

Predictive model of response to peg-IFN and RBV

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1 Discussion

2 The present study revealed that viral factors such as substitutions in ISDR and  
3 Core70 are significant and independent predictors of sustained virological response to  
4 PEG-IFN plus RBV in chronic hepatitis C. In a decision-tree model for the pretreatment  
5 prediction of sustained virological response, the number of substitutions in ISDR was  
6 the best predictor of sustained virological response, followed by younger age, wild-type  
7 sequence at Core70, higher level of LDL-C, and absent fibrosis. This decision-tree  
8 model could identify patients with high probability of sustained virological response  
9 (83%) among difficult-to-treat genotype 1b chronic hepatitis C patients. Using this  
10 model, rapid estimates of the response before treatment can be made by allocating  
11 patients to specific subgroups with a defined rate of response simply by following the  
12 flowchart form. Because more potent therapy, such as a combination of protease  
13 inhibitor, PEG-IFN, and RBV, is under clinical trial and may become available in the  
14 near future [Hezode et al., 2009; McHutchison et al., 2009], pretreatment prediction of  
15 the likelihood of sustained virological response may be useful for both patients and  
16 physicians to support clinical decisions whether to start current standard therapy or to  
17 wait for emerging new therapies.

18 Two or more substitutions in ISDR had a strong impact on sustained virological

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1 response, because this factor was selected as a top variable in decision-tree analysis and  
2 had the highest odds ratio in multivariable analysis. Moreover, even among patients  
3 with unfavorable ISDR (0 or 1 mutation), younger patients (<60 years) with the  
4 wild-type sequence at Core70 and high level of LDL-C ( $\geq 120$  mg/dL) had a high rate of  
5 sustained virological response. The sustained virological response rate of these 2  
6 subgroups of patients was 83% in the model-building patients and 75% in the validation  
7 patients. Thus, patients with high possibility of sustained virological response could be  
8 extracted by the combined analysis of ISDR and Core70. These patients may be the  
9 best-suited candidates for treatment with the current combination therapy. Conversely,  
10 the following patients with 0–1 mutation in ISDR had a low probability of sustained  
11 virological response (32%–35%): (1) older (>60 years); or (2) younger (<60 years)  
12 patients but having mutant-type sequence at Core70; or (3) younger (<60 years) patients  
13 having a wild-type sequence at Core70, but having a low level of LDL-C (<120 mg/dL)  
14 and advanced fibrosis. These patients may be advised to wait for a more effective  
15 therapy. Decision may be made on a case-by-case basis, taking into account the  
16 potential risk of disease progression while waiting.

17 In a previous decision-tree model using simple and noninvasive standard tests  
18 that are available readily worldwide [Kurosaki et al., 2010b], the rate of sustained

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1 virological response was at most 65%–76% among those in the high-probability group.  
2 That model focused on use by general physicians in routine general practice, especially  
3 where specialized resources, such as liver biopsy or determination of viral sequences,  
4 are not available. In that model, younger age, male sex, higher platelet counts, lower  
5 alpha-fetoprotein (AFP) levels, and lower GGT levels were identified as favorable  
6 predictive parameters. Higher AFP levels and lower platelet counts that are hallmarks of  
7 advanced fibrosis [Akuta et al., 2007b; Shiratori and Omata, 2000] were associated with  
8 low probability of sustained virological response in that model. On the other hand, the  
9 present analysis aimed to clarify the significance of viral factors for pretreatment  
10 prediction of sustained virological response, and to build an advanced model that may  
11 be used by specialist physicians engaged in the treatment of hepatitis. In the present  
12 model, stage of fibrosis was selected as a predictive factor, but at lower level of  
13 significance than HCV mutations. Moreover, the predicted rate of sustained virological  
14 response in the high-probability group of the present model is higher than that in the  
15 previous model (75%–83% versus 65%–76%). These results indicate that substitutions  
16 in ISDR and Core70 were important pretreatment predictors of sustained virological  
17 response. Determination of these viral factors is not available readily in clinical practice,  
18 but is of value in improving the accuracy of pretreatment prediction of sustained

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1 virological response.

