The BALAD-2 and GALAD Biomarker Models for Hepatocellular Carcinoma

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G&H Do biomarkers currently have a role in hepatocellular carcinoma?

PJ The role of biomarkers in hepatocellular carcinoma (HCC) is controversial. **[For example, the best-known biomarker in HCC?]** **[OK]**is α-fetoprotein (AFP), which has been around for more than 50 years. Many hepatologists use AFP as a diagnostic aid, but there are probably an equal number who do not think that the biomarker is any help because it is, ~~reputably~~reputably, relatively nonspecific. Thus, there are 2 schools of thought: one that believes that there is a role for biomarkers in HCC and one that does not.

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G&H How and why were the BALAD-2 and GALAD biomarker models developed?

PJ Doctors in Japan, **[which has a high incidence and prevalence of HCC?]**, have used the biomarkers AFP, des-γ-carboxyprothrombin (DCP), and AFP-L3 for many years for the diagnosis of HCC as well as for undertaking surveillance of patients who are at high risk for the disease. However, whilst there was still a need for more sensitive and specific biomarkers for HCC an alternative approach is to combine existing ones.. **[ok to add previous sentence?]** Thus, the markers were combined BALAD (bilirubin, albumin,

AFP-L3, AFP, and DCP) and GALAD (gender, age, AFP-L3, AFP, and DCP) ~~biomarker~~ models were developed **[in an attempt to improve the prognostication and diagnosis, respectively, of HCC?]**. The prognostic BALAD model was developed by Dr Hidenori Toyoda and colleagues in 2005. ~~**[Why were bilirubin, albumin, AFP-L3, AFP, and DCP chosen to be in the model and not other components?]**~~

Subsequently, my colleagues and I in Birmingham~~we~~, UK **[who—"colleagues from several European centers and I"?]** undertook a close collaboration with **[Toyoda and colleagues?]****[OK]** to combine their original data with some data of our own and perform a rigorous statistical analysis to develop BALAD-2. This biomarker model is very similar to the original BALAD model; it just involves a more **[complex?]** statistical analysis and provides a slightly better performance.

[We can readily give the formula but I am not sure if this would be very informative to your reader. A diagram showing its output might be more relevant]~~**[Why was BALAD-2 developed? Could you give more specific information on how the analysis differs? Is it possible to give the formula?]**~~

The diagnostic GALAD model uses the same 3 biomarkers of the BALAD model but also considers gender and age. **[My colleagues and I?]****[OK]** used data **[on AFP, AFP-L3, and DCP?]****[OK]** from **[Toyoda and colleagues?]****[OK]** to build a rigorously

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validated statistical model in close collaboration with the Japanese researchers. The published formula is 10.08 + 0.09 × age + 1.67 × male gender + 2.34 × log (AFP) + 0.04 × AFP-L3 + 1.33 × log (DCP). **[Please confirm or correct formula]**[OK, Again, not convinced that giving the formula helps. An illustrative figure might be more informative]

The main difference between **[individual biomarker use by Toyoda and colleagues and use of the GALAD model?]** is that the former used predefined biomarker cutoff points for being positive or negative, whereas the GALAD model considers the individual biomarkers in their continuous format. Using a continuous format is probably better than using predefined cutoffs~~.~~; ~~[Please explain why.]~~the latter "wastes" much information.

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G&H Why did you and your colleagues choose to use AFP, AFP-L3, and DCP when building HCC biomarker models? **[rewording ok?]**

PJ Those biomarkers were chosen because they are available on a commercial platform, they are very well-characterized assays, and there is a vast amount of data on them from Japan for further analysis.

G&H Based upon the data available thus far, how does the performance of the GALAD model compare with that of the individual biomarkers? **[rewording ok?]**

PJ The best way of examining the performance of a model such as GALAD is to look at its area under the receiver operating characteristic curve. This number provides a general description of how good a model is. It is clear that AFP, AFP-L3, and DCP are each diagnostically distinctive. When these 3 biomarkers are combined, **[diagnosis?]** improves in all populations and stages of the disease. The GALAD model is clearly better than using the biomarkers separately. **[Diagram to support this contention]. [Please provide some specific data from 1 or more studies.]**

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G&H How sensitive and specific is the GALAD model?

PJ It is important to keep in mind that sensitivity and specificity are reciprocally related, so if sensitivity is high, then specificity goes down, and vice-versa. Optimal sensitivity and specificity are in the order of approximately 0.85—ie, approximately 85% sensitive and approximately 85% specific. However, the sensitivity and specificity of the GALAD model vary across different subgroups and disease stages, which is why the area under the receiver operating characteristic curve is better to use. **[Should we delete this question and answer?][OK as above]**

G&H Has the GALAD model been examined in terms of different underlying liver disease and race?

PJ Yes. The model seems to be roughly as effective irrespective of disease etiology. **[Please provide some specific data]** **Diagram**

An abstract presented at last year's European Association of the Study of the Liver meeting by Dr Ju Dong Yang, on behalf of colleagues at the Mayo Clinic including lead investigator Dr Lewis Roberts, examined the use of the GALAD model in various subgroups, including different races, in several large US centers. **[edits to sentence ok?]** **[OK]**Under the aegis of the National Cancer Institute Early Detection Research Network, the researchers concluded that the performance of the GALAD model for HCC diagnosis in a multicenter US cohort was excellent. They also found that the sensitivity, specificity and AUROC varied slightly according to ethnicity, aetiology and disease stage.~~the results slightly differed according to race (black vs white).~~ **[Please provide some specific data]**

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G&H Has the GALAD model been used in early- and late-stage HCC?

