Final Project: Clinical Decision Support System for Hepatitis C

Stephen Levinson, Tracy V. Nunnery and John Wong

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INTRODUCTION

Background

Hepatitis C is a viral illness transmitted from one person to another via blood. Hepatitis C risk factors include: history of intravenous drug abuse, HIV infection, organ transplant or blood transfusion recipients prior to July, 1992, hemophiliacs who received clotting factors infusions prior to 1987, and children born to HCV positive mothers. This disease is asymptomatic in the initial stages, but over the course of decades can result in progressive liver damage leading to cirrhosis with associated complications, extrahepatic manifestations, and liver cancer. Infection is chronic in 75-85% of patients (Smith et. Al 2012). Potential complications include: ascites, hepatic encephalopathy, bleeding esophageal varices, and death. Hepatitis C is the most common cause of liver disease leading to liver transplantation (Ghany, M., Strader, D., Thomas, D., & Seeff, L. ,2009).

The most recent prevalence data on Hepatitis C comes from National Health and Nutrition Evaluation Survey (NHANES) of non-institutionalized patients. Using data collected between 1988 and 2008, Chak, E., Talal, A., Sherman, K., Schiff, E., & Saab, S. (2011). estimate the prevalence of Hepatitis C in the United States at 1.5% (or 3.9 million people) exclusive of homeless and incarcerated patients. Estimates of Hepatitis C in these latter populations fall in a range of 500,000 to 1,000,000 additional infected patients.

The natural history of Hepatitis C is variable, usually evolving over three or more decades. In various studies, 10-40% of patients with Hepatitis C progress to chronic liver disease, and 60-90% of patients remain healthy (Craxi, A. et al 2012). In one meta-analysis involving 111 studies, the 20 year prevalence of cirrhosis in patients infected with Hepatitis C was 16% (Thein, H., Yi, Q., Dore, G., & Krahn, M. 2008).
There are a number of patient-specific factors (Figure 2) that are associated with clinical progression of Hepatitis C including: age, viral load, race, concomitant alcohol use, fibrosis (scarring) on liver biopsy, and HIV status. The degree of fibrosis (and inflammation) on liver biopsy has great prognostic significance. According to a study by Ryder, S. (2004), fibrosis on a liver biopsy is a risk factor for progression of Hepatitis C.

Treatment Guidelines

Two American Association for the Study of Liver Disease (AASLD) guidelines published in 2009 (Ghany, M., Strader, D., Thomas, D., & Seeff, L. 2009) and 2011 (Ghany, M., Nelson, D., Strader, D., Thomas, D., & Seeff, 2011) respectively provide a framework for treatment. Treatment for Hepatitis C has evolved to a 2 or 3 drug cocktail, depending on viral genotype. There are six
genotypes of Hepatitis C. In the United States genotype 1 is the most common, accounting for 60-70% of cases. Genotypes 2 and 3 comprise the bulk of the remaining cases. Other genotypes are rare. For treatment purposes, stratification of patients is based on genotype. According to the guidelines, genotype 1 patients who are likely to progress to cirrhosis or liver cancer and who have no contraindications (Figure 3) should be treated.

Figure 3: Contraindications to Treatment

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active autoimmune hepatitis or other condition known to be exacerbated by interferon and ribavirin (Rebetol)</td>
</tr>
<tr>
<td>Known hypersensitivity to drugs used to treat HCV infection</td>
</tr>
<tr>
<td>Pregnant or unwilling to comply with adequate contraception</td>
</tr>
<tr>
<td>Renal failure (contraindicated for ribavirin only)</td>
</tr>
<tr>
<td>Severe concurrent cardiopulmonary illness</td>
</tr>
<tr>
<td>Uncontrolled major depressive illness, psychosis, or bipolar disorder</td>
</tr>
<tr>
<td>Untreated hyperthyroidism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decompensated cirrhosis:</td>
</tr>
<tr>
<td>Albumin level less than 3.4 g per dl (34.00 g per L)</td>
</tr>
<tr>
<td>Evidence of encephalopathy or ascites</td>
</tr>
<tr>
<td>International Normalized Ratio greater than 1.5</td>
</tr>
<tr>
<td>Platelet count less than 75 x 10^9 per mm^3 (75.00 x 10^9 per L)</td>
</tr>
<tr>
<td>Total serum bilirubin level greater than 1.5 mg per dl (25.66 μmol per L)</td>
</tr>
<tr>
<td>Baseline hematologic and biochemical indices:</td>
</tr>
<tr>
<td>Hemoglobin level less than 13 g per dl (130.00 g per L) for men and 12 g per dl (120.00 g per L) for women</td>
</tr>
<tr>
<td>Neutrophil count less than 1,500 per mm^3 (1.50 x 10^9 per L)</td>
</tr>
<tr>
<td>Serum creatinine level greater than 1.5 mg per dl (132.60 μmol per L)</td>
</tr>
</tbody>
</table>


Most experts recommend performance of a liver biopsy prior to consideration of therapy for patients with genotype 1. For patients who have fibrosis on biopsy, current algorithms default to treatment. Treatment consists of Standard therapy (Pegylated Interferon, either Pegasys or Peg-Intron weekly injections and weight based Ribavirin pills) in combination with a Protease Inhibitor (either Telaprevir or Bocepravir) for 48 weeks. The physician must check that the patient is on no other medications that could potentially interact adversely with the treatment medications. Treatment is response-guided (Figure 4). This means that viral load is determined at specified intervals after the initiation of treatment. If the viral load undergoes a 2 log decline compared to baseline by 12 weeks (early viral response or EVR) or is undetectable at four weeks (rapid viral response or RVR), then treatment continues for a specified interval according to the algorithm. If the viral load declines by less than two logs at twelve weeks or remains detectable at 24 weeks, then futility rules ensue and treatment is terminated. Treatment generally continues for 48 weeks.
For patients with genotype 2, algorithms default to treatment. Treatment consists of two drug therapy, with Pegylated Interferon (either Pegasys or Peginterferon) and Ribavirin for 24 weeks, also according to a response-guided algorithm (Figure 5). The guidelines do not recommend determination of liver biopsy fibrosis status as a precondition to treatment.

(Source: Craxi, et. al. 2010).

Figure 5: Hepatitis C, Genotypes 2 and 3 Response Guided Treatment

(Source: Craxi, et. al. 2010).
A number of patient specific variables are predictive of response to treatment (Figure 6). The most important for treatment purposes is viral genotype. According to Ghany et. al (2011), double therapy consisting of Peginterferon and Ribavirin for 24 weeks produced an 80% SVR for genotypes 2 and 3 patients, and the same therapy for genotype 1 patients treated for 48 weeks produced a 40-50% SVR rate.

Another predictor for response to Genotype 1 is a gene called IL28B on chromosome 19. There are two alleles for IL28B, T and C. Patients who are homozygous for T will have a 70% SVR rate with two drug therapy (Pegylated Interferon and Ribavirin) and 90% SVR rate with triple therapy (Pegylated Interferon, Ribavirin, and Protease Inhibitor). Patients who are homozygous for C or heterozygous will have corresponding SVR rates of 30% and 70% respectively (Liu, S., Cipriano, L., Holodniy, M., Owens, D., & Goldhaber-Fiebert, J. 2012). Additional predictors of response include: findings on liver biopsy, viral load, age, BMI, race, sex, and HIV status.

Figure 6: Predictors of Sustained Viral Response

![Predictors of Sustained Viral Response](source)


During treatment, the physician must carefully monitor CBC for the development of anemia, thrombocytopenia, or leukopenia and thyroid status for the potential development of autoimmune thyroiditis. The presence of cytopenias would trigger dosage adjustments or cessation of therapy depending on the levels. Also, the physician must monitor for potential side effects (Figure 7) that could prompt dosage adjustments, referral for treatment of complications, or discontinuation of treatment.
Figure 7: Adverse Effects of Therapy for Hepatitis C