2           Substitutions in ISDR and Core70 have been reported previously to be  
3 associated with efficacy of IFN therapy. The association between the number of  
4 substitutions in ISDR and response to therapy was demonstrated originally in patients  
5 treated with IFN mono-therapy [Enomoto et al., 1995; Enomoto et al., 1996; Kurosaki  
6 et al., 1997], but recent studies have reported a positive correlation with PEG-IFN and  
7 RBV combination therapy as well [Ikeda et al., 2009; Munoz de Rueda et al., 2008;  
8 Shirakawa et al., 2008]. Another important viral factor relevant to treatment response is  
9 amino acid substitution in Core70. The sequence of this amino acid was reported  
10 originally to be associated with non-response to therapy [Akuta et al., 2005], but  
11 subsequent studies confirmed the positive correlation of a wild-type Core70 with  
12 sustained virological response [Akuta et al., 2009]. The multiple logistic regression  
13 analysis showed that ISDR and Core70 were independent factors associated with  
14 sustained virological response along with host factors. How these important viral factors  
15 and other host factors can be combined to predict response to PEG-IFN plus RBV is an  
16 important clinical question. Decision-tree modeling can make the response probability  
17 apparent by combining all these factors. Some factors that may be associated with  
18 treatment outcome, such as levels of ferritin or homocysteine, were not included. This

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1 may be a potential limitation of the present study.

2           It is of interest that a recent study by Li et al. [Li et al., 2010] has shown that a  
3 high serum level of LDL-C is linked to the *IL28B* major allele (CC in rs12979860). In  
4 that study, a high serum level of LDL-C was associated with sustained virological  
5 response, but it was no longer significant when analyzed together with the *IL28B*  
6 genotype in multivariate analysis. Thus, the association between treatment response and  
7 LDL cholesterol levels in the present study may reflect the underlining link of LDL  
8 cholesterol levels to the *IL28B* genotype. Recent reports indicate that the *IL28B*  
9 genotype and HCV substitutions are correlated closely [Akuta et al., 2010; Kurosaki et  
10 al., 2010c]. Still, Core70 [Akuta et al., 2010] or ISDR [Kurosaki et al., 2010c] were  
11 predictors of response to therapy independent of *IL28B* genotype. Future study is  
12 needed to elucidate the possible mechanisms underlying the association between HCV  
13 sequences and host genetic factors, and also the role of host and viral factors for the  
14 prediction of treatment response.

15           In conclusion, a data mining analysis emphasized the impact of substitutions in  
16 ISDR and Core70 on pretreatment prediction of sustained virological response to  
17 PEG-IFN plus RBV therapy. A decision-tree model that includes substitutions in ISDR  
18 and Core70 of HCV could identify patients with high probability of sustained

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- 1 virological response, and could thereby improve the predictive accuracy over
- 2 predictions that are based on standard tests.

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Figure legends

*Figure 1. Decision-tree model.*

Boxes indicate the factors used for splitting and the cutoff value for the split.

Pie charts indicate the rate of sustained virological response for each group of patients

after splitting. Terminal subgroups of patients discriminated by the analysis are

numbered from 1 to 7. The rate of sustained virological response was >80% in

subgroups 1 and 2, 64% in subgroup 3, and 31%–36% in subgroups 4, 5, and 6. LDL-C

represents low-density lipoprotein cholesterol and Core70 represents amino acid

substitution at position 70 of the core region.

*Figure 2. Validation of the decision-tree analysis: Subgroup-stratified comparison of the rate of sustained virological response.*

Each patient in the validation set was allocated to subgroups 1–6 by following

the flowchart form of the decision tree, and the rates of sustained virological response

were then calculated and plotted for each subgroup. The X axis represents the rate of

sustained virological response in the model-building datasets and the Y axis represents

the rate of sustained virological response in the validation datasets. The rates of

achieving sustained virological response in each subgroup of patients correlated closely

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1 between the model-building dataset and the validation dataset (correlation coefficient:  $r^2$   
2 = 0.94).

