The goal of the American Association for the Study of Liver Disease (AASLD) single-topic conference on hepatocellular carcinoma (HCC) was to highlight areas of research necessary to further our understanding of the pathogenesis and management of this disease. Three major areas in which the necessity of extensive further research was identified include screening for HCC, staging of disease, and management, particularly studies on liver transplantation. The need for better disease models for decision analysis and better diagnostic methods was noted. For screening, better serological screening tests will be required, and, difficult though it may be, a randomized controlled study comparing screening with no screening is still a necessary study. Current staging systems are insufficiently validated and are not comparable in different areas of the world. A universal staging system is essential and would require international collaboration for it to be established. In the therapeutic area, studies are needed to improve identification of patients suitable for transplantation, and to improve management on the waiting list. Properly conducted phase 3 studies are required to establish the role of currently improperly evaluated therapies. Newer agents should also be subject to randomized controlled trials. Finally, although progress is being made in the understanding of the pathogenesis of HCC, the sequential molecular changes in hepatocarcinogenesis remain obscure. Genomics and proteomic studies are likely to yield significant insights.

The American Association for the Study of Liver Diseases sponsored a Single Topic Research Conference on Hepatocellular Carcinoma, which was held in Atlanta in September 2003. Topics were selected for presentation that reflected controversy, required additional research, or subjects that were currently under active research. The objective of this conference was to identify deficiencies in our knowledge of the pathogenesis, diagnosis, and management of hepatocellular carcinoma (HCC) and to identify areas of research and suggest study designs to explore these deficiencies in our knowledge. This document summarizes the information that was presented and the discussions that followed.

**Staging of Hepatocellular Carcinoma** (Bruno Daniele, J Michael Henderson)

A number of staging and prognostic scoring systems have been recently reported. Most cancer scoring systems and prognostic indices are developed by retrospectively identifying variables correlating with prognosis, using either chi-square or univariate analysis techniques. Whether these variables are independent of each other is then determined by multivariate analysis (usually using the Cox proportional hazards model). The independent variables are combined into a score. Kaplan-Meier survival curves are constructed for each variable and combinations of variables and the log rank test applied to show whether the curves are statistically different. Thus, the scores are combined into a staging system. The Barcelona Cancer of the Liver Clinics (BCLC) system started by classifying patients according to markers of disease severity previously used to determine the type of therapy to be applied. The Child-Turcotte-Pugh score was also incorporated into the BCLC staging. Other scores were developed using traditional methodology. The Cancer of the Liver Italian Program (CLIP) score incorporated the Child-Turcotte-Pugh score, and the Chinese University Prognostic Index incorporated the standard TNM (tumor, node, metastasis) classification.

None of these staging systems were felt to be ideal. Each system incorporates features of earlier prognostic scores, either the Child-Turcotte-Pugh score or the TNM score. The validity of using the Child-Turcotte-Pugh score for patients with HCC has never been established, and the TNM score does not include prognostic variables related to liver disease. The CLIP score does not differentiate tumor size until the tumor occupies 50% of the liver. In other systems, tumor size is important, although the diameter at which tumor size starts to make a difference to survival is uncertain. Only the CLIP score has had any
A consensus panel struck by the American Hepatopancreaticobiliary Association (AHPBA) and the American Joint Committee on Cancer (AJCC) recommended that the CLIP system be applied initially. Patients who underwent resection (including transplantation) should undergo a secondary classification using either the AJCC or the international Hepatopancreaticobiliary Association (IHPBA) classification. The AHPBA/AJCC group also recommended that all future reports on diagnosis, therapy, and prognosis should stratify patients by at least one prognostic score.

The participants in the workshop on HCC staging indicated that all current staging systems need refinement, and that none were sufficiently validated or widely applicable. In particular, a need exists to accurately stage small HCC. This should be achieved by international collaboration to prospectively validate one or more of the current staging systems, or to develop a new system that is representative of all the different risk factor groups across the world. Any system that claims to indicate prognosis must be based on a large clinical database, and may include laboratory data and radiology. The system must undergo extensive internal and external validation and must be generally applicable to HCC with different underlying etiologies. Finally, the staging system must eventually be a guide to therapy.