<table>
<thead>
<tr>
<th>Frequency (%)</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td><strong>Cardiovascular</strong>&lt;br&gt;Angina pectoris; heart failure; myocardial infarction</td>
</tr>
<tr>
<td></td>
<td><strong>Neurologic</strong>&lt;br&gt;Coma; confusion; neuropathy; retinal hemorrhage; seizures; stroke; tinnitus; vision loss</td>
</tr>
<tr>
<td></td>
<td><strong>Psychiatric</strong>&lt;br&gt;Acute psychosis; attempted suicide; hearing loss; panic attacks; suicidal ideation</td>
</tr>
<tr>
<td></td>
<td><strong>Other</strong>&lt;br&gt;Autoimmune diseases: renal, cardiac, or pulmonary failure; worsening of hepatitis</td>
</tr>
<tr>
<td>1 to 5</td>
<td><strong>Psychiatric</strong>&lt;br&gt;Severe anxiety and depression; substance abuse or relapse of alcohol abuse</td>
</tr>
<tr>
<td></td>
<td><strong>Other</strong>&lt;br&gt;Induction of autoantibodies; severe bacterial infection</td>
</tr>
<tr>
<td>&gt; 5</td>
<td><strong>Constitutional symptoms</strong>&lt;br&gt;Athralgia; fatigue; fever; malaise; myalgia; nasal stuffiness</td>
</tr>
<tr>
<td></td>
<td><strong>Dermatologic</strong>&lt;br&gt;Hair loss; itching; photosensitivity; rash</td>
</tr>
<tr>
<td></td>
<td><strong>Gastrointestinal</strong>&lt;br&gt;Abdominal discomfort; diarrhea; nausea; poor appetite</td>
</tr>
<tr>
<td></td>
<td><strong>Hematologic</strong>&lt;br&gt;Anemia; hemolysis; neutropenia; thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td><strong>Neurologic and psychiatric</strong>&lt;br&gt;Anger; anxiety; depression; difficulty concentrating and sleeping; emotional lability; headache; irritability; memory loss</td>
</tr>
<tr>
<td></td>
<td><strong>Other</strong>&lt;br&gt;Local erythema, pain, or abscess at injection site</td>
</tr>
</tbody>
</table>


**Hepatitis C Decision Considerations**

Hepatitis C is a complicated disease on two levels, patient decision-making prior to treatment and physician management once treatment is initiated. Patients with Hepatitis C face a difficult decision regarding whether to undergo treatment, and a corollary decision about whether to undergo liver biopsy. The rationale for treatment is to achieve SVR and thereby avoid attendant complications of cirrhosis, extrahepatic manifestations, and liver cancer. Because of the expense, side effects, and morbidities, treatment is ideally directed at those patients likely to progress to cirrhosis or liver cancer and is withheld from those likely to remain healthy. Liver biopsy is recommended to stratify patients. Those with fibrosis on liver biopsy are selected for treatment, since they are more likely to progress to cirrhosis. Those with no or minimal fibrosis are treated on a case-by-case basis.
Reasons to forgo treatment include: the decades long delay between infection and complications in asymptomatic patients, the benign course of Hepatitis C in the majority of patients, the morbidities and side effects associated with treatment, the requirement of frequent clinical monitoring for side effects, the incomplete efficacy of treatment, the availability of better drugs now in development, the statistical likelihood of a benign clinical course in most patients, and the presence of contraindications.

One potential barrier to treatment is the cost. According to the study by Liu et al. (2012), Pegasys and Ribavirin cost $950 per week (wholesale price), a total of $45,600 for a 48 week course of treatment. In patients with Genotype 1, the addition of Telaprevir will add $49,200, for a total cost of $94,800. These costs are exclusive of costs incurred for laboratory monitoring and medical care during treatment.

The treatment is also complicated for physicians to administer. Treatment is a clinic based endeavor requiring that physicians have access to treatment protocols and algorithms for each genotype, with additional protocols to address special circumstances like HIV status, prior treatment failures, chronic renal failure, and post-transplant status. The treatment requires careful monitoring of potential drug interactions between HCV treatment drugs and drugs on an individual patient’s medication list. The treating physician needs to have patient demographic and historical information immediately available including race, weight, age, psychiatric history, substance abuse information, and information about potential complicating illness such as cardiac or renal disease. The physician also needs a treatment timeline that documents the date of treatment initiation, followed by a longitudinal display of relevant lab values, clinical side effects, and treatment decisions (e.g. dose modifications, treatment discontinuation, or subspecialty referral for evaluation of complications) at each clinic visit. Finally, the physician needs to have access to up to date lab information at each step in the treatment algorithm (every clinic visit). The treatment algorithms involve multiple decision points based on clinical status, blood counts, viral load, and the presence or absence of side effects.

HEPATITIS C CLINICAL DECISION SUPPORT SYSTEM

Clinical Decision Support Goals

A decision support application that addresses the complexities of Hepatitis C treatment would be a useful clinical tool at the point of care. To be effective, such a tool should be formulated with four objectives:

1. Provide guidance for diagnosis
2. Assist patients with the decision to treat and associated uncertainties, by formulating a
decision tree with chance node probabilities determined by review of relevant literature and
patient utilities incorporated into each outcome
3. Assist patients with the decision to undergo liver biopsy
4. Assist physicians with monitoring and directing ongoing treatment in accordance with
accepted algorithms, once the decision to treat is affirmatively made

Provide Guidance for Diagnosis

The diagnostic algorithms for Hepatitis C are fairly straightforward and could be managed
without CDSS by most physicians who treat Hepatitis C on a regular basis.

Decision to Treat

The decision to treat is not straightforward. Review of the literature does yield studies which
address decision making from a societal level. One study by Liu et al addresses the cost effectiveness of
adding protease inhibitors to standard therapy (Peginterferon and Ribavirin) for patients with genotype
1 Hepatitis C. Using a Markov decision making model to determine Quality Adjusted Life Years and
Incremental Cost Effectiveness Ratios (cost per QALY saved), Liu et al conclude that treatment with
protease inhibitors is cost effective, especially for patients with advanced fibrosis. Similarly, Saab, S.,
Hunt, D., Stone, M., Mclune, A., & Tong. M. (2010) employed a Markov decision model in which they
compared standard therapy in patients with varying degrees of fibrosis on liver biopsy and determined
that treating patients with compensated cirrhosis yields the most favorable Incremental Cost
Effectiveness Ratio. From a societal or payer perspective, these studies provide guidance about the cost
effectiveness of treatment, especially relative to other interventions such as dialysis. The threshold for
treatment for Hepatitis C genotype 1 is comparable to other interventions. Malone, D., Tran, T., &
Poordad, F. (2005) performed decision tree analysis incorporating utility values of 1 for SVR and 0 for
no SVR to compare two different treatment regimens for Hepatitis C. Their analysis included genotypes
1-3 and was performed from “from the viewpoint of a managed care organization”. From a MCO
perspective, treatment of Hepatitis C was more cost effective with a weight-based Interferon (Peg-2b).

From an individual patient point of view, review of cost effectiveness studies performed from a
group perspective does not usually assist with decision choices. A web search quickly yields a large
number of patient support web sites that provide information on natural history, prognosis, and
treatment. One representative site, called HCV Advocate sponsored by the Hepatitis C Support Project
by two patients with Hepatitis C (Porter, L. & Franciscus, A. 2012). This provides a detailed and
excellent discussion of factors which impact treatment, and provides multiple worksheets to facilitate decision-making. A decision application based on a decision tree that assigns individual utility values to each outcome could provide additional assistance to undecided patients and their physicians.

**Decision to Undergo Liver Biopsy**

The decision to undergo liver biopsy is tied in with the decision to treat. The treatment guidelines from AASLD recommend treatment without the need for biopsy for genotypes 2 and 3 based on the high SVR rate. Prior to release of Protease Inhibitors, the 2009 AASLD guidelines advocated performance of a liver biopsy with genotype 1 patients because of the lower SVR between 40% and 50%. The liver biopsy could discriminate, based on fibrosis score which patients were more likely to progress, and thereby benefit from treatment. With the addition of Protease Inhibitors to the Genotype 1 regimen, the SVR rate rivals the rate for genotypes 2 and 3. However, experts still recommend performance of a liver biopsy for genotype 1 because of the significant added cost (Private communication S. Saab, 2012). However, patients are understandably hesitant to undergo a procedure which is typically painful and which involves a degree of risk. A decision node, incorporated into a larger Hepatitis C decision tree that evaluates the utilities of liver biopsy and the associated outcomes, could assist patients and their physicians with the decision to perform vs. forgo liver biopsy.

**Assist Physicians with Monitoring and Directing Treatment**

There are multiple treatment algorithms for Hepatitis C, each with a degree of complexity that can be intimidating. Adherence to these protocols is time and staff intensive, requiring clinical patient monitoring, ordering and retrieving lab data, comparing lab data and clinical status to protocols to make treatment decisions, reviewing potential drug interactions, memorializing each encounter and decision in the Electronic Medical Record, and scheduling follow up clinic visits. A decision application that automates these tasks would have the potential to improve workflow, simplify and organize treatment, and reduce errors of commission and omission.

**Stakeholders**

Based on the above mentioned clinical decision support objectives, our CDSS intervention will provide valuable benefits to the following groups:

**Patients**

Even though the diagnosis of HCV is relatively straight forward, we can still take advantage of a CDSS system by proactively checking the patient's own medical history, along with updated information provided by the patient's self assessment form. The combined information will allow the
system to provide a more accurate risk profile of the patient, and thus be able to recommend a treatment plan that is customized to the patient's need. In addition, specific information such as viral load count will be tracked throughout the treatment duration. This will help qualify if the patient has achieved early viral response (EVR), which can help determine the type, duration and dosage of the remaining treatment regimen. Furthermore, the CDSS alerts can help to avoid any possible adverse drug event (ADE) for the patient. And lastly, a CDSS reminder system can remind the patient of upcoming followup visit.