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4 *Figure 3. Comparison of sustained virological response rates between groups divided*  
5 *by the decision tree.*

6 The rate of sustained virological response was compared between 3 groups of  
7 patients as divided by the decision-tree analysis. White, gray, and black boxes indicate  
8 the low-probability group (subgroup 4, 5, and 6), intermediate-probability group  
9 (subgroup 3), and high-probability group (subgroup 1 and 2), respectively. The rate of  
10 sustained virological response showed significant difference between the 3 groups.

11  
12 *Figure 4. Comparison of the rate of sustained virological response between the*  
13 *decision-tree groups stratified by drug adherence.*

14 The 3 groups of patients divided by the decision tree (black, gray, and white  
15 boxes indicating the low-, intermediate-, and high-probability groups, respectively)  
16 were further stratified according to cumulative drug exposure to PEG-IFN and RBV.

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1 References

- 2 Akuta N, Suzuki F, Hirakawa M, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T,  
3 Kobayashi M, Saitoh S, Arase Y, Ikeda K, Chayama K, Nakamura Y, Kumada H.  
4 2010. Amino acid substitution in hepatitis C virus core region and genetic  
5 variation near the interleukin 28B gene predict viral response to telaprevir with  
6 peginterferon and ribavirin. *Hepatology* 52:421-429.
- 7 Akuta N, Suzuki F, Hirakawa M, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T,  
8 Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kumada H. 2009. A matched  
9 case-controlled study of 48 and 72 weeks of peginterferon plus ribavirin  
10 combination therapy in patients infected with HCV genotype 1b in Japan: amino  
11 acid substitutions in HCV core region as predictor of sustained virological  
12 response. *J Med Virol* 81:452-458.
- 13 Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi  
14 M, Arase Y, Ikeda K, Kumada H. 2007a. Predictive factors of early and  
15 sustained responses to peginterferon plus ribavirin combination therapy in  
16 Japanese patients infected with hepatitis C virus genotype 1b: amino acid  
17 substitutions in the core region and low-density lipoprotein cholesterol levels. *J*  
18 *Hepatol* 46:403-410.

- 1 Predictive model of response to peg-IFN and RBV Kurosaki et al.  
2  
3  
4  
5  
6  
7 1 Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi  
8  
9  
10 2 M, Arase Y, Ikeda K, Kumada H. 2007b. Predictors of viral kinetics to  
11  
12 3 peginterferon plus ribavirin combination therapy in Japanese patients infected  
13  
14  
15 4 with hepatitis C virus genotype 1b. *J Med Virol* 79:1686-1695.  
16  
17  
18  
19 5 Akuta N, Suzuki F, Sezaki H, Suzuki Y, Hosaka T, Someya T, Kobayashi M, Saitoh S,  
20  
21  
22 6 Watahiki S, Sato J, Matsuda M, Arase Y, Ikeda K, Kumada H. 2005. Association  
23  
24  
25 7 of amino acid substitution pattern in core protein of hepatitis C virus genotype  
26  
27  
28 8 1b high viral load and non-virological response to interferon-ribavirin  
29  
30  
31 9 combination therapy. *Intervirology* 48:372-380.  
32  
33  
34 10 Averbook BJ, Fu P, Rao JS, Mansour EG. 2002. A long-term analysis of 1018 patients  
35  
36  
37 11 with melanoma by classic Cox regression and tree-structured survival analysis at  
38  
39  
40 12 a major referral center: Implications on the future of cancer staging. *Surgery*  
41  
42  
43 13 132:589-602.  
44  
45  
46 14 Baquerizo A, Anselmo D, Shackleton C, Chen TW, Cao C, Weaver M, Gornbein J,  
47  
48  
49 15 Geevarghese S, Nissen N, Farmer D, Demetriou A, Busuttill RW. 2003.  
50  
51  
52 16 Phosphorus ans an early predictive factor in patients with acute liver failure.  
53  
54  
55 17 *Transplantation* 75:2007-2014.  
56  
57  
58 18 Bedossa P, Poynard T. 1996. An algorithm for the grading of activity in chronic hepatitis  
59  
60

