In addition, the upper detection limit of the assays should be considered when making calculations of logarithmic decreases. Some of the previously used assays indicated a viral level as being greater than a certain threshold (eg, >2 million copies/mL), which would not allow measurement of logarithmic decrease for determination of EVR. When HCV RNA level is denoted by a >X value, the patient should be followed with a wider range or the specimen should be diluted and re-evaluated. A recent comparison of quantification values determined that the 44x assay has a greater ability to detect high viral load when it does PCR. Focusing specimens (N = 256) from four sites were run through PCR and then 44xRNA. With undiluted samples, the 44x assay was better able to quantify viral levels of at least 80,000 IU/mL. Both assays performed similarly when samples were diluted and PCR was performed a second time.

Genotyping is performed by either reverse-hybridization line probe assay (INNO-LIPA), direct sequencing test (TRUGENE™ HCV 5’ NC GenoKit assay), or restriction fragment length polymorphism assay. These assays have been described in detail elsewhere and the patient should be followed with a wider range or the specimen should be diluted and re-evaluated. A recent comparison of quantification values determined that the 44x assay has a greater ability to detect high viral load when it does PCR. Focusing specimens (N = 256) from four sites were run through PCR and then 44xRNA. With undiluted samples, the 44x assay was better able to quantify viral levels of at least 80,000 IU/mL. Both assays performed similarly when samples were diluted and PCR was performed a second time.

Genotyping is performed by either reverse-hybridization line probe assay (INNO-LIPA), direct sequencing test (TRUGENE™ HCV 5’ NC GenoKit assay), or restriction fragment length polymorphism assay. These assays have been described in detail elsewhere and should be followed with a wider range or the specimen should be diluted and re-evaluated. A recent comparison of quantification values determined that the 44x assay has a greater ability to detect high viral load when it does PCR. Focusing specimens (N = 256) from four sites were run through PCR and then 44xRNA. With undiluted samples, the 44x assay was better able to quantify viral levels of at least 80,000 IU/mL. Both assays performed similarly when samples were diluted and PCR was performed a second time.

In this CME newsletter, HCV RNA Tests: Differences and Dilemmas. Dr. Goh explains the strengths, limitations, and best uses of available virologic tests and provides a guideline for a cost-effective management of antiviral therapy. Taken together, these strategies will help increase a patient's chances of successful treatment of hepatitis C, viral infection.

I hope you find this informative publication valuable to your patient care.

Sincerely,

Chair
John G. McHutchison, MD
Director, GI/Hepatology Research
Duke Clinical Research Institute
Division of Gastroenterology
Duke University Medical Center
Durham, North Carolina

Faculty
Robert G. Goh, MD
Medical Director
Liver Transplant Program
California Pacific Medical Center
San Francisco, California

References
11. Laboratory Corporation of America, data on file.

HCV RNA Tests: Differences and Dilemmas

Dear Colleagues:
Recent technological advances have improved the accuracy of hepatitis C virus (HCV) assays. Determinations of serum levels of HCV RNA and genotype, using these new technologies, allow for more accurate diagnosis and management. With new, highly sensitive, qualitative and quantitative virologic tests, we can now accurately sustain viremic response (SVR) (or lack thereof) to antiviral therapy by measuring whether a patient has had a 2-log drop in HCV RNA at week 12 of therapy. Viral clearance can be confirmed at the end of treatment and 6 months posttreatment with newer, highly sensitive qualitative tests.

In this CME newsletter, HCV RNA Tests: Differences and Dilemmas. Dr. Goh explains the strengths, limitations, and best uses of available virologic tests and provides a guideline for a cost-effective management of antiviral therapy. Taken together, these strategies will help increase a patient’s chances of successful treatment of hepatitis C, viral infection.

I hope you find this informative publication valuable to your patient care.