**Modeling Disease in Hepatocellular Carcinoma (W Ray Kim, Antoine Hadengue)**

Two types of models are in common use. Statistical models (e.g., Cox proportional hazards model) are used to determine how well an outcome correlates with explanatory variables. Decision analysis models (e.g., Markov model) are used to answer questions about the relationship between disease outcome and a number of different disease stages. The Cox proportional hazards model is the most appropriate statistical technique to model the natural history of disease. Cox models are used to identify factors either associated with, or predictive of, a disease. This is a form of regression analysis.

A Markov model attempts to define health states found in the natural history of the disease (e.g., hepatocellular carcinoma) and to determine the probability of transitioning between the different health states. The model is used to determine how changes in transition probabilities might impact overall outcome (e.g., survival or mortality rates). Markov modeling has been used to evaluate several HCC-related questions, including the cost–utility of screening policies in patients with cirrhosis, the value of partial hepatectomy or liver transplantation for early HCC, the value of liver resection and salvage transplantation for early HCC, and issues around living donor transplantation for HCC. Decision analysis is useful for providing estimates where experimentation is lacking, or where experimentation is not feasible. For example, decision analysis has identified circumstances in which screening for HCC might be an effective strategy to reduce mortality from this disease.

However, the models are highly dependent on the quality of data used to populate the model, and on the basic assumptions about natural history. Markov modeling is commonly used in assessment of the efficacy of interventions (e.g., interferon therapy for hepatitis C).

**Screening for Hepatocellular Carcinoma (Murray Krahn, Morris Sherman, Brian McMahon, Franco Trevisani)**

To date, no studies directly assess the question of whether HCC screening decreases the gold standard of disease-specific or all-cause mortality.

**The At-Risk Population.** The population that needs to undergo screening has only been defined in outline, namely, patients with cirrhosis, and among patients without cirrhosis, those with chronic hepatitis B. The European Association for Study of the Liver (EASL) consensus conference on HCC recommended that patients with hepatitis C and stage 3 fibrosis also undergo screening. The risk of HCC is not high, but screening is recommended because the transition to cirrhosis cannot be defined without repeated liver biopsies. The efficacy and cost-effectiveness of this recommendation have not been determined.

Studies are needed to better identify the at-risk population. These studies should define overall HCC incidence in specific groups and subgroups of the at-risk population (e.g., men vs. women, or at different ages). They should also identify markers of imminent HCC risk (e.g., within 3 years vs. lifetime risk). Modeling techniques could then be used to determine whether screening was effective or cost-effective in the specific subgroups.

**Screening Tests.** Most of the information we have about the behavior of HCC comes from observation of clinically detected cancer. However, screening detects lesions before they become clinically active. It cannot be assumed that the cancer behaves in a similar manner in the two situations.

The sensitivity and specificity of a diagnostic test changes with cancer stage, and thus they are also likely to be different in preclinical cancers. The sensitivity and specificity of diagnostic or screening tests cannot be considered reliable when the disease in question has not been verified, such as when the diagnosis of small HCC is made...
The most recent potential screening test is the glypican-3 assay. This is a protein expressed on the cell surface in HCC and not in normal liver. Approximately 50% of patients with HCC have detectable levels of circulating glypican-3. Glypican-3 has not been evaluated in a screening mode, but the fact that it is expressed in early lesions suggests that it may be a suitable marker, at least in those patients in whom it is positive.

The most widely used screening test is periodic ultrasonography. Although improvements in ultrasonographic techniques, including contrast-enhanced ultrasound, are under development, these are unlikely to be used for screening, because one of the requirements of a screening test is that it should be simple to administer and should be widely available. Contrast-enhanced ultrasound does not meet this test. Clearly, however, ultrasound detection of small HCC has to be improved. The major weakness of ultrasonography is the extent to which the findings are dependent on the care and skill of the operator. Methods to automate the examination and reduce the dependency on the operator will make ultrasound more reliable.

The members of the workshop on screening and surveillance for HCC believed that, although designing and running a trial of screening for HCC would be difficult, considerable support existed for testing whether screening was effective by performing a randomized controlled trial of screening versus no screening. The group recommended that future studies of screening should bank serum to assess new screening tests as they develop. In addition, given the profusion of small serum banks, a registry of serum banks should be developed. Other issues discussed included the fact that currently no universally accepted “gold standard” exists for the diagnosis of HCC in screening studies. Authors have used biopsy or explant diagnosis, or have used combined clinical and radiological diagnoses. These diagnoses have not been standardized.