- 1 Predictive model of response to peg-IFN and RBV Kuroski et al.  
2  
3  
4  
5  
6  
7 1 C. The METAVIR Cooperative Study Group. *Hepatology* 24:289-293.  
8  
9  
10 2 Breiman LJH, Friedman RA, Olshen CJ, Stone CM. 1980. Classification and regression  
11  
12 3 trees. Calif: Wadsworth.  
13  
14  
15 4 Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. 2003. Early  
16  
17 5 virologic response to treatment with peginterferon alfa-2b plus ribavirin in  
18  
19 6 patients with chronic hepatitis C. *Hepatology* 38:645-652.  
20  
21  
22 7 Enomoto N, Sakuma I, Asahina Y, Kuroski M, Murakami T, Yamamoto C, Izumi N,  
23  
24 8 Marumo F, Sato C. 1995. Comparison of full-length sequences of  
25  
26 9 interferon-sensitive and resistant hepatitis C virus 1b. Sensitivity to interferon is  
27  
28 10 conferred by amino acid substitutions in the NS5A region. *J Clin Invest*  
29  
30 11 96:224-230.  
31  
32  
33 12 Enomoto N, Sakuma I, Asahina Y, Kuroski M, Murakami T, Yamamoto C, Ogura Y,  
34  
35 13 Izumi N, Marumo F, Sato C. 1996. Mutations in the nonstructural protein 5A  
36  
37 14 gene and response to interferon in patients with chronic hepatitis C virus 1b  
38  
39 15 infection. *N Engl J Med* 334:77-81.  
40  
41  
42 16 Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, Jr., Haussinger  
43  
44 17 D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. 2002.  
45  
46 18 Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N*  
47  
48  
49  
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51  
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53  
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- 1 Predictive model of response to peg-IFN and RBV  
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4  
5  
6  
7 1 Engl J Med 347:975-982.  
8  
9  
10 2 Garzotto M, Beer TM, Hudson RG, Peters L, Hsieh YC, Barrera E, Klein T, Mori M.  
11  
12 3 2005. Improved detection of prostate cancer using classification and regression  
13  
14 4 tree analysis. J Clin Oncol 23:4322-4329.  
15  
16 5 Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, Heinzen EL, Qiu P,  
17  
18 6 Bertelsen AH, Muir AJ, Sulkowski M, McHutchison JG, Goldstein DB. 2009.  
19  
20 7 Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance.  
21  
22 8 Nature 461:399-401.  
23  
24 9 Hezode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, Bronowicki JP,  
25  
26 10 Bourliere M, Gharakhanian S, Bengtsson L, McNair L, George S, Kieffer T,  
27  
28 11 Kwong A, Kauffman RS, Alam J, Pawlotsky JM, Zeuzem S. 2009. Telaprevir  
29  
30 12 and peginterferon with or without ribavirin for chronic HCV infection. N Engl J  
31  
32 13 Med 360:1839-1850.  
33  
34 14 Ikeda H, Suzuki M, Okuse C, Yamada N, Okamoto M, Kobayashi M, Nagase Y,  
35  
36 15 Takahashi H, Matsunaga K, Matsumoto N, Itoh F, Yotsuyanagi H, Koitabashi Y,  
37  
38 16 Yasuda K, Iino S. 2009. Short-term prolongation of pegylated interferon and  
39  
40 17 ribavirin therapy for genotype 1b chronic hepatitis C patients with early viral  
41  
42 18 response. Hepatol Res 39:753-759.  
43  
44  
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- 1 Predictive model of response to peg-IFN and RBV Kurosaki et al.  
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5  
6  
7 1 Izumi N, Nishiguchi S, Hino K, Suzuki F, Kumada Y, Itoh Y, Asahina Y, Tamori A,  
8  
9  
10 2 Hiramatsu N, Hayashi N, Kudo M. 2010. Management of hepatitis C; Report of  
11  
12 3 the consensus meeting at the 45th annual meeting of the Japan society of  
13  
14 4 hepatology (2009). *Hepatol Res* 40:347-368.  
15  
16  
17  
18  
19 5 Jensen DM, Morgan TR, Marcellin P, Pockros PJ, Reddy KR, Hadziyannis SJ, Ferenci P,  
20  
21  
22 6 Ackrill AM, Willems B. 2006. Early identification of HCV genotype 1 patients  
23  
24 7 responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy.  
25  
26  
27 8 *Hepatology* 43:954-960.  
28  
29  
30  
31 9 Kurosaki M, Enomoto N, Murakami T, Sakuma I, Asahina Y, Yamamoto C, Ikeda T,  
32  
33  
34 10 Tozuka S, Izumi N, Marumo F, Sato C, Ogura Y. 1997. Analysis of genotypes  
35  
36 11 and amino acid residues 2209 to 2248 of the NS5A region of hepatitis C virus in  
37  
38 12 relation to the response to interferon-beta therapy. *Hepatology* 25:750-753.  
39  
40  
41  
42  
43 13 Kurosaki M, Matsunaga K, Hirayama I, Tanaka T, Sato M, Yasui Y, Tamaki N,  
44  
45  
46 14 Hosokawa T, Ueda K, Tsuchiya K, Nakanishi H, Ikeda H, Itakura J, Takahashi Y,  
47  
48  
49 15 Asahina Y, Higak M, Enomoto N, Izumi N. 2010a. A Predictive Model of  
50  
51 16 Response to Peginterferon Ribavirin in Chronic Hepatitis C using Classification  
52  
53  
54 17 and Regression Tree Analysis. *Hepatol Res* 40:251-260.  
55  
56  
57  
58  
59 18 Kurosaki M, Sakamoto N, Iwasaki M, Sakamoto M, Suzuki Y, Hiramatsu N, Sugauchi F,  
60

