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Simulating healthcare quality innovation based on a novel medical treatment: The case of Hepatitis-C in Europe

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ABSTRACT

In 2014, a novel medication for treating Hepatitis C virus (HCV) infections caused severe difficulties for European decision makers in the public medical sector. Even though new drugs cure HCV in nearly all cases, related costs in the short run are extremely high. Thus, the estimation of overall costs for the national healthcare systems was of great importance for profound far-reaching decisions on policies regarding the medication and their reimbursement. As this budget estimation is extremely difficult due to the complexity of the virus spread and the existence of further discomforts that lead to additional costs, a new microsimulation model was developed that considers the problem from an individual's perspective and finally aggregates numbers on the macro level. While developing the model, general insights into the cost burden due to the new medication for the next 3 years were generated. Using the introduced model, a decision maker is able to test for impact of one financial unit in several policies in order to maximize the overall benefit for the healthcare system. As initial results imply the need to change current reimbursement strategies in Europe, further research demand is discussed at the end of this article.

1. Introduction

Hepatitis C Virus (HCV) is not only a worldwide major healthcare issue. In the past year, HCV became the number one topic in healthcare management and health politics. A radical pharmaceutical innovation reanimated the market for HCV medication which promises that >95% of HCV-infected people become virus-free in one treatment period, whereas conventional treatment could only heal about 40–50% of infected individuals (McHutchison et al., 2009; Strader et al., 2004). This might lead to an overall change in the system, including long-term treatment of infected patients, the high need of liver transplantations, or long-term medication demands. Therefore, this innovation can be considered as an overall healthcare quality innovation.

Worldwide it is estimated that >185 million people are infected with HCV. The number of infected individuals in Europe is about 10 million. Globally the number of infections is constantly increasing and showed a rise in prevalence and the number of infected people from 1995 to 2005 from 2,3% to 2,8%. Central and East Asia, North Africa and the Middle East are estimated to be countries with a high HCV prevalence, whereas Asia Pacific, Tropical Latin America, and North America have the lowest prevalence rates (Mohd Hanafiah et al., 2013). Although the total number of HCV infections is constant or decreasing in many countries, the burden of the disease is expected to increase (Davis et al., 2010; Deuffic–Burban et al., 2012; Razavi et al., 2013). This is justified by the fact that fewer people get infected although the number of complications which become manifest in a late state of illness increases (Razavi et al., 2014).

HCV is caused by infection with the Hepatitis C virus which infects liver cells. About 40% of infected individuals recover from the virus, about 60% become chronic. As a consequence of the disease patients often suffer from a cirrhosis or liver cancer. The disease is classified into 11 genotypes, which have an effect on treatment and chances for healing. Due to their occurrence in Europe and America studies report their findings and information about treatment for genotypes 1–6 (Bruggmann et al., 2014). In Europe the virus is almost exclusively spread by infected needles in the drug scene by receiving infected blood (Hsu et al., 1994; Lemon and Brown, 1995).

Factors, such as being HIV positive, previous therapy with former HCV medication, fibrosis or cirrhosis and the HCV-genotype have an influence on the success of these new forms of medication (Manns et al., 2014). Like every radical innovation, the new medication brings change to the market. Pharmaceutical companies offering new treatment options for HCV with high success rates act as monopolists and set prices. Therefore the costs of an average HCV therapy in Central Europe rose in 2014 from about 15,000 with standard therapy to 100,000 Euro with new therapy options (Ostermann et al., 2015).

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1.1. Background

As the disease extends a long time-horizon, the costs and the economic burden of HCV are high. Infected individuals for instance have a 20% chance of developing cirrhosis in the first 20 years after infection, 20% of those with cirrhosis develop liver cancer (European Association for the Study of the Liver, 1999). The combination of treatment (diagnosis, medication, treatment) and long-term consequence costs (cirrhosis, liver cancer and liver transplantation) explains the high economic burden of HCV (Blachier et al., 2013).