**Recall.** The recall process includes the initial testing undertaken to evaluate an abnormal screening test and, in the case of negative investigations, includes all follow-up studies performed over time to confirm or refute the presence of HCC. Unresolved issues in recall include the value of liver biopsy, the sensitivity and specificity of radiological investigations, and the identification of false-positive screening tests.

**Radiological Tests in the Diagnosis of Small HCC (Elliot Fishman)**

Once an ultrasound result suggests the possibility of a small HCC, the next step is usually a triphasic CT scan. The larger the lesion, the more confident one can be about the diagnosis. However, when the lesion is smaller than approximately 2 cm, other vascular lesions such as
small hemangiomas, peliosis, and cirrhotic and dysplastic nodules, mimic HCC vascular patterns on CT.\textsuperscript{29,30} Contrast-enhanced magnetic resonance imaging (MRI) has the same problems, although with MRI other helpful features may be present. HCC and dysplastic nodules are different on T1 and T2 images; unfortunately, the sensitivity and specificity of these features are not sufficiently high that they can be relied on in isolation.\textsuperscript{31} The EASL single-topic conference on HCC\textsuperscript{13} suggested that lesions smaller than 1 cm should be monitored by repeat scanning over time. Enlarging lesions are likely to be HCC. Lesions larger than approximately 2 cm can be confidently diagnosed on the basis of radiological features of HCC in the setting of cirrhosis and do not need additional investigations. For lesions between 1 and 2 cm, biopsy was recommended. There is evidence for accepting that lesions larger than 2 cm in the correct clinical setting are HCC. However, no evidence exists that performing a biopsy for lesions between 1 and 2 cm is the best strategy.

Newer imaging techniques, such as the multidimensional CT scanning devices currently found\textsuperscript{16} and planned for the future,\textsuperscript{32} will allow much smaller slices of liver to be analyzed.\textsuperscript{33} Together with new software to reconstruct three-dimensional images, the quality of images will likely improve dramatically. Improved quality will likely result in enhanced detection of small lesions, but whether it will also result in enhanced characterization of small lesions and better distinction between small HCC and nonmalignant lesions is not clear. Unlike most other medical fields, the radiological literature lags behind clinical practice by 1 to 2 years. Thus, radiological clinical practice is driven by the availability of technology, rather than by scientific evidence. The lack of technology makes setting up studies in this area difficult.

Nonetheless, studies will still be necessary to determine the optimal use of newer and existing technologies in the evaluation of HCC. Studies are required to determine the most effective and most cost-effective tests and sequence of tests required to confirm or refute the presence of HCC in patients with small liver nodules discovered on screening.

**Liver Biopsy (Adrian DiBisceglie, Ian Wanless)**

The proper role of liver biopsy has still to be determined. The sensitivity and specificity of biopsy of small lesions are unknown. No internationally accepted standard exists for separating high-grade dysplasia from cancer.\textsuperscript{34} Of 26 lesions examined by an international working group, only 4 were unanimously called by all observers. Japanese pathologists tend to “overcall” HCC, whereas Western-trained pathologists tend to “undercall” HCC. Even once inter-observer variation has been reduced, whether a particular appearance is called malignant versus dysplastic is still a matter of definition, because the natural history of these lesions remains unknown.

In addition to the difficulty with biopsy diagnosis of HCC, reports exist of needle track seeding. Most of these are seen in nodules larger than those found on screening. Whether the risk of needle track seeding is as high in small HCC has not been determined.

Additional studies are ongoing to reduce inter-observer variation in the diagnosis of small nodules. The next step will be to determine whether the pathological classification corresponds to clinical behavior. It will likely be impossible to verify whether nodules diagnosed as malignant behave as cancers, because these will be treated. However, verification that those tumors diagnosed as nonmalignant behave as nonmalignant lesions is equally important.

Newer histological markers of HCC need to be identified. These should be shown to correlate highly with behavior consistent with malignancy.

Finally, studies should address whether confirmation of the diagnosis of HCC by histology is necessary in small HCC, or whether the lesions should be managed according to the way they behave over time.