- 1 Predictive model of response to peg-IFN and RBV  
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 3  
 4  
 5  
 6  
 7 1 Yatsuhashi H, Izumi N. 2010b. Pretreatment prediction of response to  
 8  
 9  
 10 2 peginterferon plus ribavirin therapy in genotype 1 chronic hepatitis C using data  
 11  
 12 3 mining analysis. J Gastroenterol in press.  
 13  
 14  
 15 4 Kurosaki M, Tanaka Y, Nishida N, Sakamoto N, Enomoto N, Honda M, Sugiyama M,  
 16  
 17 5 Matsuura K, Sugauchi F, Asahina Y, Nakagawa M, Watanabe M, Sakamoto M,  
 18  
 19 6 Maekawa S, Sakai A, Kaneko S, Ito K, Masaki N, Tokunaga K, Izumi N,  
 20  
 21  
 22 7 Mizokami M. 2010c. Pretreatment Prediction of Response to  
 23  
 24 8 Pegylated-Interferon Plus Ribavirin for Chronic Hepatitis C using Genetic  
 25  
 26 9 Polymorphism in *IL28B* and Viral Factors. J Hepatol in press.  
 27  
 28  
 29 10 LeBlanc M, Crowley J. 1995. A review of tree-based prognostic models. Cancer Treat  
 30  
 31 11 Res 75:113-124.  
 32  
 33  
 34 12 Lee SS, Ferenci P. 2008. Optimizing outcomes in patients with hepatitis C virus  
 35  
 36 13 genotype 1 or 4. Antivir Ther 13 Suppl 1:9-16.  
 37  
 38  
 39 14 Leiter U, Buettner PG, Eigentler TK, Garbe C. 2004. Prognostic factors of thin  
 40  
 41 15 cutaneous melanoma: an analysis of the central malignant melanoma registry of  
 42  
 43 16 the german dermatological society. J Clin Oncol 22:3660-3667.  
 44  
 45  
 46 17 Li JH, Lao XQ, Tillmann HL, Rowell J, Patel K, Thompson A, Suchindran S, Muir AJ,  
 47  
 48 18 Guyton JR, Gardner SD, McHutchison JG, McCarthy JJ. 2010.  
 49  
 50  
 51  
 52  
 53  
 54  
 55  
 56  
 57  
 58  
 59  
 60