Sincerely,

Chair
John G. McHutchison, MD
Director, GI/Hepatology Research
Duke Clinical Research Institute
Division of Gastroenterology
Duke University Medical Center
Durham, North Carolina

Faculty
Robert G. Goh, MD
Medical Director
Liver Transplant Program
California Pacific Medical Center
San Francisco, California

Inside this Reporter

Download additional copies of this CME To Reporter at www.projectsinknowledge.com/hcvrna/
Introduction
Numerous molecular tests (assays), (also termed Nucleic Acid Tests), are now available to determine HCV RNA and genotype. These measurements are critical in making treatment management decisions. HCV RNA levels indicate whether virus is present or has been cleared, and determine when and whether treatment should be stopped or continued in the setting of antiviral therapies. Genotype predicts the likelihood of a response to any therapy and also guides the treatment duration. Thus, accurate measurements are critical at baseline, throughout treatment, and in the posttreatment period. Since assays vary with regard to range of detection, specificity and sensitivity, as well as other features, it is important to optimize our use of available tests.

Using Virologic Determinations: The Current Standard of Care
Management of hepatitis C has become increasingly sophisticated in recent years based, in part, on the availability of increasingly accurate and sensitive diagnostic and monitoring tools. Using newer tests to guide management decisions, treatment should be tailored to individual patients based on viral levels before and during therapy, as well as on HCV genotype (Fig 1).

The primary goal of treatment is sustained virologic response (SVR), defined as absence of detectable HCV RNA in the serum by a qualitative HCV RNA assay with a lower limit of detection a50 IU/mL at 24 weeks after the end of treatment. With peginterferon/ribavirin combination therapy, SVR can be achieved by 42% to 51% of patients with genotype 1 and by 73% to 82% of patients with genotypes 2 and 3. Early virologic response (EVR)—defined as undetectable HCV RNA or a a2-log10 decrease in HCV RNA after 12 weeks of therapy—is predictive of SVR and is recommended as a routine part of monitoring patients with genotype 1 infection. About 19% of patients fail to meet these criteria for EVR at week 12. If treatment is discontinued at week 12, in this subgroup, only 0.6% of patients with SVRs would be incorrectly identified and thus denied the benefits of continued treatment and sustained response, and a 10% and a lower reduction in costs would be achieved.1

However, the clinical decision to terminate therapy beyond 12 weeks should take into account other factors (eg, patient tolerance and stabilization of fibrosis progression in patients with advanced histology) provided that there has been some reduction in alanine aminotransferase or HCV RNA levels. For those who do have a a2-log10 decrease at 12 weeks, therapy should be continued and HCV RNA should be retested at 24 weeks by a qualitative test. If HCV RNA is still detectable at that time, treatment should be discontinued. In patients infected with genotype 1 who demonstrate an EVR, adherence to treatment can have a substantial impact on the likelihood of achieving SVR. Thus, educating patients about EVR, viral clearance, and genotype (chances of an SVR) may provide a major motivating factor to continue therapy. Genotype testing is performed at baseline because these determinations influence treatment decisions. There are six distinct genotypes, classified by homology (<70% different genotypes). Approximately 77% to 79% of HCV-infected individuals in the United States are infected with genotype 1, which is associated with a lower rate of response to treatment; the remainder are infected primarily with genotypes 2 and 3. In patients infected with genotype 1, peginterferon/ribavirin regimens are more effective than standard interferon/ribavirin regimens.12,14,15 In patients infected with genotype 1, 48 weeks of treatment and standard doses of ribavirin (1000–1200 mg/d) are necessary, while 24 weeks of treatment appear to be sufficient for patients with genotype 2 or 3.5 Because of the high response rates in patients with genotypes 2 and 3, early HCV RNA testing may not be necessary in most of these patients. However, in the symptomatic patients with cirrhosis and interferon- and ribavirin-related side effects, treatment decisions based on viral clearance may be useful to both the patient and the medical care provider.