The direct costs for HCV treatment can be divided into diagnosis, medication and other healthcare services. Medication for HCV is responsible for the largest proportion of direct costs with an amount of approximately 7500–21,000 Euros in median lifetime costs or 15,000 Euros per treatment cycle of 24–48 weeks (Ostermann et al., 2015) in Europe for traditional treatment (Blachier et al., 2013; Ostermann et al., 2015). New medication for HCV has the potential to increase these costs to about 55,000–210,000 Euros per treatment cycle. Costs for diagnosis and other healthcare services such as the consultation of a physician or laboratory services are estimated in Austria to be approximately 1000 Euros per year (Jonas et al., 2004).

Direct costs are also caused by complications due to HCV such as cirrhosis, liver cancer or liver transplantation. As patients that undergo traditional treatment have a chance of only 40–50% of becoming virus-free and an unknown number of infected individuals live undetected (Lang and Weiner, 2008; McHutchison et al., 2009), these costs make up a significant amount of the total burden of HCV.

Indirect costs of the disease are costs that do not affect the healthcare system, but other factors of the economy due to a loss of productivity (Fröschl et al., 2012). A US study on indirect costs of HCV estimates the cost of sick days and lower productivity per HCV infected employee to amount to about 8400 USD per year in 2010 (Unit Economist Intelligence, 2013).

As patients claim access to new medication and payers are responsible for balancing budgets, healthcare systems require decision support. As a first reaction to new HCV medication, many decision makers in Europe decided to reimburse innovative HCV drugs only for patients with severe health conditions. At first glance this may make sense, but if one takes into account reinfections and healing rates, it would be possible to invest this money more effectively. The background of this model was the healthcare decision makers' question how the budget burden develops under different treatment scenarios. As demand for new medications grows, the uncertainty and degree of innovation is high, decision makers insisted on a decision support tool within a short time to deliver information and/or treatment for infected patients. The main focus was thereby on the developments in the healthcare system based on this innovation in the coming 3 years.

The paper at hand presents this decision support tool and gives insights into some results and discussions of further research that should be conducted in the field in order to improve the model, its validity, and its explanatory power. The paper proceeds as follows: In Section 2 we present a brief literature review that considers approaches and models that allow for adequately modelling the spread and treatment of HCV. Section 3 presents our microsimulation model developed for the European area and parameterized for the Austrian healthcare system. In Section 4 we present some selected scenarios that were conducted and present results of the study. We conclude with some discussions of the results and the need for further research in Section 5.

2. Existing models

For getting in-depth insights into existing approaches to model the spread and treatment of Hepatitis C and comparable infections, an extensive literature review on the topic was conducted. We thereby identified three main streams in mathematical models of HCV: i) predicting effects of treatment, ii) predicting transmission among people who inject drugs, and iii) analysing economic effects of HCV treatment.

The effects of antiviral therapies were deeply analysed and evaluated using different mathematical models that also yielded many insights into the pathogenesis. Perelson and Guedj recently published a review on prediction models that analyse the different treatment effects on HCV therapy (Perelson and Guedj, 2015). In doing so, one of the major fields of interest is the question regarding the minimal duration of treatment for the novel therapy. Numerous models have their origin in HIV research, based on simple heuristic arguments. This basic idea was adapted in order to predict decreases of viral loads of HCV after treatment in a biphasic model. In the first phase it proved dose-dependent effectiveness in blocking viral production, while the next phase shows a decrease due to dying and not efficiently replaced cells. However, this rather simple approach was extended to more sophisticated models in order to analyse the complex processes of liver regeneration, drug pharmacokinetics including empirical models, and the effect of ribavirin. For analysing viral kinetics with direct-acting antiviral agents, the blocking of viral assembly and secretion combined with replication, as well as curing infected cells and drug-resistance were modelled. A recent disease progression model concludes that the traditional treatment rate and efficiency is not sufficient to overcome the burden of HCV and claims the need for a novel therapy (Razavi et al., 2014), such as the one being discussed in this article.