- 1 Predictive model of response to peg-IFN and RBV Kurosaki et al.  
2  
3  
4  
5  
6  
7 1 Interferon-lambda genotype and low serum low-density lipoprotein cholesterol  
8  
9  
10 2 levels in patients with chronic hepatitis C infection. *Hepatology* 51:1904-1911.  
11  
12  
13 3 Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R,  
14  
15  
16 4 Goodman ZD, Koury K, Ling M, Albrecht JK. 2001. Peginterferon alfa-2b plus  
17  
18  
19 5 ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of  
20  
21  
22 6 chronic hepatitis C: a randomised trial. *Lancet* 358:958-965.  
23  
24  
25 7 McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R,  
26  
27  
28 8 McNair L, Alam J, Muir AJ. 2009. Telaprevir with peginterferon and ribavirin  
29  
30  
31 9 for chronic HCV genotype 1 infection. *N Engl J Med* 360:1827-1838.  
32  
33  
34 10 Miyaki K, Takei I, Watanabe K, Nakashima H, Omae K. 2002. Novel statistical  
35  
36  
37 11 classification model of type 2 diabetes mellitus patients for tailor-made  
38  
39  
40 12 prevention using data mining algorithm. *J Epidemiol* 12:243-248.  
41  
42  
43 13 Munoz de Rueda P, Casado J, Paton R, Quintero D, Palacios A, Gila A, Quiles R, Leon  
44  
45  
46 14 J, Ruiz-Extremuera A, Salmeron J. 2008. Mutations in E2-PePHD,  
47  
48  
49 15 NS5A-PKRBD, NS5A-ISDR, and NS5A-V3 of hepatitis C virus genotype 1 and  
50  
51  
52 16 their relationships to pegylated interferon-ribavirin treatment responses. *J Virol*  
53  
54  
55 17 82:6644-6653.  
56  
57  
58 18 Shirakawa H, Matsumoto A, Joshita S, Komatsu M, Tanaka N, Umemura T, Ichijo T,  
59  
60

- 1 Predictive model of response to peg-IFN and RBV Kurosaki et al.  
2  
3  
4  
5  
6  
7 1 Yoshizawa K, Kiyosawa K, Tanaka E. 2008. Pretreatment prediction of  
8  
9  
10 2 virological response to peginterferon plus ribavirin therapy in chronic hepatitis  
11  
12 3 C patients using viral and host factors. *Hepatology* 48:1753-1760.  
13  
14  
15  
16 4 Shiratori Y, Omata M. 2000. Predictors of the efficacy of interferon therapy for patients  
17  
18 5 with chronic hepatitis C before and during therapy: how does this modify the  
19  
20 6 treatment course? *J Gastroenterol Hepatol* 15 Suppl:E141-151.  
21  
22  
23  
24  
25 7 Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M,  
26  
27  
28 8 Spengler U, Dore GJ, Powell E, Riordan S, Sheridan D, Smedile A, Fragomeli V,  
29  
30  
31 9 Muller T, Bahlo M, Stewart GJ, Booth DR, George J. 2009. IL28B is associated  
32  
33 10 with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat*  
34  
35 11 *Genet* 41:1100-1104.  
36  
37  
38  
39  
40 12 Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa  
41  
42 13 M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S,  
43  
44 14 Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I,  
45  
46 15 Imamura M, Ito K, Yano K, Masaki N, Sugauchi F, Izumi N, Tokunaga K,  
47  
48 16 Mizokami M. 2009. Genome-wide association of IL28B with response to  
49  
50 17 pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat*  
51  
52 18 *Genet* 41:1105-1109.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
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5  
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57  
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59  
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- 1 Valera VA, Walter BA, Yokoyama N, Koyama Y, Iiai T, Okamoto H, Hatakeyama K.  
2 2007. Prognostic groups in colorectal carcinoma patients based on tumor cell  
3 proliferation and classification and regression tree (CART) survival analysis.  
4 Ann Surg Oncol 14:34-40.
- 5 Yu ML, Dai CY, Huang JF, Chiu CF, Yang YH, Hou NJ, Lee LP, Hsieh MY, Lin ZY,  
6 Chen SC, Wang LY, Chang WY, Chuang WL. 2008. Rapid virological response  
7 and treatment duration for chronic hepatitis C genotype 1 patients: a randomized  
8 trial. Hepatology 47:1884-1893.
- 9 Zlobec I, Steele R, Nigam N, Compton CC. 2005. A predictive model of rectal tumor  
10 response to preoperative radiotherapy using classification and regression tree  
11 methods. Clin Cancer Res 11:5440-5443.