In addition to pretreatment genotype determination and early testing of viral response during treatment, a follow-up qualitative HCV RNA test should be performed, particularly at the end of treatment, to confirm the absence of active HCV replication. Further studies determine whether SVRs are sustained over the long term following successful antiviral therapy, periodic determinations of HCV RNA levels may need to be performed.2,3

Virologic Assay: Not All Are Created Equal
A number of HCV RNA assays have been developed. In polymerase chain reaction (PCR) testing, primers and enzymes are added to a patient’s RNA or DNA sample. Amplified RNA copies are produced, and signal is detected from one detection probe per amplified copy, allowing for either qualitative or quantitative detection. This process is labor intensive and requires several steps, including thermocycling, and transfer of amplification product to microtubes, which carries a risk of contamination. A recently developed transcription-mediated amplification (TMA) assay similarly requires addition of primers and enzymes to the RNA sample, which produces an RNA product. One detection probe per copy produces signal that allows qualitative detection. The TMA (a FDA-approved assay) is a simpler process than PCR, requiring fewer steps and allowing the product to remain in the original tube; thus, there is less risk of error or contamination. This assay can be performed in many local laboratories with simple training and equipment.

The branched DNA (bDNA) assay involves a signal amplification process in which multiple detection probes and a biotin-labeled molecule attach to the RNA or DNA in the sample, and light emission (signal) is proportional to the quantity of the virus or sequence present in the specimen. This FDA-approved assay can also be performed easily in local laboratories and provides a wide dynamic range and high level of accuracy of HCV RNA levels. The National Genetics Institute (NGI) PCR assay is also important because it was used in a number of the clinical trials that led to licensing of available hepatitis C treatments, and is still in use in many hepatitis C trials. The Quest assay is commonly used by local laboratories for virologic testing ordered by physicians in community practice. The new TaqMan real-time quantitative PCR assay provides a rapid determination but is dependent on a local laboratory process. More information on accuracy, sensitivity, and specificity is available to determine the role of the TagMan assay in clinical practice. In making determinations of EVR, end-of-treatment response, or SVR, it is important to consider differences in available HCV RNA assays. Available tests vary with regard to dynamic range of HCV RNA detection (Fig 2). They also vary with regard to linearity, sensitivity and specificity, and precision (Tables 1 and 2). In general, qualitative assays have a lower range of detection than quantitative assays. Detection of especially low levels of virus is necessary in accurately determining response and relapse, since relapse may represent virus that is either latent or has very low replication levels and persists in serum below the detection limit of available assays.6 The TMA RNA assay has a lower limit of detection, of approximately 5 to 10 IU/mL, and may prove to be especially useful at the end of treatment in helping to define long-term response and in long-term care management strategies and decisions.7,8 Comparison of the TMA assay with qualitative PCR (Roche Amplicor®) showed a positive result on TMA but a negative PCR result in 66 of 1012 samples. The reverse (ie, positive by PCR but not by TMA) occurred in five samples. Thus, overall concordance rate was 95% and discordance rate was 5%.9

Figure 1. Molecular Testing for HCV RNA in Monitoring Therapy: Peg IFN/RBV Testing Algorithm for Naive Patients

PEG IFN/RBV Testing Algorithm for Naive Patients1

Figure 2. Ranges of HCV RNA Assays

Table 1. HCV Quantitative Assay Characteristics

<table>
<thead>
<tr>
<th>Assay Name</th>
<th>Lower Limit of Sensitivity</th>
<th>Upper Limit of Sensitivity</th>
<th>Sensitivity</th>
<th>Precision</th>
<th>Specificity</th>
<th>Dynamic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche Amplicor® PCR</td>
<td>&lt;0.5 IU/mL</td>
<td>&gt;100,000 IU/mL</td>
<td>&gt;99%</td>
<td>&lt;15%</td>
<td>&gt;97%</td>
<td>3–10,000,000 IU/mL</td>
</tr>
<tr>
<td>Quest Quantitative</td>
<td>&lt;0.5 IU/mL</td>
<td>&gt;1000 IU/mL</td>
<td>&gt;99%</td>
<td>&lt;10%</td>
<td>&gt;97%</td>
<td>3–10,000,000 IU/mL</td>
</tr>
<tr>
<td>Bayer bDNA (3.0)</td>
<td>0.1 IU/mL</td>
<td>&gt;1000 IU/mL</td>
<td>&gt;97%</td>
<td>&lt;10%</td>
<td>&gt;97%</td>
<td>3–10,000,000 IU/mL</td>
</tr>
</tbody>
</table>