In high-income countries, the main population at risk of being infected with HCV is people who inject drugs. Their seroprevalence ranges from 15 to 90% (Vickerman et al., 2010). Therefore, a recent literature review deals only with models capturing this problem of virus transmission (Cousien et al., 2015). In this review, 37 models were analysed with the main objectives of illustrating the transmission of HCV and providing analytical results; evaluating the impact of harm reduction policies; comparing epidemic dynamics of HCV and HIV; evaluating the impact of treatment of HCV infection on transmission and cost; and evaluating the impact of vaccination strategies. From a methodological perspective, macro-view compartmental models were the most frequently used approach (31 out of 37, see (Cousien et al., 2015) for further details), dividing the overall population into individual compartments according to the state in the infection process. The major benefit of these models is the low computation time, which can be explained with the method's main shortcoming: the assumption of a homogenous and totally mixed population. This shortcoming is overcome in the presented individual-based models that differentiate within the population according to characteristics of individuals or even take into account the individuals' social networks. The reproduction of characteristics from real networks was addressed in intersection graph models, household graph models, and stochastic block models.

The effectiveness and cost-effectiveness where addressed in several studies as a minor part of the analysis. However, there are also publications that focus on this aspect. One of these models is a Markov model that focuses on the prioritization of treatments for groups of patients in Egypt. The main result is that immediate treatment of early HCV stages is less expensive and more effective than delaying therapies (Obach et al., 2014). The economic evaluation is thus bound to lifetime costs, life expectancy, quality-adjusted life expectancy, and incremental cost-effectiveness ratio (Obach et al., 2014). A Hepatitis C policy model for Germany was developed based on a Markov cohort simulation. The cost-effectiveness of four different therapy options was compared over a 20-year horizon (Wasem et al., 2006). Another mathematical model considered infections via contaminated tattoo equipment and analysed the cost-effectiveness and optimal timing of intervention policies (Behrens et al., 2008).

In addition to the individual-based models mentioned, several recent papers consider microsimulation and agent-based simulation as being a suitable approach for modelling healthcare questions such as epidemics (Crooks and Hailegiorgis, 2014; Jaffry and Treur, 2008), cancer strategies (An and Kulkarni, 2015), cost-effectiveness in various

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fields such as cost effectiveness of vaccinations (Kim and Goldie, 2008) or effects of drug abuse (Gutfraind et al., 2015). Sufficient computational power as well as the availability of data seem to be the main reasons for this trend.

3. Microsimulation model

The US National Research Council proposes limited, special-purpose models to answer specific policy questions. They see a major advantage of microsimulation models for testing policies' effects at the level of the individual (Citro and Hanushek, 1997). Due to the availability of data on a micro-level we decided to develop a limited microsimulation model that considers the situation of Hepatitis C on the individuals' level (Kwakkel and Pruyt, 2013). The main aim of the model was to get an idea of which effects the novel medication could have on the further spread of the disease and the national healthcare budget based on sectors. To the best of our knowledge there is no model available in the literature that would have allowed one to tackle this question in this context. Using microsimulation we can combine the three identified fields from the literature review. We evaluate the effect of the novel therapy on an individual level, separate the population into groups and consider the individual treatment costs that are finally aggregated to the national level.

The approach at hand allows one to trace single individuals over time and get a clear picture of possible future scenarios based on real data and realistic assumptions (Gordon, 2003). Furthermore, the storage of data on an individual level allows one to differentiate between persons who have been medically treated before and those who were not, which has a huge impact on overall probability of treatment success. However, the model does not consider epidemiologic processes in detail but tries to indicate the effects of a novel healthcare innovation on the overall quality for patients and the emerging costs caused by it.

The model was implemented in a Java programme using the libraries *Aspose.Cell, Java FX* and *Math Class*. Scenario input data is read from xlsx files and results are written into xlsx with a record of each time step and a general analysis and overview.

3.1. Model structure

The model considers an overall population that is split into groups of non-infected and infected people. Each agent runs through several states at each time step and has individual characteristics, where each time step equals 1 year. This leads to different end stages in the modelling horizon: *acute hepatitis C*, *chronic hepatitis C (CHC) by genotype*, *virus-free*, or *dead*. Thus, within the simulation, the infected population is split into groups of acute and chronic infection with HCV. More precisely, this means that when a healthy person becomes infected with the virus, he or she is acutely infected for 1 year. After this year the person is either successfully treated and therefore becomes virus-free, dies (out of another reason than the virus), or becomes chronically infected. Chronic infection with Hepatitis C is split into six groups based on the genotype of the infected person (genotype 1–6 for Europe and the U.S.).