Table 1. Comparison of pre-treatment factors between model building and validation patients

	Model (n=304)	Validation (n=201)	P value
age (years)	55.6 (9.4)	56.0 (12.2)	0.80
male (%)	53 (%)	55 (%)	0.13
body mass index (kg/m <sup>2</sup> )	23.1 (3.1)	23.1 (4.0)	0.99
albumin (g/dL)	4.0 (0.3)	4.0 (0.3)	0.47
creatinine (mg/dl)	0.72 (0.15)	0.72 (0.14)	0.62
AST (IU/L)	63.3 (45.6)	58.9 (46.4)	0.91
ALT (IU/L)	78.7 (58.6)	74.5 (67.5)	0.68
GGT (IU/L)	53.2 (49.1)	57.4 (63.5)	0.43
total cholesterol (mg/dl)	170.9 (32.6)	169.4 (34.1)	0.33
triglyceride (mg/dl)	107.0 (44.7)	105.7 (48.0)	0.90
LDL-C (mg/dl)	95.5 (28.0)	96.4 (28.8)	0.34
White blood cell count (/ $\mu$ L)	4902 (1489)	4906 (1319)	0.86
Hemoglobin (g/dL)	14.1 (1.3)	14.3 (1.4)	0.09
Platelets ( $10^9$ /L)	164 (56)	172 (55)	0.68
HCVRNA ( $10^3$ IU/ml)	1859 (1468)	2021 (1393)	0.09
ISDR mutations: $\geq 2$ (%)	15 (%)	20 (%)	0.11
Core 70: mutant (%)	36 (%)	29 (%)	0.22
Core 91: mutant (%)	40 (%)	36 (%)	0.20
Fibrosis: F2-4 (%)	49 (%)	48 (%)	0.36
Activity: A2-3 (%)	42 (%)	34 (%)	0.10

Data expressed as mean (SD)

AST: aspartate aminotransferase

ALT: alanine aminotransferase

GGT: gamma-glutamyltransferase

LDL-C: low-density-lipoprotein-cholesterol

ISDR: interferon sensitivity determining region

Table 2. Multivariable logistic regression analysis for factors associated with SVR

Parameter		Odds	95% CI	p value
Age (years)	<60 vs. ≥60	2.28	1.31-3.94	0.003
Gender	Male vs. Female	3.36	1.87-5.99	<0.0001
GGT(IU/L)	<40 vs. ≥40	2.65	1.45-4.85	0.002
LDL-C(mg/dl)	≥120 vs. <120	1.79	0.91-3.53	0.094
Platelets (10 <sup>9</sup> /L)	≥120 vs. <120	2.69	1.22-5.90	0.014
ISDR mutations	≥2 vs. 0-1	9.92	3.71-26.54	<0.0001
Core 70	Wild vs. Mutant	1.92	1.07-3.47	0.030

GGT: gamma-glutamyltransferase

LDL-C: low-density-lipoprotein-cholesterol

ISDR: interferon sensitivity determining region