CV = coefficient of variation; IU = International Units; IU = International Units
The primary goal of treatment is sustained virologic response (SVR), defined as the absence of detectable HCV RNA in the serum by a qualitative HCV RNA assay with a lower limit of detection a<0.5 IU/mL at 24 weeks after the end of treatment. With peginterferon/ribavirin combination therapy, SVR can be achieved by 42% to 51% of patients with genotype 1 and by 73% to 82% of patients with genotypes 2 and 3.1 Early virologic response (EVR)—defined as undetectable HCV RNA or a ≥ 2-log10 decrease in HCV RNA 12 weeks of therapy—is predictive of SVR and is recommended as a routine part of monitoring patients with genotype 1 infection.2 About 19% of patients fail to meet these criteria for EVR at week 12. If treatment is discontinued at week 12 in this subgroup, only 0.6% of patients with SVRs would be incorrectly identified and thus denied the benefits of continued therapy and sustained response, and a 10% drop in treatment costs would be achieved.4,5 However, the clinical decision to terminate therapy beyond 12 weeks should take into account other factors (eg, patient tolerance and stabilization of fibrosis progression in patients with advanced histology) provided that there has been some reduction in alanine aminotransferase or HCV RNA levels. For those who do have a ≥ 2-log10 decrease at 12 weeks, therapy should be continued and HCV RNA should be restested at 24 weeks by a qualitative test.6,7 If HCV RNA is still detectable at that time, treatment should be discontinued. In patients infected with genotype 1 who demonstrate EVR, adherence to treatment can have a substantial impact on the likelihood of achieving SVR.8 Thus, educating patients about EVR, viral clearance, and genotype (chances of an SVR) may provide a major motivating factor to continue therapy. Genotype testing is performed at baseline because these determinations influence treatment decisions. There are six distinct genotypes, classified by homology (<70% with different genotypes).9 Approximately 70% to 75% of HCV-infected individuals in the United States are infected with genotype 1, which is associated with a lower rate of response to treatment; the remainder are infected primarily with genotypes 2 and 3. In patients infected with genotype 1, peginterferon/ribavirin regimens are more effective than standard interferon/ribavirin regimens, but among patients with genotype 2 or 3, SVR is achievable to either peginterferon/ribavirin or standard interferon/ribavirin regimens.10 For patients infected with genotype 1, 48 weeks of treatment and standard doses of ribavirin (1000–1200 mg/d) are necessary, while 24 weeks of treatment appear to be sufficient for patients with genotype 2 or 3. Because of the high response rates in patients with genotypes 2 and 3, early HCV RNA testing may not be necessary in most of these patients. However, in the symptomatic patients with extensive interferon- and ribavirin-related side effects, treatment decisions based on viral clearance may be useful to both the patient and the medical care provider. In addition to pretreatment genotype determination and early testing of viral response during treatment, a follow-up qualitative HCV RNA test should be performed, particularly at the end of treatment, to confirm the absence of active HCV replication. Further studies determine whether SVRs are sustained over the long term following successful antiviral therapy, periodic monitoring of HCV RNA levels may need to be performed.2,5,6,11

**Figure 1. Molecular Testing for HCV RNA in Monitoring Therapy: Peg IFN/ribavirin Testing Algorithm for Naive Patients**

**Figure 2. Ranges of HCV RNA Assays**

**Table 1. HCV Quantitative Assay Characteristics**

**Table 2. HCV Qualitative Assay Characteristics**

**TREATMENT REPORT: GASTROENTEROLOGY**
In addition, the upper detection limit of the assays should be considered when making calculations of logarithmic decreases. Some of the previously used assays indicated a viral level as before becoming a constant threshold (eg, >2 million copies/mL), which would not allow measurement of logarithmic decrease for determination of EIR. When HCV RNA level is denoted by a 10^-X value, the patient should be treated using an assay with a wider range or the specimen should be diluted and re-evaluated. A recent comparison of quantification values determined that the HCV RNA assay has a greater ability to detect high viral loads when using PCR.79 Fourteen specimens (N = 254) from four sites were run through PCR and then HCV RNA. With undiluted sera, the HCV RNA assay was better able to quantify viral levels of at least 80,000 IU/mL. Both assays performed similarly when samples were diluted and PCR was performed a second time. Genotyping is performed by reverse-hybridization line probe assay (INNO-LIPA), direct sequencing test (TRUGENE™ HCV 5’NC GeneKIt assay), or restriction fragment length polymorphism assay. These assays have been found to have a high degree of concordance and reliability.10,11