**Payers**

For the payers, the CDSS system will help to reduce the cost of managing the long term care of such chronic disease like HCV via improved care management. The evidence base treatment plan with continuous adjustment based on specific viral load evidence will minimize any possible disputes in claims. It will also track compliance, quality and performance measures. The combination of reduce costs and improve patient outcome will increase member satisfaction.

**Employers**

A CDSS system that can provide the most optimal treatment can increase the probability of a patient to achieve SVR. This will result in fewer sick leave from the patient, and more productivity due to better health outcome.

**Providers**

For providers, the CDSS system will provide extremely valuable assistance to keep track of a patient's treatment history. Upon the request of the physician, the CDSS system can provide the optimal treatment plan for a patient, based on his / her latest viral load count. The physician can spend more quality face time with a patient, instead of spending the time reviewing treatment progress and adjusting treatment plan. The CDSS can provide active alerts during CPOE to avoid potential drug to drug interactions with any of the triple therapy drugs and the drugs on the patient's medication list. The web services and knowledge engine can also assist the physician with latest industry findings on Hepatitis C treatment. It can also, provide a convenient mechanism for the physician to provide feedback on the recommended treatment guidelines. Similar to how the reminder system can help the patient, it can also provide helpful reminder.

More specifically, from the list of clinical objectives defined in earlier section, and the list of CDSS intervention that we will be introducing to meet the various objectives, we can identify a detail
breakdown of the list of stakeholders in our hospital, and their roles in each one of the clinical objectives that will be met by our CDSS System (See Appendix 1).

**Intervention Selection**

The CDSS to assist with Hepatitis C will function at the point of care, in the clinic. This application will be integrated with the EMR and CPOE/eprescribing module and will be accessible via a client server that interfaces with the EMR, or via a tablet-based appliance such as an iPad enabled for network access. Once the physician determines the likely diagnosis of Hepatitis C, the physician activates the Hepatitis C CDSS application. The CDSS will be integrated with the EMR, and all relevant information from the EMR including demographics, physical exam elements, and laboratory data will populate the application. Any data relevant to treatment, but missing from the EMR will prompt the physician for the missing information.

The application will first confirm the laboratory diagnosis of Hepatitis C according to Hepatitis C diagnostic algorithms (Appendix 2).

The patient decision module will consist of a decision tree program for Hepatitis C treatment, with the decision node of Treatment vs. No Treatment, and chance nodes for Genotype, viral load, BMI, and other demographic factors relevant to treatment outcome. An optional chance node will account for the presence or absence of fibrosis on liver biopsy. Once the patient is diagnosed with certainty, the patient, with the assistance of a trained clinic staff member will complete a utility questionnaire based on the standard gamble, to assign utilities to various terminal outcomes on the decision tree. The staff member will input the patient utility results and verify the accuracy of the migrated EMR data. The decision application will fold back the decision tree to arrive at a patient optimized result. Probabilities assigned to each branch of the chance nodes will be culled from reliable published studies at the discretion of the physician responsible for knowledge maintenance. Migrated data items from the EMR, such as: genotype, viral load, BMI, and age will populate the branches of the decision tree.

The physician management module will be a knowledge-based application with logical If..then programming rules. The knowledge engine will be integrated with the EMR and will pull demographic and lab data from the EMR database. This will necessitate that specific patient data be input as structured data rather than non-searchable free text. Lab data will be downloaded directly from the lab, using a standard ontology such as LOINC integrated into the knowledge base. A menu of treatment
algorithms from the latest clinical guidelines will be programmed into the knowledge base. Once a treatment decision is made, the appropriate algorithm will be activated.

**Workflow without CDSS**

The treatment of Hepatitis C is clinic based, time intensive, and staff intensive. The typical interface between physician and patient involves an initial clinic visit, usually of a patient referred to a liver specialist (Gastroenterologist or Hepatologist) for evaluation of elevated liver enzymes or with known Hepatitis C. The physician takes a history, examines the patient, formulates a diagnostic plan, memorializes the encounter, and schedules a follow up appointment to discuss the results. The patient returns to the office, and the physician discusses the diagnosis of Hepatitis C, reviews the natural history of the disease, discusses treatment options and scenarios, provides web based and other resources for patient education, and discusses the potential value of a liver biopsy. During a subsequent visit, the physician and patient meet to address patient questions and concerns and to discuss treatment options. Usually, over the next few clinic visits, the physician will often address patient indecision and speak to other family members who might influence the decision-making process. If the patient decides to move forward, and agrees to a liver biopsy, then the physician orders the biopsy. When the biopsy result is available, the physician meets again with the patient to discuss the biopsy result and the appropriateness of treatment based on the biopsy result. If the patient opts for treatment, the physician reviews the algorithm most specific to patient circumstances (e.g. Genotype 1, no prior treatment, HIV negative), reviews the patient’s medication list to check for potential drug interactions, and orders the medication.

Once the treatment is approved by the insurance company, the office must arrange for educating the patient on injection technique and on the specific requirements for clinic follow up and blood testing. The patient must get specific lab work performed and return to the clinic at proscribed intervals. At each clinic visit, the physician reviews the patient demographics and treatment timeline, examines the patient, and elicits a history about treatment side effects and tolerance. The physician then must review the protocol and make decisions about potential dosage adjustments and treatment duration, based on CBC and viral load data respectively. This process continues at regular intervals until either treatment is terminated early because of adverse side effects or until 6 months after the recommended duration of treatment to document an SVR.

**Workflow with CDSS**

With a Clinical Decision Support Tool to assist with decision-making and treatment, the workflow will change. After the physician confirms the diagnosis, the physician would then discuss
treatment options and offer the patient access to the utility-based decision tree. The result of this analysis would provide a frame of reference for the physician in discussions with the patient about treatment and liver biopsy. Similarly, the result could assist the patient with decisions.

If the patient decides to have a biopsy, or alternatively opts to undergo treatment without biopsy, then the treatment algorithm specific to the patient’s circumstances would be activated. For example, if the patient had genotype 1 and was treatment naïve, then the protocol for genotype 1, treatment-naïve patients would go into effect. The CDSS would recommend the appropriate drug combination, scan for potential drug interactions with the patient’s existing drugs, flag any potential contraindications, and then populate the appropriate fields in the eRx module of the EMR. The application would then prompt the physician to arrange for patient lab and clinic follow up at an appropriate interval. At the next clinic visit (and subsequent visits), the patient would open the EMR, open the CDSS and review the timeline. Then the physician would review the lab, examine and evaluate the patient, and document the interaction in the EMR. The CDSS would review the lab and the reported side effects, and in accordance with the algorithms, would determine any dosage adjustments, invoke futility rules if appropriate, display a recommended treatment duration, and prompt the physician to order subsequent lab and to schedule a subsequent clinic visit. This would repeat until the patient completes treatment and follow up.

Based on the list of objectives and desired action described in the stakeholders section, a high level description of the various intervention types, and how they can be integrated into a typical clinical workflow for HCV treatment, can be found in Appendix 3.

**INTERVENTION SPECIFICATION**

**The Model: High Level Overview**

In order to meet the clinical objectives for the treatment of Hepatitis C patients, we will be using a CDSS system to handle predetermined complex treatment protocols that needs to be followed and adjusted over a long period of time.

(Source: Berner, 2007)
Specifically, we will be implementing a CDSS system that is embedded into our existing EMR system by the use of web services using service oriented architecture (SOA).

The physician would interactively invoke the program and solicit recommendations from the CDSS. The model consists of a decision tree application to facilitate utility-based patient decisions, and predicate logic-based if-then rules to encode the approved practice guidelines published by the American Association for the Study of Liver Disease (AASLD) (Keefe, 2010) and endorsed by the National Quality Foundation (NQF).

As discussed in various articles, the use of SOA will allow the sharing and interaction of our CDSS system among various "loosely coupled co-operative services (Jahnke-Weber, 2012). Since our CDSS systems belongs to a category of standards-based systems (Wright, 2008), it will be built using Arden Syntax standard that is approved by the American National Standards Institute (ANSI) and is maintained by the HL7 organization.

Specifically, our Arden Syntax knowledge base is made up of many medical logic modules (MLMs) (Fehr, 2011). Since temporal variables that track the history and viral load count of HCV patients, are extremely important factors in the determination of a patient's treatment regimen, it makes sense to use Arden syntax MLM that combines if-then rules with procedural formalism to evaluate patient's data over time. The Arden Syntax MLM is interpreted and compiled by an Arden Syntax compiler and executed by an Arden Syntax engine. A MLM manager sits on top of the compiler and engine to manage data exchange and communication with other application.