**Therapy.** Several major difficulties arise in comparing outcomes of different therapeutic modalities for HCC. Patients included in different studies are not homogeneous. Several different endpoint measurements are used, such as disease-free survival, time to death, or time to recurrence. The use of disease-free survival should be discouraged. This is a composite endpoint, which obscures both recurrence rates and true survival, both of which are important independent endpoints. A therapy could arrest cancer growth but not eradicate disease. As a result, the disease-free survival would be short or nonexistent, despite that fact that the treatment may produce significant benefit. The participants generally agreed that the use of disease-free survival as an endpoint was inappropriate. Rather, time to recurrence and survival should be presented as separate endpoints.

**Resection (Scott Helton)**

No solid evidence exists that resection of HCC improves survival. Furthermore, few reports include patients stratified according to some recognized staging system. As a result, survival in patients with small lesions and good liver function is analyzed together with that of patients with large lesions and less good liver function.

Resection is becoming less common, as liver transplantation for HCC gains in popularity, at least in the West. The role of adjuvant therapy before or after surgery is not clear. Similarly, use of interferon postoperatively in pa-
tients with hepatitis C–related HCC also seems to reduce recurrence risk. However, most these studies are not of high quality.

Liver Transplantation for HCC (Andrew Klein, Amodeo Marcos, Nathan Bass)

Theoretical arguments arise in favor of total hepatectomy and liver transplantation as therapy for HCC. Liver transplantation may be curative for the index lesion as well as the field defect that might lead to future cancers. In patients with cirrhosis, the possibility for surgical cure exists for patients who might not tolerate resection. Several centers have now reported series that, although not randomized and not matched, indicate that patients who undergo orthotopic liver transplantation have a considerably better survival than do patients undergoing resection. With the increasing demand for donor organs, however, the time from listing to transplantation has increased, threatening the eligibility of patients with HCC while on the waiting list. In an attempt to prevent this, the United Network of Organ Sharing has established priority criteria for patients with “early stage” HCC, which allows them to “jump the queue.” The model for end-stage liver disease (MELD) score for patients with stage II (single tumors larger than 2 cm but smaller than 5 cm or fewer than 3 tumors all smaller than 3 cm) HCC is 24 points and 20 points for stage I (single HCC smaller than 2 cm) disease. Several studies have suggested that these selection criteria are somewhat restrictive and that, in fact, the criteria may be expanded to extend transplant priority to patients with larger tumor burdens, with little loss of overall benefit. This issue remains controversial, and not all investigators agree that expanding the criteria for transplantation results in comparable outcomes.

Because the duration of time on the waiting list is so important in determining whether a patient is suitable for transplantation, understanding the growth patterns of HCC is important. An understanding of how tumors grow, and identification of different predictors of rapid or slower growth, may aid in determining priority for transplantation.

Insufficient data exist to determine whether adjuvant or neoadjuvant therapy before or after liver transplantation has any effect on outcome. Chemoembolization, chemotherapy, and stem cell transplantation have been reported in small series. No reports exist of the effects of local ablation on the outcome of liver transplantation.

Living donor transplantation could extend the indications for transplantation to patients who would not otherwise qualify for a deceased donor allograft, even under extended criteria. This topic was the subject of a debate at the meeting. The points for and against this argument can be summarized as follows: The 5-year survival of patients undergoing transplantation for early-stage HCC under current listing criteria equals that of patients receiving transplants for benign diseases. Given that these patients lack alternatives, expecting such high survival rates for patients with cancer is unreasonable. As an example, liver transplantation for fulminant hepatic failure has approximately a 60% one-year survival. Which HCC stage constitutes an acceptable risk for liver transplantation is debatable. Two groups of patients must be considered: patients who initially meet United Network of Organ Sharing (UNOS) listing criteria but experience dropout because of tumor progression while on the waiting list, and patients outside current listing criteria at the time of presentation.

Markov analysis of the benefits of liver transplantation suggest that living donor transplantation extends life by approximately 4.5 years compared with cadaveric liver transplantation. This analysis is highly dependent on the dropout rate on the waiting list and on posttransplant survival. However, living donor transplantation is a scarce resource that relies on public trust. The idea of living donation must not be placed at risk by placing the life of a healthy individual in jeopardy for futile expectations.

The criteria for transplantation, whether the original “Milan” criteria or the expanded UCSF criteria have not been validated. Neither set of criteria conforms to any HCC staging systems. A staging system has been developed specifically for transplantation for HCC, but the criteria can only be applied in the explanted liver. Radiological staging underestimates the tumor burden and therefore is not an accurate surrogate for explant staging.