Each representation of the disease leads to a different probability for successful treatment or death and causes different costs. For example, patients with chronic hepatitis C infection receive medical treatment and therefore cause relatively high intramural and comparable low extramural costs, while a patient with a long virus-history and pre-existing liver cirrhosis causes rather low intramural costs and rather high extramural costs. Furthermore, different genotypes cause different probabilities of the treatments' success rates. The basic model structure is presented in Fig. 1.

The model considers additional HIV infections, liver cancer, liver cirrhosis, and the overall development of the HCV infection over years. All parameters mentioned have an influence on the probabilities and costs of treatment. Especially for different policies of treatment strategies we also differentiate between patients with and without symptoms. Table 1 shows parameters considered in the model and the data type used.

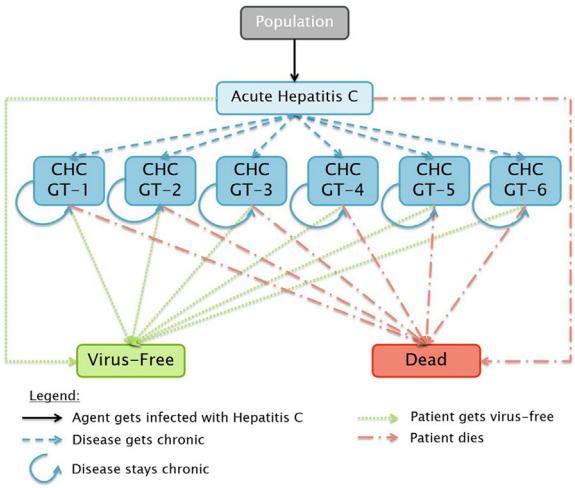

Fig. 1. Model structure.

Every agent in the simulation has an ID that allows for easily separating and following them over time. We consider every agent's age and note if he or she is currently infected with HCV (Ill), the corresponding genotype the infection is based on, and the time period during which he or she has been suffering from HCV (IllForYears).

Especially the question of prior medical treatment is of great importance, as treatment-naive patients have a significantly higher probability of successful treatment. The probabilities and costs of the different medications available (especially the main differentiation between old and new drugs) is read from an external xlsx file. Aside from the possibility of dying from CHC, patients might also die from cancer, HIV, or natural death based on the mortality table.

The model's results are based on the individual patient data and are summed up to the collective healthcare system. As such, we can test for impacts on the overall healthcare quality through several policy scenarios. The analysis is thereby based on patients still being infected, suffering from CHC-caused liver cirrhosis, dead patients, or being virus-free at the end of the model horizon. This result is compared to the intramural and extramural costs of the considered policy that arise for treatments.

3.2. Model parameterization

Due to the actuality of the public decision making process and the availability of data, the model was parameterized for the Austrian healthcare system. Therefore, recent publications, public data on treatments, and own calculations and estimations were used to parameterize the model.

The basis for medication costs and probabilities of treatment success were taken from the providers of medical compounds. A detailed analysis of probabilities (healing rates, death rates, etc.), available treatment

Table 1
Parameters and data types used.

Parameter	Data type
Agent ID	Double
Age	Integer
Ill	Boolean
Genotype	Integer (1–6)
IllForYears	Integer
Cirrhosis	Boolean
Liver Cancer	Boolean
HIV	Boolean
Symptoms	Boolean

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options, and costs based on sectors for the Austrian healthcare market were conducted by the GÖG (Gesundheit Österreich GmbH). Bruggmann et al., 2014 assume 30,000 infected persons in Austria, whereby 1100 of them are currently in medical antiviral treatment. This amounts to a prevalence of 0.4% of the Austrian population and a incidence of about 2%. This data is also approved by the Ministry of Health (Austrian Federal Ministry of Health, 2012). Based on this data and information, the authors assume 600 patients annually in naïve treatment.

The distribution of different genotypes differs strongly between countries. The Austrian distribution was calculated in (Bruggmann et al., 2014) and is shown in Table 2.

The age distribution of infected patients was taken from real data of Austrian HCV patients, the distribution of the overall population accords to the overall population of the country, excluding people below 18 years of age (European Medicines Agency, 2014).