(Source: Fehr, 2011)

Data exchange with other application will utilize web services on standard communication protocols using XML. In general, the specific HL7 Arden Syntax MLM request is embedded inside an XML document, and the corresponding XML document is wrapped into a Service Oriented Architecture protocol (SOAP) message (See figure). The message is transferred via HTTP. An enterprise service bus will be used to manage and ensure that the message will reach its destination and any applicable reply will be transported back to the requesting application.
Knowledge Management

The knowledge content is authored, reviewed and deployed by our Knowledge Review Organization (KRO), which consists of members from interdisciplinary teams. The inference engine will combine user input and data from the knowledge base to arrive at two types of output, a guideline-based treatment guidance and a utility based patient decision. The CDSS will also have an external web search engine that can monitor websites for additional references.

The problem of knowledge maintenance is important for all types of CDSS, not just the alerts and reminders (Berner, 2009). Therefore, in order for our CDSS system to provide accurate and up to date information, we will adopt a collaborative knowledge management approach, similar to the one imposed by IHC, in which "knowledge experts retain the authority to create and modify most of the knowledge content necessary for the CPOE system" (IHC, 2009). During the implementation phase of the CDSS system, our KRO team will review approved practice guidelines from reputable sources such as the American Association for the Study of Liver Disease (AASLD). The initial set of rules will be agreed upon and entered into the knowledge base. On a regular basis, the KRO will actively monitor latest news and guidelines on the diagnosis and treatment of HCV. Potential and promising proposal will be authored, and submitted to the committee on a quarterly basis for review and discussion. Upon the approval of the proposal, the updated guideline will be entered into the knowledge engine repository and will be incorporated by the inference engine. Upon the invocation of the CDSS by the physician, the appropriate treatment plan will be provided. The physician can elect to adopt, reject, or modify the suggested plan. All acceptance, rejection, and modification, with detail explanation by the physician, will be captured. The KRO will meet every quarter to review the associated metrics, and recommendations will be proposed to amend, add, or delete information from the knowledge engine.
Furthermore, data mining and business intelligence analysis will be performed on historical data, to uncover any potential trend regarding patients' profile, drug information, treatment regimen, etc. The goal is to achieve continuous quality improvement, with updated logistic regression analysis that can help with more accurate prognosis and more appropriate treatment plan.

In addition to evidence based knowledge, the treatment of HCV is also highly dependent on inputs from other sources. These inputs will be incorporated into the local EMR using standard HL7 protocol:

- Direct data exchange with our EMR database
- Data entry input from patient's self assessment forms
- HCV Viral Load laboratory results
- Genotype tests results
- Liver biopsy results

Since temporal information is vital in the treatment process, our CDSS system will also have a time drive module to keep track on the HCV viral load throughout the course of the treatment.

Based on the above inputs, and combined with information from the knowledge base, our inference engine can provide the following web accessible outputs:

- Initial CPOE order sets and treatment flowsheets
- Alerts for drug contraindication
- Educational printouts for patients
- Scheduling and reminder of followup visits
- Graphical viral load trend analysis for prognosis and treatment duration
- Updated patient self assessment form to determine tolerance of drugs
- Updated CPOE order sets for the remainder of treatment
CDSS Intervention: Architecture, Design and Implementation Detail

As mentioned in the overview, the application will contain three modules. The first is a diagnostic module with logic-based if…then rules written in accordance with the latest diagnostic algorithm (see appendix 1).

The second module is a decision tree. An abbreviated tree is demonstrated in Figure 8. This decision tree is formulated to include all of the potential outcome paths encountered in practice. The decision tree can be expanded to include prognostic indicators at appropriate chance nodes. These indicators include IL28B status, genotype, race, age, BMI, HIV status, concomitant alcohol usage, and viral load. These prognostic indicators would impact the probability of a SVR and would be placed proximal to the SVR branch of the chance node. All probabilities would be populated into the decision tree using data collected from large clinical studies referenced in AASLD treatment guidelines. Individual utility data would derive from questionnaires completed by patients using a standard gamble approach. Terminal node outcomes would be rated by the patients and a value between 0 and 1 would be assigned to each terminal node.
Figure 8: Decision Tree: Treat vs. Forgo Treatment, Liver Biopsy vs. No Liver Biopsy
The third module is a treatment module with specific treatment algorithms written in accordance with the latest AASLD guidelines. This module will be a logic-based application, also with if…then rules in accordance with the specific algorithm. Figure 9 shows the logic rules for Hepatitis C, genotype 1, treatment naïve patients, Telaprevir plus standard treatment (Peginterferon and Ribavirin). This chart addresses the timing of viral load determination during the course of treatment. Depending on the result of a quantitative viral load or whether the virus was merely detectable, the physician would follow one of three paths: continue treatment, modify the duration of treatment, or discontinue treatment. The rules engine would be programmed to include the subsets of patients covered by the published guidelines. For genotype 1 patients, this would include flow charts addressing both treatment naïve and treatment experienced patients. This former category would include patients without cirrhosis and those with compensated cirrhosis. This latter category would include prior relapsers (undetectable at end of treatment, but detectable within 24 weeks after treatment), prior partial responders (> or = to 2 log decrease in viral load compared to baseline, but detectable at end of treatment), and prior null responders (< 2 log decrease in viral load at 12 weeks). For genotype 2 and 3 patients, similar flow charts would be programmed specifying rules for dual therapy with Peginterferon and Ribavirin.

Figure 9: Logic Rules for Genotype 1, Treatment-Naïve, Telaprevir-based Therapy (According to viral load determination)

The rules engine will also contain logic-based rules governing the response to CBC values at predetermined intervals. For patients with genotype 2 or 3 for example, a Hemoglobin level < 10 would prompt a Ribavirin dose reduction from 800 mg to 600 mg. daily, and a level < 8.5 would prompt...
discontinuation of Ribavirin. Similar rules based responses to leukopenia (decreased white blood cell count) and to degrees of clinical depression would prompt dosage adjustments to Peginterferon.

**Change Management**

Treatment of Hepatitis C is labor-intensive, time-consuming, and complicated. The algorithms that govern treatment involve rigid rules and necessitate careful attention to detail. In response to any new treatment, and prior to CDSS installation, the stakeholders at each clinical setting will evolve a workflow that optimizes efficiency (given resource limitations) at that site. A CDSS for Hepatitis C offers the potential to assist with decision analytics and to streamline workflow, but at the risk of perturbing such time-tested routines. The ultimate goal is to embed evidence-based clinical guidelines into clinical practice to improve patient outcomes. As Osheroff et. al. (2012) points out, success with a CDSS requires “an environment where improvement is a cultural priority”. Additional prerequisites to successful CDSS implementation include an organization’s “adaptive reserve” and a leadership structure to effect change. The leadership must have an explicit objective, and a plan to achieve the objective. Leadership should consist of stakeholders invested in the outcome, who can address the politics of the organization, sell the plan, and achieve participant buy-in. The actual CDSS implementation will require a master blueprint, an inventory of resources, and open channels of communication with all involved. Stakeholders should have a role in planning and implementation. Prior to “go live”, the clinicians who will be using the CDSS should undergo training on the system and should have the option to practice with simulated patient encounters. The ramp up to full usage should be gradual to facilitate workflow integration. After the CDSS comes on line, dual systems (new and old) can be used until clinicians achieve facility with the CDSS. Undoubtedly, setbacks and workflow interruptions will intervene, but a committed group of participants should be able to adjust and compensate. An organization seeking to improve as a cultural imperative should be open to a CDSS, that if successful, offers the promise of both outcome and workflow enhancement.

**Information System Inventory**

The system should be designed with the following technical objectives in mind as guiding principles:

1. Highly scalable and extensible technologies
2. Interoperability with other systems
3. Standards-based vocabularies
4. Evidence-based rules engine and knowledge bases
From a technology-based perspective, the technologies needed for a robust CDSS must be highly scalable, extensible and interoperable. The system should be able to grow in size as without the need for changes in the overall architecture to accommodate more users, a greater volume of rules engine data or increased capacity needs. The system should also be flexible in that the application should be agnostic regarding the software and hardware on which it depends.

One of the most critical aspects of technical design is the ability of the system to be interoperable with other systems. Through health information exchange (HIE) and interoperability between systems, physicians can have access to a record of longitudinal data for a particular patient. Without some means to integrate this healthcare data, patient care can become fragmented. This fragmentation can lead to duplicative tests and procedures, errors, time delays, communication issues among members of the care team and lack of coordination of care. Interoperability at the point of care can facilitate clinical decision support as well as prescription ordering, requests for patient charts, ordering of lab tests, follow-up, CPOE and also promote adherence to best practices and standards of care. Interoperability can not only have an impact on patient care but can also have a financial impact of providers of care through increased efficiencies, increased reporting abilities, reduced delays in lab orders and chart requests and reduced redundancies. “Net savings from national implementation of fully standardized interoperability between providers and five other types of organizations could yield $77.8 billion annually, or approximately 5 percent of the projected $1.661 trillion spent on U.S. health care in 2003” (Walker, 2005).