The objectives of research in liver transplantation for HCC should be to develop better modeling for allocation of livers to patients with HCC versus no HCC. Current priority criteria for HCC have resulted in too many patients who do not have HCC being transplanted for HCC because biopsy is not required. Randomized controlled trials that compare adjuvant therapy with no adjuvant therapy are needed. Pre-transplantation, the comparisons should be transarterial chemoembolization (TACE) versus no TACE, and TACE versus radiofrequency ablation (RFA). Study endpoints should be overall survival, recurrence, and presence of cancer on histology of the explant. These studies should include an assessment of whether treatment-induced “down-staging” of HCC makes patients suitable for orthotopic liver transplantation, or whether “down-staged” tumors still have the prognosis associated with the original tumor burden. Post-transplantation, the suggested comparisons were chemotherapy versus no chemotherapy. Whether such trials should
include some form of preferential allocation of organs to those who form the control group has to be decided. Such studies should include studies on the quality of life of patients undergoing orthotopic liver transplantation for HCC compared with patients undergoing transplantation for other diagnoses.

The group suggested that the National Institutes of Health should develop and fund a database to collect information on transplantation for HCC. Such a data repository can be used for clinical decision making on screening while patients waiting for transplant, therapies, and outcomes, as well as provide data for clinical staging.

**Local Ablation.** Local ablation has been performed with many different agents, including injection of alcohol, hot saline, and concentrated acetic acid, and physical destruction of the lesion with heat (microwave or radiofrequency), cold (cryosurgery), sound (focused ultrasound), or light (laser therapy). None of these modalities has been compared with untreated controls, and none has been compared with each other in randomized prospective studies of sufficient sample size. Furthermore, in most studies, the follow-up has been short, up to 2 years. The procedures have a 1-year survival of approximately 50% to 75% and a 2-year survival of 30% to 45%.45 Because many studies did not include biopsy, the accuracy of these survival figures is unreliable. Randomized prospective studies comparing different methods of achieving local ablation are needed.

Studies of resection versus local ablation may be feasible. Most series of local ablation suggest that at 5 years the survival rivals that of surgery, with a comparable recurrence rate. However, many studies of local ablation did not include a biopsy of the lesions being treated. Because up to 50% of vascular lesions smaller than 2 cm found on screening are not HCC, in the absence of biopsy a proportion of the lesions treated by local ablation (at least in the West) must have been benign. Therefore, outcomes in studies of local ablation in which biopsy is not performed are misleading. Prospective randomized comparisons are required.

**Monitoring the Response to Locoregional Therapy (Jean-Francois Geschwind)**

The standard Response Evaluation in Solid Tumors (RECIST) criteria, which are based on alterations in tumor size, may not be helpful in HCC.46 In many cases, in spite of tumor changes, the lesion does not initially shrink. Shrinkage of tumor may take 6 months or more to attain the RECIST criterion for a partial response, namely, a decrease in diameter of 25%. CT scans after either local ablation or chemoembolization may show that the mass is less vascular and is necrotic. CT scanning after chemoembolization can be difficult to interpret because of the presence of the Lipiodol, which obscures tumor vascularity. The time to progression of disease might be a more appropriate end-point for evaluation of HCC therapy.

Contrast-enhanced ultrasound appears to be as sensitive and as specific as CT scanning in predicting response after chemoembolization. Pathology correlation studies have shown that contrast ultrasound reliably identifies tumor vascularity and necrosis. This technique is also useful for assessing response after local ablation. Clearly, additional studies are needed.

Functional MRI also has been used to assess tumor response by measuring changes in free water content.47 Free water content increases once necrosis breaks down the barriers to diffusion into the tumor. Studies have shown that the area of necrosis delineated by functional MRI corresponds well with necrotic lesions observed in surgical specimens and also shows a significant difference between pre-chemoembolization and post-chemoembolization pictures. However, use of functional MRI as a measure of response does not solve the issue of whether RECIST criteria can be used to assess response.

