand for other organs, this effect is not well documented and hence excluded from the present analysis.

Our study is the first empirical application of the Boxma model, a model for organ transplantation, to a specific organ transplantation system and policy change. It thus provides a potential framework for future studies of changes to organ allocation systems.

This study has several limitations. First, although the model estimates closely fit the observed UK waitlists for liver, heart, and lung, its fit for kidney was not as close. We hypothesize that the less accurate fit for kidney transplants may have been because donors can potentially donate 2 kidneys, and that living kidney donations are more common than other organ donations.

In addition, the model assumes that no other changes occur in the organ transplant system between introduction of the CHC cure policy and the system reaching equilibrium. In reality, comprehensive policies for HCV screening and linkage to care must be implemented to achieve HCV elimination. Moreover, the policy environment for organ donation is changing as discussions are underway for adopting an opt-out policy in the United Kingdom. Evidence from various countries suggests that organ donation rates would be higher under such a system,[65] and indeed we estimate a substantially greater social value from CHC treatment combined with opt-out compared with the current policy.

Certain simplifying assumptions were applied to make the Boxma model tractable. For example, some parameters were assumed to have distributions that may not describe real-life events. The model also did not account for human leukocyte antigen matching, which is especially important in kidney transplants.[66] In this case, the model, which assumes a “first-in, first-out” queue system for transplant waitlists, may also not accurately describe the UK organ transplant system.

In addition, we assumed that all HCV-infected individuals will be screened, treated, and cured. In reality, the effects of universal treatment would be muted as HCV-infected individuals remain undiagnosed and lack access to treatment.[12] Hence, our results further highlight the benefits of removing barriers to diagnose and treat HCV-infected individuals.

Finally, our supplemental analyses suggest that an opt-out policy may enhance the social value of universally treating CHC. Moving to opt-out would be a larger departure from the base case than the CHC cure policy; hence, the model estimates for opt-out are further out-of-sample and likely less reliable than our base-case and CHC cure results. Opt-out organ transplant systems demonstrate an increase of about 21% to 30% in organ donation rates or about 3 to 6 more donors per million population, and could potentially further alleviate the organ shortage in the United Kingdom.[67,68]

The spillover benefits of curative therapies could potentially matter beyond the CHC context. For instance, evolving treatments for acute lymphoblastic leukemia have increased survival rates considerably since the 1960s,[69] with approximately 90% cure rates in developed countries.[70] Chimeric antigen T-cell therapy may further improve these outcomes,[71–73] potentially allowing cured patients to become organ donors.[74] Similarly, a novel mitochondrial transplant has been successful in reviving damaged heart muscles in infants and could potentially reduce the demand for heart transplants.[75] Such curative therapies may provide spillover benefits for patients on organ waitlists too.

Conclusions

Treating CHC has largely unrecognized positive spillovers to uninfected individuals. Specifically, CHC treatment reduces the need for liver transplant and allows cured individuals to potentially donate organs such as liver, heart, lung, and kidneys, amounting to more than £53 million in estimated social value annually in the United Kingdom. Because CHC directly affects the liver, the bulk (64%) of this value stems from additional liver transplants made possible for uninfected individuals; nevertheless, an additional 36% of this value stems from spillovers to other organs. Although substantial, these spillover benefits have not been included in traditional cost-effectiveness analyses and value assessments.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.09.2923.

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