The infection history of patients was calculated based on overall annual infection rates and the age distribution of patients. This approach was chosen because it follows the logic of existing data for Austria. Patients who are newly infected with the virus exhibit a history level "IllForYears" of 0 as the duration is below one year. CHC patients with a disease history of >20 years (IllForYears > 20) have a high probability of 20% to additionally suffer from liver cirrhosis (European Association for the Study of the Liver, 1999). The cirrhosis causes additional costs to the healthcare system and might lead to liver cancer and an organ transplant (at cost) (Gschwantler et al., 2010; Maieron et al., 2010). The distribution and probabilities for liver cancer were calculated based on (Zechmeister et al., 2006). The distribution, costs and probabilities for liver transplants were calculated based on (Bruggmann et al., 2014; Priebe et al., 2014) and for HIV based on (Peck-Radosavljevic, 2004).

Just as the model tracks the health status of each agent in every modelling cycle, it also records costs involved per agent and cycle. Included costs are all direct healthcare costs that arise with the presence of HCV. We considered medication costs, costs for diagnosis and laboratories, consultations of physicians, costs for different stages of cirrhosis, liver-cancer and transplantation. Costs also vary as probabilities over time and duration of infection in our model (e.g. a transplantation causes high costs in the first cycle when the procedure is executed, but yields additional costs in the following cycles as a patient needs further consultations of physicians and additional medication due to the transplantation.)

3.3. Model verification and validation

Model verification was conducted in a multiple-step-based analysis and based on (Sargent, 1988, 2011). In doing so, we started with a degenerate test in order to see if the model performs well in its categories such as infection, healing, or dying. In the next step we tested event validity for the established medication therapy and tested the results with historical data. In a further step, extreme validity was tested for cases where everyone is treated, no one is treated, and treatment is at no cost. Another verification analysis was the internal validity, where we tested the consistency of results over several simulation runs. In a final step of the model verification we tested the model with fixed values and compared the results to manual calculations. All the verification methods were analysed on macro-level results and traces analysis, where single individuals were traced over time. All results of the verification process were satisfactory and imply an error-free model.

After all experiments were conducted, the validity of the model and its results was tested with experts in the field. In doing so, the results of the executed "status quo" simulation were compared to real numbers in terms of a Turing test. Furthermore, using the predictive validation, experts were asked to predict the system's behaviour, which was subsequently compared to the simulation results. The results in the validation process were satisfactory for the defined research questions (Arnopoulos, 1979). However, future research potential was identified and will be discussed in Section 5.

Table 2
CHC – share of genotypes in Austria.

Genotype	Share in %
1	72,0
2	5,0
3	19,0
4	4,0
5	0,0
6	0,0

4. Simulation experiments and results

In this paper we present simulation experiments for five different scenarios. In doing so, we want to show the model's ability to provide strategic policy support. The scenarios were generated based on several possible policies on the reimbursement strategy for the novel medication and the related degree of service quality innovation for the healthcare system. The division of scenarios is as follows:

Scenario 1: Conventional treatment
Scenario 2: New medication
Scenario 3: New medication with a high demand for new medication (factor 1.5)
Scenario 4: New medication with high demand and additional treatment of 50% of all patients with cirrhosis
Scenario 5: New medication with high demand and additional treatment of 100% of all patients with cirrhosis

Scenario 1 is used as the status quo case (also in the validation) and represents the index basis for comparisons among the scenarios. The experiments deliver reasonable results, significant outcomes for different scenarios in epidemiology and costs and first insights regarding trends for reimbursement and treatment strategies.

The epidemiological results show expected outcomes. In scenarios 1 and 2 the same number of infected individuals are treated with different types of medications. In scenario 2 more people get virus-free as new medication gives significantly higher healing rates than conventional treatment. Over the time horizon of 3 years a small but observable decrease in new infections and treated individuals occurs in scenario 2. This effect is explained by the decrease in potential carriers of the virus and an overall higher healing rate. In scenario 3 we assume a higher demand for new medication. The number of treated individuals is higher than in scenarios 1 and 2. This design is justified with the information that physicians knew already a few years ago that new therapies were set to enter the market. Therefore doctors told patients to wait with their first treatment until new medications were made available, because chances of become virus-free is higher for individuals that are treatment naïve. In addition to the increase in patients that are expecting to get treatment, we added 50% and 100% of all individuals with cirrhosis to the model in scenarios 4 and 5. In this step especially the effect on the total costs should be investigated as a 'what if scenario' for all potential patients to start treatment. Furthermore, the effect on long-term costs should be investigated in addition to the short time horizon. On the basis of scenario 2, the results of scenario 3–5 show an increasing rate of treated and healed individuals.