Standards, Protocols and Ontology

There are a number of standards-based vocabularies (See Appendix 4) which can help in the sharing of data between systems. These include SNOMED, DICOM, LOINC and RxNorm. When systems use standards such as these, data sharing becomes less complicated since there can be an agreement between regarding the meaning of terms. In terms of the actual mechanics of data sharing, there are also standard formats including HL7 CDA, CCR/CCD as well as many other standardized and proprietary formats. These specify the structure of the data being communicated rather than the actual content. Meaningful use and HITECH grants as a part of the American Reinvestment and Recovery Act (ARRA) have components to assist HIE efforts.

As discussed in the Institute of Medicine’s (IOM) Crossing the Quality Chasm, an agenda for meeting the six aims for improving quality of care (safe, effective, patient-centered, timely, efficient and equitable) is outlined. One important component of a successful program for providers of care is to “create an environment that fosters and rewards improvement by (1) creating an infrastructure to
support evidence-based practice, (2) facilitating the use of information technology, (3) aligning payment incentives, and (4) preparing the workforce to better serve patients in a world of expanding knowledge and rapid change” (IOM, 2001).

Figure 10: Evidence-based medicine and Clinical Decision Support Systems Architecture


Of the recommendations from the IOM, the importance of evidence-based rules engines is extremely important to ensure quality of care as well as adherence to established best practices and standards of care. “The use of clinical decision support systems to facilitate the practice of evidence-based medicine promises to substantially improve health care quality” (Sim, 2001). Recommendations for the increased adoption of evidence-based medicine imbedded in CDSS include:

- “Capture of both literature-based and practice-based research evidence into machine-interpretable formats suitable for CDSS use.
- Establishment of a technical and methodological foundation for applying research evidence to individual patients at the point of care.
- Evaluation of the clinical effects and costs of CDSSs, as well as how CDSSs affect and are affected by professional and organizational practices.
- Promotion of the effective implementation and use of CDSSs that have been shown to improve clinical performance or outcomes.
- Establishment of public policies that provide incentives for implementing CDSSs to improve health care quality” (Sim, 2001).

In addition to standard ontologies, the system infrastructure also calls for standardization across its communication platforms and protocols between systems. The system should be designed to facilitate clinical care for physicians using an EMR, from tablets and other mobile devices as well as to interface with other laboratory systems and other data sources. A list of technical standards necessary for this system is described in Appendix 5.

**Design Document and Architecture**

General project design for the CDSS would benefit from the Design for Six Sigma or Define, Measure, Analyze, Design and Verify (DMADV) process (See Appendix 6).

For a complete project specification, the technical design document for this system would need to be structured and contain the information as described in Appendix 7.

A conceptual design of this CDSS to support clinical decision for care of hepatitis C patients can be extremely complex. The architecture of a CDSS such as this is comprised of many disparate systems, operating among various domains. Interoperability requires standardized ontologies and interface standards between them.

At the clinical (client) level, the central component is an electronic Medical record (EMR). This serves as the primary interface for clinicians and consolidates data from multiple sources and also communicates with the web services which provide the CDSS functionally. The clinicians would also be able to access the EMR as well as the CDSS tools from mobile platforms.
External databases are also required so that laboratory, demographic and medication data is available to the EMR. This would also include a hepatitis-specific data-set to store hepatitis-specific data including viral load and genotype. Other systems required include a survey engine to collect patient preferences which could be part of the EMR or a patient-facing personal health record (PHR) as well as a database and system to provide drug interaction information.

The business layer handles communication between the EMR at the client layer and provides security and translational services for service requests. This business layer then communicates with the data layer which houses the data repository for the knowledgebase and the rules engine. This data layer performs the bulk of the necessary processing needed to generate CDSS output. Then, facilitated by the business layer, this output is then transmitted back to the clinicians at the client layer in the form of clinical summary reports and recommendations. Since a centralized core is responsible for maintaining the knowledgebase and rules engine algorithms, results are standardized and consistent across all systems that use the system and is able to adapt when new research or clinical care practices of care are adopted.
Hardware required for a CDSS can be localized or distributed. In a localized system, the EMR, CDSS, knowledgebase and rules engine are all part of the same system. Although it may receive data from external sources, the general infrastructure resides in a single location. This option is limited in that the system cannot take advantage of shared knowledge, may be more costly to implement and support and may be more difficult to interoperate with other systems. A distributed system, such as those using a Service Oriented Architecture (SOA), can be shared among many systems and are built in such a way that allows for disparate systems to connect to various modules. Different systems are able to connect to only the modules they need, regardless of their operating system or the application languages used locally. Using SOA principles, services can be provided from a centralized location, ensuring that all users who connect are accessing the same information, using the same data sources and ontologies. In this case, this distributed environment seemed to have the most practical application for this CDSS.

The two primary clinical care CDSS components for hepatitis C are 1) the initial treatment options for hepatitis patients and 2) recommended treatment for daily disease management. Both components are part of a web-based system and, through the SOA, can be embedded as a function of the EMR with relative ease. These components will access an external knowledgebase and rules engine securely and in real-time using web services architecture. The system architecture also allows the flexibility of servicing requests from an EMR system as well as from mobile platforms.

Figure 12: Conceptual design: Treatment options

First, based on information from the EMR including demographic and lab data, input from the provider and patient preferences, treatment options and associated probabilities would be extrapolated. This is shown in figure 12. The output would include a summary for the clinician including the expected utilities of liver biopsy vs. no liver biopsy. If the patient refuses a liver biopsy, then the decision to treat vs. no treatment would also be calculated and presented.
The second physician-facing component of the CDSS as shown in Figure 13, daily disease management, would be accessed at the point of care and utilized at intervals for patients who are under treatment. This process includes monitoring of each step of the treatment process and adjusting accordingly based on relevant laboratory values (CBC, viral load, etc.), potential drug interactions and stage of treatment. Based on this data, the CDSS recommends adjustments to the patient’s therapeutic regimen, presents a patient summary and a longitudinal view of the patient’s disease state.

Figure 13: Conceptual design: Daily disease management

User Interface

The user experience is of utmost performance when designing a system which is aimed at improving patient care and also providing utility for physicians. This experience and, ultimately, acceptance of such systems hinges on several critical factors including value of service (either real or perceived), ease of adoption, ease of use and overall trust in the system. Delivering a system or tool in such a way that the intended user embraces the new functionality it offer can be a complex task but is critical for a successful implementation. A second (and sometimes secondary) component is the “power” of the quality improvement gains to be had and the “value of service.” There may be positive or negative costs associated with meeting or failing to meet performance measures, improvements and efficiencies in physician workflow and improvements in quality of care. An additional consideration is the total perceived pain of adoption for new initiatives, especially with regard to new technologies. As described by Coburn, consumers will adopt new technology if there is less pain associated with learning and using the technology than there is without it (Coburn, 2006). This total perceived pain is based on how disruptive the new system is on existing practices, the level of user-centered design of the interface and an overall trust of the service provided by the system. In general, the evaluation of the CDSS “should take into account the following four perspectives: (1) appropriate evaluation design; (2)
specification of criteria for determining DDSS efficacy in the evaluation; (3) evaluation of the boundaries or limitations of the DDSS; and (4) identification of potential reasons for “lack of system effect” (Berner, 2007).

This system assimilates input from multiple sources: physician input, patient input, EMR data, external system data as well as data from external knowledge bases and rule engines. The physician-entered data is either directly solicited input for missing values or from previously entered data in the EMR. Patient input is solicited to determine utility values in the initial decision choices regarding treatment options. The EMR data may include information from many sources including medications lists, billing information and demographic data. External data is also incorporated from laboratory systems, external data sets and genotypic data. This collection of data, along with the knowledgebase content, is then used as inputs for the rules engine. The output is then presented to the physician via web services to the EMR and can be used for clinical decision-making. Since CDSS “are most likely to succeed if they can be integrated into a clinical environment so that patient data capture is already performed by automated laboratory and/or hospital information systems” (Berner, 2007), the CDSS engine can be called on-demand by the physician when treatment decisions are to be made and is always available within the EMR. It does not offer unsolicited advice and only alerts users in the case of drug interactions, overdue milestones, out of range values, dosing errors or duplicative tests. All advice from the system can be overridden by the physician and are strictly recommendations for options of treatment. Documentation of the logic used in the treatment options are provided by external links to the supporting documentation provided by the knowledge base.