**Chemoembolization (Jordi Bruix)**

Despite the wide application of screening and surveillance for HCC, most patients are still diagnosed at a stage at which curative ablative therapy is not feasible. Of all the non-curative therapies available, only intra-arterial chemotherapy and chemoembolization have been subjected to randomized controlled trials of sufficient size and quality to be confident of the results.48–50 Small randomized controlled trials of octreotide, and uncontrolled trials of various forms of immunotherapy, internal radiation using 131I-lipiodol, and external radiation therapy also exist.

Several randomized controlled trials have been performed using chemoembolization49,50 or bland embolization, and a meta-analysis of the pooled data from some of these studies has been performed.51 No study has shown any advantage for bland embolization compared with no treatment. The meta-analysis of all randomized trials also concluded that chemoembolization improves survival.51 Chemoembolization should now be the standard of care for appropriate patients.

Many unanswered questions about chemoembolization remain, including when chemotherapeutic agents to use, and what doses should be given. These questions have to be resolved by randomized controlled trials. Funding agencies should issue requests for proposals to design and run such trials.
Chemoembolization has also been studied as treatment for patients with HCC who are awaiting liver transplantation, but remains controversial and unproven. Published studies have small sample sizes and yield conflicting results. Further study of this area was thought to be important and would require multicenter studies to complete.

Other Palliative Therapy (Brian Carr)

A large number of treatments have been studied in phase I and II trials. Only one of these forms of palliative therapy was presented and discussed at the meeting. This therapy involved the use of Yttrium 99–labeled glass microspheres injected into the hepatic artery feeding the tumor.52 No randomized controlled trials of this therapy exist. However, the outcome of phase II studies was compared with historical controls (unmatched but stratified by Okuda stage). For both Okuda stages 1 and 2, patient survival was improved over historical controls. This study involved 65 subjects. However, until the use of Yttrium 99 microspheres is compared with no therapy or with a control group, the value of this therapy remains uncertain.

This issue, namely the lack of phase III randomized controlled trials, applies to a large number of potentially useful therapies. Thus, a need exists for funding agencies to stimulate the design and running of randomized controlled trials to explore the value of these various treatments. A decision has to be made as to whether the control group should be untreated or whether doxorubicin should be used as a control. The group believed that doxorubicin was ineffective and toxic and should therefore not be used.

Chemoprevention of HCC (Antonio Craxi)

The logical agents to be studied are those that have been used to treat the underlying liver disease, particularly viral hepatitis. Populations that might be suitable for chemoprevention should be populations at high risk for HCC. Although identification of at-risk populations is relatively easy, still no way exists to identify patients at imminent risk for HCC. Chemoprevention in such high-risk populations might be cost effective compared with applying chemoprevention to larger populations at finite, but not imminent, risk of HCC.

Two mechanisms might underlie chemoprevention, elimination of premalignant clones of cells, or delaying the carcinogenic pathway.

In humans, only interferon therapy in chronic viral hepatitis has been identified as possibly preventing HCC. In chronic hepatitis C, the meta-analysis suggests that treated patients who have cirrhosis do have a reduced risk of cancer, although the magnitude of the risk reduction is small.53 Whether patients without cirrhosis have a similar or greater risk reduction is less certain, because such studies are harder to perform.

In hepatitis B virus infection, the data are too scant to determine whether interferon or nucleoside analog therapy actually reduces HCC incidence. Similarly, other agents that might exert a chemoprotective effect have not been adequately studied.

Large-scale randomized controlled studies can determine whether treatment of chronic viral hepatitis will reduce cancer risk, but these are difficult to perform.

Clinical Application of Molecular Studies on HCC (Snorri Thorgeirsson)

In recent years, a number of steps in the pathogenesis of HCC have been defined. The main etiological agents have been identified, and some of the molecular changes that the hepatitis viruses induce have been described. In addition, through study of a very large number of human and experimental tumors, many of the genetic changes that occur in HCC have been documented. However, the database is as yet incomplete, and despite all this information, the molecular pathways that result in HCC are not well characterized.

Advances in genomics and proteomics have the potential to identify characteristics of HCC that may be related to prognosis or to etiology, and these may be useful in HCC screening or diagnosis. At present, however, the science is insufficiently advanced to be clinically useful.

The role of genomics and proteomics in HCC research was discussed in a workshop. The group believed that accumulation of sera and tissue banks would facilitate such studies and were essential. However, all retrospective studies using stored samples would have to be validated in prospective studies.

References


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