Conclusion
A description of viral status includes three parameters detection of virus (HCV RNA), quantification of virus, and HCV genotyping. These determinations are clinically important and help determine management strategy. Technologic advances have been made in the assays used to make these determinations, and consideration should be given to the advantages and limitations of these assays when making decisions and determinations are made. Since logarithmic calculations are necessary to determine EIR, it is necessary to use a highly accurate quantitative assay, with a high range of detection to make HCV RNA determinations at baseline and week 12. To support viral clearance at the end of treatment and in the post-treatment period, a test with a low HCV RNA sensitivity should be used. This is generally a qualitative test or a very sensitive quantitative test that has a particularly low range of detection. Genotyping testing using any of the available genotyping assays, all of which are accurate and concordant, should be performed at baseline. Genotype is used to predict response and determine duration of treatment. Physicians may need to contact laboratory directors to find out which tests are being used at local laboratories and to request specific data or product information regarding those tests. Appropriate use of available provides important and accurate information that can help select the best course of care for individual patients, increasing the likelihood of successful treatment outcomes, reducing healthcare costs, and allowing discontinuation of medications when therapy has very a low probability of efficacy.

References
12. Laboratory Corporation of America. data on file.

Dear Colleague:
Recent technologic advances have improved the accuracy of hepatitis C virus (HCV) assays. Determinations of serum levels of HCV RNA and genotype, using these new technologic advances, allow for more accurate diagnosis and staging of hepatitis C. With new, highly sensitive, qualitative and quantitative virologic tests, we can now accurately sustain sustained virologic response (SVR) (or lack thereof) to antiviral therapy by measuring whether a patient has had a 2-log reduction in HCV RNA at week 12 of therapy. Viral clearance can be confirmed at the end of treatment and 6 months posttreatment with newer, highly sensitive qualitative tests.

In this CME newsletter, HCV RNA Tests: Differences and Dilemmas. Dr. Gish explains the strengths, limitations, and best uses of available virologic tests and provides a guideline for a cost-effective management of antiviral therapy. Taken together, these strategies will help increase a patient’s chances of successful treatment of hepatitis C viral infection.

I hope you find this informative publication valuable to your patient care.

Sincerely,
Chair
John G. McHutchison, MD
Director, GI/Hepatology Research
Duke Clinical Research Institute
Durham, North Carolina

Faculty
Robert G. Gish, MD
Medical Director
Liver Transplant Program
California Pacific Medical Center
San Francisco, California

End of this ﬂeaflet

Introduction ................................................................. 2
Using Virologic Determinations: The Current Standard of Care .... 2
Virologic Assays: Not All Are Created Equal .................. 3
Conclusion ................................................................. 4
References ................................................................. 4
PostScript/Evaluation .................................................. See Inside

Download additional copies of this CME To Reporter at www.projectsinknowledge.com/hcvma/

TARGET AUDIENCE
This activity is intended for gastroenterologists and hepatology healthcare professionals who treat patients with hepatitis C.

ACTIVITY GOAL
The goal of this activity is to discuss recent advances in HCV molecular testing and to describe important limitations, indications, and use of specific HCV HVR and genotyping assays now available.

LEARNING OBJECTIVES
After completing this activity, the physician should be able to: 1) implement management strategies for HCV-infected patients based on virologic information and the use of antiviral therapy; 2) predict response based on early virologic quantifications; 3) understand the strengths and limitations of available qualitative and quantitative HCV RNA assays and genotyping assays; and 4) recognize the importance of the dynamic range of detection of various HCV RNA assays in determining response and confirming viral clearance.