The user interface design principles should incorporate both human-centered design as well as value-centered design. The design emphasis should be targeted toward providing value to the physician and patient as end users of the system. Based on user feedback, the system should be flexible and responsive to unanticipated needs. “Technology shapes the usage but also usage should shape the technology. A continuous dialogue will be needed between users and technology developers. The technology should not just provide ready-made solutions but also give the users the freedom to innovate new ways of utilizing the technology” (Boehm, 2003), (Cockton, 2004). “System evaluation in biomedical informatics should take place as an ongoing, strategically planned process, not as a single event or small number of episodes” (Berner, 2007). The user interface design should be evaluated using methods that promote a dialogue between the user and system designer.

“Measuring and managing users’ attitudes toward various aspects of information
systems is an important part of making computer systems successful. No clinical computer system can be successful without gaining the support of practitioners” (Berner, 2007). Benchmark testing can be done to measure the technical performance of the CDSS and other methods of acceptance testing can also be conducted including user surveys as well as studies to compare the system with historical controls. “Randomized controlled clinical studies can provide the most valid information about the efficacy of computerized information systems in patient care” (Berner, 2007).

**Usability**

Usability of a CDSS should be carefully considered, utilizing feedback from all user domains, constituents and stakeholders. This type of tool has “the potential to reduce adverse medical events, but improper design can introduce new forms of error. Evaluation of CDSS will be of utmost importance in the future with increasing use of electronic health records. Usability engineering principles can identify interface problems that may lead to potential medical adverse events, and should be incorporated early in the software design phase” (Graham, 2008). Recommendations to avoid these types of issues include the aforementioned feedback loops from stakeholders and early identification usability issues. These are key steps to ensure stakeholders see value in the service, experience a seamless adoption and ease of use and share an overall trust in the system.

**EVALUATION**

In order to measure the effectiveness of our CDSS intervention, we will be conducting both qualitative and quantitative analysis.

Application and functionality wise, we will have an active "feedback" button at the bottom of every screen in our CDSS application. Users can, at any point during the CDSS intervention, click the feedback button to enter any comment and experience they may encounter. In addition, we will also track and monitor users activities in the CDSS log files. The log files will help us to back track and identify the sequence of events that may lead to potential problems and errors reported by the users. At the end of every month, we will send out a survey to the various stakeholders to ask for their feedbacks and suggestion for improvement on the CSDS system. At the end of every quarter, we will conduct face to face interviews with CDSS users to solicit their feedbacks. Based on the objectives defined in implementation section of this paper, we will define our performance goal, and how well did we meet that goal.

CDSS Program Enhancement Plan
Quantitative wise, the logs will give us an idea of how often a physician may utilize the CDSS intervention in helping to define and refine the HCV treatment plans. We will track how closely or differently did the user follow the plan as suggested by the system. We will also monitor the number of alerts triggered, and the number of times the users rejected or accepted the alerts. The results of these assessments will allow us to modify and adjust our CDSS intervention accordingly.

Performance Against Objectives

Performance wise, using information from our enterprise datawarehouse, we will be conducting statistical t-test analysis at months 0, 3, 6, 12, 24 on performance metrics. The performance metrics will consists of standard guidelines as suggested by NQF (see appendix 8), plus other measurements that were agreed upon by our stakeholders. In addition, during the pilot phase of our CDSS implementation, we will conduct a randomized control trial between a control group with no CDSS intervention help versus another group with CDSS intervention support.

Knowledge management wise, as mentioned in the previous knowledge management section, our Knowledge Review Organization (KRO) team will perform periodic assessment and review of the guidelines, rules, and algorithms that are stored in our knowledge base. More specifically, we will assign an expiration date on each of the rules and guidelines, similar to the system utilized by the National Quality Forum. Upon the expiration, our committee will conduct a formal assessment and updates of the existing rules, based on the latest guidelines, information from data mining, surveys, interviews, and randomized controlled trials. We will also enable detail version control so that we can, at any point in time, review prior rules to determine its impact on any particular intervention historically.
All in all, from the combination of the above mentioned evaluations, we will be able to provide an effectiveness analysis of our CDSS intervention. We can then devise an enhancement and improvement plan to provide continuous improvement to our CDSS system.

DISCUSSION

As we mentioned in previous sections, the most difficult piece in the management of HCV treatment, is the coordination of a multitudes of information over a long period of time, to result in the best medicine regimen, dosage, and duration, that is most suitable for the particular patient. Given the fact that the underlying information for the various components of our proposed CDSS system, namely, the diagnostic module, the decision tree, and the treatment module, are already well defined, we believe that we have all the necessary pieces of the puzzle ready, for the implementation of our CDSS system.

Furthermore, since the diagnosis of HCV is quite straightforward, we will only implement the treatment module of our CDSS system, in phase 1 of our CDSS implementation. Also, during the pilot / beta phase, we will be using our CDSS system to treat adult chronic HCV patients with genotypes 1 to 4, and with no other comorbidities such as HIV infection.

After the pilot / beta phase, we will include additional rules and rollout subsequent CDSS interventions and treatment plans for the following HCV patients:
- Acute HCV
- HCV – HIV patients
- Children (< 18 years old)
- Patients with decompensated cirrhosis
- Patient with liver transplant

After phase 1, we will include diagnostic and testing modules in our CDSS system, to help physicians in lab testing order entries such as Anti-HCV test, HCV-RNA testing, liver biopsy testing, and genotype testing.

In addition, as we mentioned throughout this paper, keeping the information, rules, and guidelines up to date in our knowledge base is one of the most important tasks to ensure the effectiveness of our CDSS system. For our initial CDSS implementation, we want to have more control over the knowledge base, that the information is more applicable to our local demographics, therefore, we would keep and maintain our own local knowledge base. However, as time progress, we may find that it may
be more practical to share a centralized knowledge base and engine, with other health care organizations. Since we are already adopting a service oriented architecture approach for the exchange of information among the various applications within our hospital systems, it would be an easy and natural transition to connect our internal CDSS system with the shared knowledge engine. In such a shared model, members from our knowledge review organization will serve in the shared knowledge base committee. This would allow the shared community to quickly respond, review, and adopt the latest findings for the treatment of HCV (e.g. the just published findings of the use of triple protease inhibitors without using interferon for those who cannot tolerate the side effects of interferon (Kowdley, 2012)), and to ensure that our CDSS system is using the latest evidence based knowledge that is approved and used by our industry.

**CONCLUSION**

The complete management of Hepatitis C (HCV) involves many different CDSS intervention types that traverse throughout the care lifecycle of HCV. The pre-diagnostic workflow for HCV detection (Anti-HCV test for confirmation, HCV RNA test for qualitative and quantitative analysis, genotype test, and liver biopsy) is quite straightforward that a physician may manage well without CDSS interventions. On the other hand, for Hepatitis C treatment, the complexity of an optimal treatment regimen with multiple followup visits that can last from 24 to 72 weeks, would mean that effective CDSS interventions can provide powerful guidance to a physician during initial treatment ordering and subsequent treatment adjustments.

All in all, the insertion of CDSS interventions, especially in the ordering and the post visit phases, will make the logical sense for long term care diseases such as Hepatitis C infection. We have confidence that such CDSS interventions can also be extended to other conditions that require similar customized approach and long term monitoring, such as HIV infection.
REFERENCES


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## Appendix

### Appendix 1: Project Stakeholders roles and responsibilities

<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Objective Class</th>
<th>Desired Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy Director, Chief Quality Officer</td>
<td>Prevent Errors of Commission</td>
<td>Decrease likelihood of prescribing drugs that may be contraindicated. For example, The use of peginterferon is contraindicated in patients with compensated cirrhosis</td>
</tr>
<tr>
<td>Chief Medical Officer, Chief Nursing Officer, Gastroenterology Department Head</td>
<td>Prevent error of omission</td>
<td>Avoid missed steps in a necessary sequence: The determination of genotypes is essential to determine treatment regimen, dosage, and duration</td>
</tr>
<tr>
<td>Medical Director of Clinical Decision Support, Chief Medical officer, Chief Information Officer</td>
<td>Optimize choice of individual tests and therapies based on additional considerations</td>
<td>Incorporates information from EMR, patient's questionnaires. Factors: Children, HIV patients, Liver compensated patients, etc.</td>
</tr>
<tr>
<td>Chief Quality Officer / Chief Medical Officer</td>
<td>Improve compliance with simple care guidelines</td>
<td>Provides recommendation based on practice guidelines: e.g. Use of triple therapy (peginterferon + ribavirin + protease inhibitors) based on latest recommended guidelines</td>
</tr>
</tbody>
</table>
| Chief Medical Officer / Physician Group Chairs                              | Improve appropriateness of overall workup and treatment plan for a given situation | -Full complement of indicated interventions ordered  
-Most effective and efficient diagnostic evaluation ordered                                                                                                                                                                                                                                                                                                   |
<p>| Medical Director of Clinical Decision Support                               | Improve compliance with complex short term multi-step protocols | Improve decision making and management of treatment protocol                                                                                                                                                                                                                                                                                           |
| Chief Medical Officer, Chief Nursing Officer                                | Optimize treatment of chronic conditions over time; long term management | Monitoring of HCV viral load in week 4, 8, 12, 24 to determine optimal duration                                                                                                                                                                                                                                                                       |</p>
<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Objective Class</th>
<th>Desired Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chief Information Officer</td>
<td>Improve Documentation of care, including eliciting key data from history and physical examination</td>
<td>Complete documentation of potential HCV patients to access for risk factors associated with HCV infection</td>
</tr>
</tbody>
</table>
| Patient Safety Officer, Patient Representatives | Improve patient education, empowerment and satisfaction with care | -Promote appropriate patient understanding and self management of specific conditions  
-Improve communication to patients about upcoming admissions and procedures |
Appendix 2: Hepatitis C Diagnostic Algorithms

Recommendations:

1. The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin (Class 1, Level A).
2. Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin (Class 1, Level A).