In contrast to the epidemiological results, the economic results are not so straightforward. Table 3 shows the total cost as well as costs per patient and per virus-free patient per scenario for the time horizon of 3 years as indexes of the base case scenario with conventional treatment. In general, total costs rise from scenario 1 to 5 as new medication is used and more patients are treated. Therefore total costs for the treatment with new medication is 1.7 to 7.5 times higher than with conventional medication. But as more patients are treated, the number of

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Table 3
Simulation results with indexed costs and epidemiology.

Scenario	Total cost	Cost per treated patient	Cost per virus-free patient	Patients treated with CHC medication	Patients virus-free
1	100	100	100	2.700	1.200
2	171	196	121	2.700	1.700
3	204	186	102	3.400	2.400
4	485	193	99	7.800	5.900
5	751	191	93	12.200	9.700

individuals who become virus-free increases as well. As a consequence of less infected individuals, long-term complications (cirrhosis, cancer and transplantation) as well as their costs decrease. While costs per patient treated are higher with new medication and vary in scenarios 2–5, costs per virus-free patient decrease the more individuals are treated and healed.

Although these initial insights into the complex field of HCV give only a short-term view of the issue of new medication and its effect on patients and the economic burden, the results show clear trends in costs and epidemiology. According to our results, the reimbursement strategies of European countries, which is preferred treatment of patients with cirrhosis, may be inefficient in terms of the ratio of patients healed and money invested. Therefore a deeper insight into modelling HCV is needed to draw final conclusions on reimbursement strategies for new medication for HCV.

5. Conclusion and discussion

The paper at hand presents a decision support model that allows one to test the economic and epidemiological effects of several reimbursement strategies of a novel HCV medication. It was developed in a rather short time horizon in order to allow for sophisticated decisions on reimbursement strategies of the novel medication and their effects on the healthcare system concerned. We therefore used microsimulation in order to evaluate the situation from an individuals' perspective. This is especially beneficial, as treatment history plays a major role in the treatments' costs and probability of success.

The epidemiological results show an obvious trend. As patients get treatment with new medication, healing rates increase and more people become virus-free. The economic results show an increase in total costs in all scenarios as new medication is used and more patients are treated. As a consequence of less infected individuals, long-term complications and their costs decrease. Therefore costs per patient treated increased with the number of patients treated, but costs per virus-free patient decrease the more individuals are treated and healed.

In spite of robust results, our findings imply that 3 years are a too narrow time window of analysis for such a decision, as epidemiological effects of extensive treatment strategies lead to savings in the long run. As mentioned above, complications (e.g. cirrhosis, cancer and transplantations) as a consequence of HCV mainly arise after a time period of >20 years. New pharmaceuticals bring healing to patients within on treatment cycle, which is shorter than 1 year. Therefore, the results for 3 years show extensive costs for treatment but are unable to show cost savings which would occur after 20 years due to the reduction of long-term consequences. However, the model at hand does not explicitly consider several aspects such as the situation of infection through *drug abuse* that was identified in the literature review as being crucial. The range of policies and their acceptance would need to be identified in detail for this sub-group. In doing so, *differencing network structures* would also be needed to allow for differentiating in infection behaviour. From todays' perspective one can only make assumptions about the infection behaviour of drug abusers and divergent network effects for society at large. This would also allow for in-depth analysis and comparison of further policies such as free needle exchange. Furthermore, the *prison system* seems to be a hotspot for HCV infections, which would call for another sub-category in the model. Another field of further research is the current movement of *refugees* to Europe, as a group of people with significantly higher incidence rates is joining central Europe. The question whether this could increase the incidence among European citizens might also be evaluated in a comparable simulation model but would require far more input data. However, due to the fact that infections mainly take place through drug abuse and not through common social contact, it is assumed that this aspect will not play an important role in further infections.

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