CME INFORMATION
Statement of Accreditation
Duke University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation
Physicians in this activity will receive 2.5 hours of CME credit. This activity will take place between November 1-5, 2002. This CME activity is provided by Projects In Knowledge solely as an independent CME activity, and is not controlled by a commercial interest. This activity is planned and implemented as an independent CME activity and is not controlled by a commercial interest.

This newsletter is planned and implemented as an independent CME activity in accordance with the ACCME™-accredited educational Activities and Projects. Successful completion for 2.5 hours of CME credit requires a passing grade on the quizzes and completing the evaluation form. Information on how to obtain CME credit is available online.

Disclosure Information
The Disclosure Policy of Projects In Knowledge requires that faculty and planning committee members disclose any potential conflicts of interest related to the content of this activity. In addition, the preparation and planning of this activity requires disclosure of information about the development, sponsorship, funding, and/or loan of materials used in this activity, if disclosure includes 1) sponsorship that is contingent on the content or presentation of the information, or 2) any potential conflicts of interest that might arise in the presentation of the content or presentation of the information. At this time, Project In Knowledge is not aware of any potential conflicts of interest related to the content of this activity, if disclosure includes 1) sponsorship that is contingent on the content or presentation of the information, or 2) any potential conflicts of interest that might arise in the presentation of the content or presentation of the information.

For complete prescribing information on the products discussed during this CME activity, please visit the manufacturer’s website or call 1-800-722-4722.

The opinions expressed in this activity are those of the faculty and do not necessarily reflect the opinions of the planning committee, the ACCME, or the CME provider.

Robert G. Gish, MD, has received grant/research support from, or served on a speakers bureau of, Amgen Inc, Bionor, Biogen, Biogen-DynaCure, Novartis, and Schering-Plough Corporation, and is on the speakers bureau of Amgen Inc, Bayer, Biogen, Biogen-DynaCure, Novartis, and Schering-Plough Corporation. Robert G. Gish, MD, has received grant/research support from, or served on a speakers bureau of, Amgen Inc, Bionor, Biogen, Biogen-DynaCure, Novartis, and Schering-Plough Corporation. Robert G. Gish, MD, has served on the speaker’s bureau for Amgen Inc, Bionor, Biogen, Biogen-DynaCure, Novartis, and Schering-Plough Corporation.

The options associated with the activity entries appear only for the faculty and do not necessarily reflect these activities of the planning committee or the ACCME.

This independent CME activity is supported by an educational grant from Solvay Pharmaceuticals, Inc.
HCV RNA Tests: Differences and Dilemmas

CME Instructions
To receive CME credit for your participation in this CME activity, please complete the following steps:

1. Read this newsletter carefully.
2. Complete the CME Posttest.
4. Mail or fax your completed CME Posttest and Evaluation to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424; fax: to 1-973-890-8866 by January 23, 2005.*

*If you complete these steps and score 70% or higher, Projects In Knowledge will mail you an acknowledgement of participation within 6 weeks of receipt of your materials. You may earn up to .5 credit(s) for your participation in this activity. If you score lower than 70%, Projects In Knowledge will notify you by mail and you will be given another chance to take the posttest.

Name __________________________________________________________________ Degrees/Credentials ________________
Mailing Address ______________________________________________________________________________________________
City _____________________________________________________________________ State ________ ZIP ________________
Phone _________________________________________________ Fax _________________________________________________
E-mail ______________________________________________________________________________________________________

Please select the most appropriate response to each question.

1. Measured at week 12, EVR is defined as
   a. Undetectable HCV RNA
   b. Undetectable HCV RNA or a \( \geq 1 \)-log decrease in HCV RNA compared with baseline
   c. Undetectable HCV RNA or a \( \geq 2 \)-log decrease in HCV RNA compared with baseline
   d. None of the above because response should not be determined before week 24

2. Which of the following assays uses multiple detection probes per DNA or RNA product?
   a. PCR
   b. bDNA
   c. TMA
   d. None of the above

3. It is important to consider an HCV RNA assay’s lower limit of detection when:
   a. Making baseline measurements
   b. Making calculations of logarithmic decreases in HCV RNA
   c. Determining response/relapse at the end of treatment and in the period thereafter
   d. All of the above