For Treatment-Nave Patients:

3. The recommended dose of boceprevir is 800 mg administered with food three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 24-44 weeks preceded by 4 weeks of lead-in treatment with peginterferon alfa and ribavirin alone (Class 1, Level A).
4. Patients without cirrhosis treated with boceprevir, peginterferon, and ribavirin, preceded by 4 weeks of lead-in peginterferon and ribavirin, whose HCV RNA level at weeks 8 and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (4 weeks lead-in with peginterferon and ribavirin followed by 24 weeks of triple therapy) (Class 2a, Level B).
5. Treatment with all three drugs (boceprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24 (Class 2a, Level B).

6. The recommended dose of telaprevir is 750 mg administered with food (not low-fat) three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12-36 weeks of peginterferon alfa and ribavirin (Class 1, Level A).
7. Patients without cirrhosis treated with telaprevir, peginterferon, and ribavirin, whose HCV RNA level at weeks 4 and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks (Class 2a, Level A).
8. Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon and ribavirin should receive therapy for a duration of 48 weeks (Class 2b, Level B).
9. Treatment with all three drugs (telaprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >1,000 IU/mL at treatment weeks 4 or 12 and/or detectable at treatment week 24 (Class 2a, Level B).

For treatment-experienced patients:

10. Re-treatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin (Class 1, Level A).
11. Re-treatment with telaprevir, together with peginterferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin (Class 2b, Level B.)

12. Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers (Class 2a, Level B for boceprevir; Class 2b, Level C for telaprevir), may be considered for partial responders (Class 2b, Level B for boceprevir; Class 3, Level C for telaprevir), but cannot be recommended for null responders (Class 3, Level C).

13. Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B).

14. Patients re-treated with telaprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 1,000 IU at weeks 4 or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B).

15. Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose (Class2a, Level A).

16. Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (≥1 log increase in serum HCV RNA above nadir) is observed (Class 1, Level A).

17. Patients who fail to have a virological response, who experience virological breakthrough, or who relapse on one protease inhibitor should not be re-treated with the other protease inhibitor (Class 2a, Level C).

18. IL28B genotype is a robust pretreatment predictor of SVR to peginterferon alfa and ribavirin as well as to protease inhibitor triple therapy in patients with genotype 1 chronic hepatitis C virus infection. Testing may be considered when the patient or provider wish additional information on the probability of treatment response or on the probable treatment duration needed (Class 2a, Level B).

(Ghany, 2011).
### Appendix 3: CDSS Workflow Analysis

<table>
<thead>
<tr>
<th>Objective Class</th>
<th>Desired Action</th>
<th>CDSS Intervention Type</th>
<th>Workflow Step Affected</th>
<th>Specific CDSS Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent Errors of Commission</td>
<td>Decrease likelihood of prescribing drugs that may be contraindicated. For example, The use of peginterferon is contraindicated in patients with compensated cirrhosis</td>
<td>Alerts to prevent errors</td>
<td>Ordering</td>
<td>Order set (CPOE)</td>
</tr>
<tr>
<td>Prevent error of omission</td>
<td>Avoid missed steps in a necessary sequence: The determination of genotypes is essential to determine treatment regimen, dosage, and duration</td>
<td>Flowsheets, Order sets</td>
<td>Ordering</td>
<td>Order set (CPOE)</td>
</tr>
<tr>
<td>Optimize choice of individual tests and therapies based on additional considerations</td>
<td>Incorporates information from EMR, patient’s questionnaires. Factors: Children, HIV patients, Liver compensated patients, etc.</td>
<td>-Order sets -Choice lists -Alerts to foster best care -Reference material -Patients documentation forms</td>
<td>-Ordering - Documentation</td>
<td>-Order set (CPOE) -Patient self assessment forms</td>
</tr>
<tr>
<td>Improve compliance with simple care guidelines</td>
<td>Provides recommendation based on practice guidelines: e.g. Use of triple therapy (peginterferon + ribavirin + protease inhibitors) based on latest recommended guidelines</td>
<td>-Clinical data flow sheets -Alerts can reminders to foster best case -Order sets -Clinician encounter forms</td>
<td>-Start of visit - Documentation - Ordering - Discharge - Results</td>
<td>-Patient self assessment forms -Reference Materials - Order set (CPOE)</td>
</tr>
<tr>
<td>Objective Class</td>
<td>Desired Action</td>
<td>CDSS Intervention Type</td>
<td>Workflow Step Affected</td>
<td>Specific CDSS Intervention</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>---------------------------</td>
</tr>
</tbody>
</table>
| Improve appropriateness of overall workup and treatment plan for a given situation | -Full complement of indicated interventions ordered  
-Most effective and efficient diagnostic evaluation ordered | -Reference Information  
-Order sets  
-Flowsheets  
-Clinician documentation forms  
-Alerts to foster care plan  
-Aggregate reports  
-Clinical pathways | -Start of visit  
-Documentation  
-Ordering  
-Order handling  
-Therapies/Procedure  
-Results  
-Discharge  
-Post visit | -Order set (CPOE)  
- Reactive Alerts |
| Improve compliance with complex short term multi-step protocols | Improve decision making and management of treatment protocol | -Clinical pathways  
-Alerts  
-Order sets | -Documentation  
-Ordering  
-Results | -Clinician Documentation Forms  
-Order sets (CPOE) |
| Optimize treatment of chronic conditions over time; long term management | Monitoring of HCV viral load in week 4, 8, 12, 24 to determine optimal duration | -Flowsheets – BCDE  
-Alerts to foster optimal care  
-Order sets  
-Reference material  
-Multi-step protocol support / clinical pathways | -Pre-Visit  
-Start of visit  
-Clinician’s H&P and plan  
-Documentation  
-Orders  
-Results  
-Post-Visits | -Order sets (CPOE)  
-Proactive alert  
-Serial reminders and flowsheets notifications |
| Improve Documentation of care, including | Completion documentation of potential HCV patients to access for risk factors | -Nursing assessment forms  
-Clinician | -Pre-Visit  
-Start of Visit  
-Documentation | -Patients self assessment |
<table>
<thead>
<tr>
<th>Objective Class</th>
<th>Desired Action</th>
<th>CDSS Intervention Type</th>
<th>Workflow Step Affected</th>
<th>Specific CDSS Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>eliciting key data from history and physical examination</td>
<td>associated with HCV infection</td>
<td>documentation forms -Patient self assessment forms -Multidisciplinary Forms</td>
<td>-Post-Visits</td>
<td></td>
</tr>
<tr>
<td>Improve patient education, empowerment and satisfaction with care</td>
<td>-Promote appropriate patient understanding and self management of specific conditions -Improve communication to patients about upcoming admissions and procedures</td>
<td>-Patient self assessment forms -Relevant data display -Multidisciplinary documentation forms -Alerts to foster better care -Order sets -Reference information</td>
<td>-Pre-Visits -Start of Visit -Documentation -Orders -Order handling -End of Visit -Post Visit</td>
<td>-Order Set -Patient self assessment forms</td>
</tr>
</tbody>
</table>