PJ Yes, the abstract by Yang and colleagues found that the GALAD model works well in both settings~~.~~ **[Please provide some specific data]** **and**

~~I~~in a study published **[by my colleagues and I?]****[OK]**, the GALAD model even worked well irrespective of tumor size, which was a surprise. **[Please provide some specific data]** **[Figure]**

G&H Does the GALAD model have any other roles in HCC?

PJ That is an area of active investigation at the moment. The GALAD score appears to be proportional to the tumor cell mass. Thus, in the future, the GALAD model might be useful for monitoring treatment. Even more controversially, the score appears to be elevated before cancer can be seen on a scan, which means that it may have a role in the surveillance setting for very early diagnosis of HCC. However, more research is needed on both of these issues. **[edits throughout this paragraph ok?]**[OK as is]

G&H What studies have been conducted using the BALAD-2 model?

PJ A large, recent, international, multicenter study conducted by Dr Sarah Berhane and colleagues (of which I was a part) described the prognostic use of BALAD-2 in detail. We~~The authors~~ concluded that BALAD-2 provides an extremely good indication of the prognosis of HCC patients irrespective of etiology and cancer size~~.~~ and in ~~**[Could you provide more detail/data?]**~~

~~In~~ a recent nationwide study of Japan conducted by Toyoda and colleagues, BALAD-2 showed a modest improvement (ie, better prognostic performance) over the original BALAD model across all stages of disease and all etiologies. **[Could you provide more detail/data?]** **[Figures]**

G&H What are the advantages and disadvantages of the GALAD model?

PJ One advantage is that it is entirely objective; it does not require any subjective factors or interpretation of radiographic images. Another advantage is that it is easy to determine the score, which can be done with an online calculator (eg, at http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/galad) or a smartphone application.

A disadvantage of both models is that, at the moment, there is a relatively small number of laboratories that will perform the 3 biomarker assays. Such laboratories are numerous in Japan and are starting to increase in Europe and the United States, but are not yet widespread. A second disadvantage, common to all serological approaches to early diagnosis, is that whilst the GALAD model may suggest that an HCC has developed it doesn't say "where" it is. Only radiology can perform this task.

[Do the above 2 advantages and 1 disadvantage also apply to BALAD-2? If so, can we change the question to "What are the advantages and disadvantages of the 2 biomarker models?" and then still include the disadvantage of the BALAD-2 listed below?]

G&H What are the advantages and disadvantages of the BALAD-2 model? [Answered above]

PJ The BALAD-2 model works well. If a patient's AFP, AFP-L3, and DCP are available, it is possible to obtain a good idea of the patient's outlook.

However, I think that the BALAD-2 score is very much a secondary output from these 3 biomarkers, with the GALAD score being more important. I think it is fair to say that a **[medical center?]** would not measure AFP, AFP-L3, and DCP **[only to obtain?]**[OK] a BALAD-2 score. The reason that these biomarkers would be measured every day would be to obtain a GALAD score (ie, for diagnosis) and since the 3 biomarkers are measured, then that information could also be used for the BALAD-2 model ~~for screening (ie,~~ for prognosis~~)~~. **[edits to sentence ok?]**

G&H Do you think that these models will eventually replace the use of individual biomarkers and/or imaging?

PJ It remains to be seen. **[However, there may always be a need for radiologic imaging?].** For example, the GALAD score can indicate whether a patient has a cancer or is likely to develop one. What it cannot do is show where that cancer is located in the liver. **[this sentence - a disadvantage of GALAD could come in here or as inserted above - up to you]**For many forms of treatment, particularly early treatment, it is necessary to know exactly where the cancer is located. Most likely, if these models prove to be successful in prospective trials, they would be used in combination with current radiology. **[edits ok?]**

G&H Are other biomarker models also being investigated in HCC?

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PJ There are currently numerous biomarker models being examined. However, in many cases, these are developed in individual laboratories, reported~~there is little research on these models in the literature~~, and then no further steps are taken because the assays are not robust enough to be transferred consistently around the world. **[edits to sentence ok?]****[OK]**

G&H What are the next steps in research regarding the GALAD and BALAD-2 models?

PJ The most important next step is further prospective study, and there are at least 2 prospective studies currently being conducted. One is being performed in Toronto, Canada with Dr Morris Sherman as the lead investigator. The other study, which is being led by Dr Hashem El-Serag in Texas, will be reporting its findings in the next few weeks. These studies will help determine whether the GALAD~~is~~ model **~~[which model?]~~** becomes more widely applied.

[Do you have any conflicts of interest to disclose pertaining to the content of the column?] **None**

[Please feel free to add to or delete any of the articles listed below.]
[H1] Suggested Reading

Berhane S, Toyoda H, Tada T, et al. Role of the GALAD and BALAD-2 serologic models in diagnosis of hepatocellular carcinoma and prediction of survival in patients. *Clin Gastroenterol Hepatol*. 2016;14(6):875-886.e6.

Johnson PJ, Pirrie SJ, Cox TF, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. *Cancer Epidemiol Biomarkers Prev*. 2014;23(1):144-153.

Toyoda H, Kumada T, Tada T, Sone Y, Kaneoka Y, Maeda A. Tumor markers for hepatocellular carcinoma: simple and significant predictors of outcome in patients with HCC. *Liver Cancer*. 2015;4(2):126-136.

Toyoda H, Tada T, Johnson PJ, et al. Validation of serological models for staging and prognostication of HCC in patients from a Japanese nationwide survey [published online February 21, 2017]. *J Gastroenterol*. doi:10.1007/s00535-017-1321-6.

Yang JD, Dai J, Addissie B, et al. Validation of the GALAD score for hepatocellular carcinoma diagnosis in a US cohort. *J Hepatol*. 2016;64(2 suppl):S330.

[box] A copy of this interview is appearing in the April 2017 issue of *Clinical Advances in Hematology & Oncology*.