4. It is important to consider an HCV RNA assay’s upper limit of detection when:
   a. Confirming a positive enzyme immunoassay test result
   b. Making baseline measurements or calculations of logarithmic decreases in HCV RNA
   c. Determining response/relapse at the end of treatment and in the period thereafter
   d. All of the above

5. Which of the following should be used to determine HCV genotype?
   a. INNO-LiPa
   b. Direct sequencing (TRUGENE)
   c. Restriction fragment length polymorphism assay
   d. Any of the above; they all have good concordance and reliability
HCV RNA Tests: Differences and Dilemmas

Name _____________________________________________________ Degrees/Credentials _______________________________

Address ___________________________________________________________________________________________________

City ______________________________________________________ State ________________ ZIP _______________________

Instructions: Please complete this survey, along with the Posttest, and mail or fax (both sides) to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424; fax: 973-890-8866.

1. Please rate the extent to which you achieved the learning objectives:
   - Implement management strategies for HCV-infected patients based on results of molecular testing. ❑❑❑❑❑
   - Predict response based on early virologic quantifications. ❑❑❑❑❑
   - Compare the strengths and limitations of available qualitative and quantitative HCV RNA assays and genotyping assays. ❑❑❑❑❑
   - Recognize the importance of the dynamic range of detection of various assays in determining response and confirming viral clearance. ❑❑❑❑❑

2. Please rate the extent to which this activity achieved the stated goal:
The goal of this activity is to discuss recent advances in HCV molecular testing, and to describe advantages, limitations, and best clinical uses of specific HCV RNA and genotyping assays now available. ❑❑❑❑❑

3. Course was free from commercial bias:
   If you “Disagree” or “Strongly Disagree,” why?
   ..................................................................................................................................................................................................................................
   ..................................................................................................................................................................................................................................

   □ Just Right □ Too Advanced □ Too Basic

4. Please rate the level of the material presented:
   □ □ □

5. Please list any changes in your practice that you would consider making as a result of participating in this activity:
   ..................................................................................................................................................................................................................................
   ..................................................................................................................................................................................................................................
   ..................................................................................................................................................................................................................................
   ..................................................................................................................................................................................................................................

1665ES WEB—Page 1 of 2
6. Please rate your interest in self-directed or distance learning in the following formats:

<table>
<thead>
<tr>
<th>Format</th>
<th>Very Interested</th>
<th>Moderately Interested</th>
<th>Not Interested</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Audioconference</td>
<td>❑</td>
<td>❑</td>
<td>❑</td>
</tr>
<tr>
<td>b. Videoconference</td>
<td>❑</td>
<td>❑</td>
<td>❑</td>
</tr>
<tr>
<td>c. Enduring materials (audio CDs, videotapes, monographs)</td>
<td>❑</td>
<td>❑</td>
<td>❑</td>
</tr>
<tr>
<td>d. Internet (online discussions with experts, educational activities)</td>
<td>❑</td>
<td>❑</td>
<td>❑</td>
</tr>
<tr>
<td>e. Multimedia (online, CD-ROM)</td>
<td>❑</td>
<td>❑</td>
<td>❑</td>
</tr>
</tbody>
</table>

7. Please tell us how long it took you to complete this newsletter: ............................................................. .............................................................

8. Please list topics and/or experts you would find interesting and professionally relevant for future CME activities:

   ..................................................................................................................................................................................................................................
   ..................................................................................................................................................................................................................................
   ..................................................................................................................................................................................................................................
   ..................................................................................................................................................................................................................................

9. Follow-up:
   As part of our ongoing continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our CME courses on professional practice. Please indicate your willingness to participate in such a survey:

   ❑ Yes, I would be interested in participating in a follow-up survey.
   ❑ No, I’m not interested in participating in a follow-up survey.

Additional comments about this activity:

   ..................................................................................................................................................................................................................................
   ..................................................................................................................................................................................................................................
   ..................................................................................................................................................................................................................................
   ..................................................................................................................................................................................................................................

Thank you for your participation.