(Source: Osteroff, 2012)
## Appendix 4: Standards-Based Vocabularies

| **LOINC:** LOINC (Logical Observation Identifiers Names and Codes) is a database and standard for measuring laboratory results. Vreeman, D. (2010) states LOINC was developed to provide a definitive standard for identifying clinical observation in electronic reports. This standard has been designated for use in the U. S. Federal Government systems for the exchange of clinical health information, (U.S. National Library of Medicine). |
| **SNOMED-CT:** SNOMED-CT (Systemized Nomenclature of Medicine-Clinical Terms), according to the International Health Terminology Standards Development Organization, is the most comprehensive, multilingual healthcare terminology in the world. This standard is able to cross-map to other international standards and is used in more than fifty countries. SNOMED can assist in recording, storing and retrieving data within the EMR as well. |
| **RxNorm:** According to the National Library of Medicine, RxNorm provides normalized names for clinical drugs and links its names to many of the drug vocabularies commonly used in pharmacies. NLM adds that RxNorm now includes the National Drug File-Reference Terminology (NDF-RT) from the Veterans Health Administration, (National Library of Medicine). |
| **DICOM:** “DICOM is a global Information-Technology standard that is used in virtually all hospitals worldwide,” states DICOM (Digital Imaging and Communications in Medicine). Among other functions, DICOM is designed to create interoperability of systems used to produce, store, retrieve and view medical images. This standard ensures interoperability among many medical departments and units. Examples include radiology, cardiology and neurology. |
| **HL-7:** HL-7 provides a comprehensive framework and related standards for the exchange, integration, sharing, and retrieval of electronic health information (Health Level 7 International). HL-7 standards define how information is packaged and communicated from one party to another, setting the language, structure and data types required for seamless integration between systems. |
| **CCD:** A continuity of care document is an electronic summary of all of a patient’s clinical information. This standard provides physicians with the ability to share a patient’s medical history and current condition in a comprehensive representation. CCD is typically used in among other capacities, emergency departments. CCD is one of two formats required by the government to achieve meaningful use (Astin, 2012). |
## Appendix 5: Technical Standards

<table>
<thead>
<tr>
<th>Technical Standards</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertext Transfer Protocol (HTTP) and Hypertext Transfer Protocol Secure (HTTPS)</td>
<td>The primary communications protocol for transmitting data via web interfaces and is primarily used to describe how information appears. This is done securely using Secure Socket Layer (SSL) in the case of HTTPS.</td>
</tr>
<tr>
<td>Extensible Markup Language (XML)</td>
<td>A language designed to transmit and store data.</td>
</tr>
<tr>
<td>Simple Object Access Protocol (SOAP)</td>
<td>SOAP is an XML-based protocol used by applications to exchange data using HTTP. The SOAP specification defines the format of an XML message.</td>
</tr>
<tr>
<td>XML Web Services</td>
<td>A general concept for conveying SOAP messages, containing XML using HTTP.</td>
</tr>
<tr>
<td>Web Service Description Language (WSDL)</td>
<td>WSDL is an XML file which further describes SOAP messages and how they are exchanged.</td>
</tr>
<tr>
<td>Universal Discovery Description and Integration (UDDI)</td>
<td>UDDI is a directory of locator records so that systems can find web services.</td>
</tr>
<tr>
<td>Continuity of Care Record (CCD)</td>
<td>CCD is an XML-based standard intended for summarizing patient information for clinical exchange. It contains encoding, structure and content of a patient record.</td>
</tr>
</tbody>
</table>

(Source: Wolter, 2001)
**Appendix 6: Six Sigma DMADV Process**

<table>
<thead>
<tr>
<th>Define.</th>
<th>The organization defines design goals that are consistent with customer demands and organizational strategy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure.</td>
<td>The process redesign team measures the critical-to-quality needs of their customers through a process known as voice of the customer, which is a methodical approach to understanding customer requirements. Customers include key external and internal stakeholders — patients, families and family caregivers, payers, physicians, staff nurses, ancillary staff, and case management, to name just a few.</td>
</tr>
<tr>
<td>Analyze.</td>
<td>A high-level design is created, using various analysis tools to develop and design alternatives that can improve quality and reduce costs. High-level design features are selected that can deliver the level of performance demanded by the project's customers. These design features are formally evaluated against the critical-to-quality criteria specified in the Measure phase.</td>
</tr>
<tr>
<td>Design.</td>
<td>Detail-level design is completed, including detailed workflows, policies and procedures, facilities plans, equipment and supply plans, change management plans, and risk assessments. Additionally, if necessary, simulation may be conducted to test the new design prior to launching pilots. What's more, the IT plan is created in this phase, which directly impacts the design of the EMR.</td>
</tr>
<tr>
<td>Verification.</td>
<td>Once a design has been analyzed and tested, it is verified through one or more pilots. Following successful verification, it is ready to be spread throughout the organization (Duhig, 2009).</td>
</tr>
</tbody>
</table>
Appendix 7: Technical Design Document Structure for CDSS Implementation

1. Preface
   a. Document purpose
   b. Overview
2. Introduction
   a. Purpose
   b. Scope
   c. Guiding principles
   d. Glossary of acronyms, abbreviations, terms and definitions
3. System overview
   a. System architecture
   b. Infrastructure
   c. Topology diagram
4. System Design
   a. Application architecture
      i. Client layer
      ii. Business layer
      iii. Data layer
      iv. Rules engine
5. Application Implementation
   a. Interfaces (internal and external)
6. Description of components
   a. Dependencies
7. Document Control
   a. Sign off
8. Change Control
## Appendix 8: Performance metrics

<table>
<thead>
<tr>
<th>NQF#</th>
<th>Title</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>393</td>
<td>Hepatitis C: Testing for Chronic Hepatitis C â€“ Confirmation of Hepatitis C Viremia</td>
<td>Percentage of patients aged 18 years and older with a diagnosis of hepatitis C seen for an initial evaluation who had HCV RNA testing ordered or previously performed</td>
</tr>
<tr>
<td>394</td>
<td>Hepatitis C: Counseling Regarding Use of Contraception Prior to Antiviral Treatment</td>
<td>Percentage of female patients aged 18 to 44 years and all men aged 18 years and older with a diagnosis chronic hepatitis C who are receiving antiviral treatment who were counseled regarding contraception prior to the initiation of antiviral treatment</td>
</tr>
<tr>
<td>395</td>
<td>Paired Measure: Hepatitis C RNA Testing Before Initiating Treatment (paired with 0396)</td>
<td>Percentage of patients aged 18 years and older with a diagnosis of chronic hepatitis C who are receiving antiviral treatment for whom quantitative HCV RNA testing was performed within 6 months prior to initiation of antiviral treatment</td>
</tr>
<tr>
<td>396</td>
<td>Paired Measure: HCV Genotype Testing Prior to Treatment (paired with 0395)</td>
<td>Percentage of patients aged 18 years and older with a diagnosis of chronic hepatitis C who are receiving antiviral treatment for whom HCV genotype testing was performed within 6 months prior to initiation of antiviral treatment</td>
</tr>
<tr>
<td>397</td>
<td>Hepatitis C: Prescribed Antiviral Therapy</td>
<td>Percentage of patients aged 18 years and older with a diagnosis of chronic hepatitis C who were prescribed peginterferon and ribavirin therapy within the 12 month reporting period</td>
</tr>
<tr>
<td>398</td>
<td>Hepatitis C: HCV RNA Testing at Week 12 of Treatment</td>
<td>Percentage of patients aged 18 years and older with a diagnosis of chronic hepatitis C who are receiving antiviral treatment for whom quantitative HCV RNA testing was performed at 12 weeks from initiation of antiviral treatment</td>
</tr>
<tr>
<td>399</td>
<td>Paired Measure: Hepatitis C: Hepatitis A Vaccination (paired with 0400)</td>
<td>Percentage of patients aged 18 years and older with a diagnosis of hepatitis C who have received hepatitis A vaccination, or who have documented immunity</td>
</tr>
<tr>
<td>400</td>
<td>Paired Measure: Hepatitis C: Hepatitis B Vaccination (paired with 0399)</td>
<td>Percentage of patients aged 18 years and older with a diagnosis of hepatitis C who have received hepatitis B vaccination, or who have documented immunity.</td>
</tr>
<tr>
<td>401</td>
<td>Hepatitis C: Counseling Regarding Risk of Alcohol Consumption</td>
<td>Percentage of patients aged 18 years and older with a diagnosis of hepatitis C who received counseling regarding the risk of alcohol consumption at least once within the 12 month reporting period</td>
</tr>
<tr>
<td>412</td>
<td>HIV/AIDS: Hepatitis B Vaccination</td>
<td>Percentage of patients, regardless of age, with a diagnosis of HIV/AIDS who have received at least one hepatitis B vaccination, or who have documented immunity</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>414</td>
<td>HIV/AIDS: Other Infectious Diseases - Hepatitis C</td>
<td>Percentage of patients aged 13 years and older with a diagnosis of HIV/AIDS for whom Hepatitis screening was performed at least once since the diagnosis of HIV infection, or for whom there is documented immunity.</td>
</tr>
<tr>
<td>475</td>
<td>Hepatitis B Vaccine Coverage Among All Live Newborn Infants Prior to Hospital or Birthing Facility Discharge</td>
<td>Percent of live newborn infants that receive hepatitis B vaccination before discharge at each single hospital/birthing facility during given time period (one year).</td>
</tr>
<tr>
<td>584</td>
<td>Hepatitis C: Viral Load Test</td>
<td>This measure identifies the percentage of patients with Hepatitis C (HCV) who began HCV antiviral therapy during the measurement year and had HCV Viral Load testing prior to initiation of antiviral therapy.</td>
</tr>
</tbody>
</table>

(Source: NQF, 2012)