Challenges of Clinical Research on Hepatocellular Carcinoma

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Tumor Markers

Tumor markers are routinely used in screening, diagnosis, treatment response evaluation, assessment of tumor malignancy and diagnosis of tumor recurrence, and among them, alpha-fetoprotein (AFP) has long been appreciated as a tumor marker for HCC. In Japan, prothrombin induced by vitamin K absence-II (PIVKA-II), and the L3 fraction of AFP (AFP-L3) [2–4] are routinely used alongside AFP to screen for HCC. However, in other countries, the clinical guidelines for HCC, such as those issued by the American Association for the Study of Liver Diseases (AASLD) [5] and the European Association for the Study of the Liver (EASL) [6], do not recommend the use of PIVKA-II or AFP-L3 in daily clinical practice. Even AFP is not recommended for the surveillance of liver cancer because of its low sensitivity and specificity, that is, due to its poor cost effectiveness, leaving ultrasound (US) as the only screening method recommended per the Western guidelines [7]. This signifies a huge difference in the way of thinking between researchers in Japan and those in Western countries. In Japan, all of these 3 tumor markers are fully covered by the National Health Insurance System, and an increase in any of them when used in combination can lead to the detection and diagnosis of small HCC. From this perspective, it is important to perform prospective clinical trials to demonstrate that the regular use of tumor markers, including AFP, is an essential part of liver...
cancer screening. For this purpose, a clinical trial headed by the University of Tokyo for HCC, the ALDUS Study, is currently ongoing and its results are eagerly awaited.

AFP has numerous future roles. Both AFP levels and HCC incidence decrease markedly when a sustained virologic response (SVR) is achieved by the eradication of hepatitis C virus by interferon (IFN) therapy for chronic hepatitis C. However, it is unclear whether this reduction in AFP reflects improvement of the inflammation or of the background liver tissue that served as the primary origin. According to Asahina et al. [8], the rate of hepatocarcinogenesis is low in SVR patients when AFP level is <6 ng/ml, but is high in patients with AFP ≥6 ng/ml even after they have achieved SVR. It has also been reported that post-SVR carcinogenesis rates vary among hepatitis C patients with AFP levels lesser or higher than 10 ng/ml [9]. On the basis of these reports, AFP is used as a surrogate marker for carcinogenesis in SVR patients after antiviral therapy for hepatitis C. Although IFN-free antiviral therapy with direct acting antivirals (DAAs) is expected to become the mainstream therapy for chronic hepatitis C, it is currently unclear whether the suppression of carcinogenesis is similar between patients who have achieved SVR after taking DAA agents that act directly on the virus and those who achieved SVR after receiving IFN-based therapy, which exerts antitumor and immunostimulatory effects. It becomes clear that an all-oral DAA regimen can decrease AFP levels that serve as an indicator. However, it is not clear whether low-dose long-term IFN therapy can decrease AFP levels in SVR patients with AFP ≥6 ng/ml after DAA therapy. It seems, then, that AFP in both its conventional and newer uses has clear prospects for the future, but certain challenges such as those mentioned above are yet to be addressed.

PIVKA-II, which is an independent marker for HCC and has no correlation with AFP, is also used in screening, treatment response evaluation [10], diagnosis of recurrent HCC and assessment of biological malignancy grade. The association between PIVKA-II level and vascular invasion is of particular interest. According to Koike et al. [11], patients with high PIVKA-II levels have a high incidence of portal invasion. Vascular invasion, however, is suppressed by the administration of vitamin K, which downregulates PIVKA-II. This evidence prompted a large-scale clinical trial to investigate whether Vitamin K suppresses the recurrence of HCC in patients who received curative treatment such as resection [12, 13] or ablation [14, 15]. The study was unsuccessful though, and it completely ruled out the possibility of vitamin K for tertiary prevention after curative treatment of HCC [16]. PIVKA-II levels are also known to increase during treatment more often in patients who respond to sorafenib, a molecular targeted agent, suggesting that PIVKA-II can serve as a surrogate marker for the suppression of angiogenesis or as an indicator of treatment response [17]. This possibility needs to be investigated further in systemic therapy [18, 19].

AFP-L3 does not correlate with AFP or PIVKA-II in patients with HCC [2, 4]. In recent years, the measurement of highly sensitive AFP-L3 has been attracting attention because this innovative method enables AFP-L3 to be measured even when total AFP levels are ≤10 ng/ml. Compared with conventional AFP-L3, highly sensitive AFP-L3 has a high positive rate even in patients with early-stage HCCs (e.g. stages I and II), making the marker useful in the early diagnosis of HCC [20, 21]. The malignancy rate of AFP-L3-positive liver cancer is extremely high, and while the survival of AFP-L3-negative patients who had high AFP-L3 levels before treatment is similar to the survival of patients negative for AFP-L3 throughout treatment, and the survival of patients who maintain high AFP-L3 levels even after treatment is significantly poor [4, 22].

As we gain a more comprehensive understanding of these markers’ characteristics, it is likely that AFP, PIVKA-II and AFP-L3 will be increasingly used for prognostic prediction and assessment of the biological malignancy. In addition, we need to report actively on the utility of PIVKA-II and AFP-L3 to the world, especially the United States and Europe where use of these 2 markers is not recommended in their guidelines [7].

**Diagnosis**

**Ultrasonography**

Guidelines published all over the world recommend B-mode US as a first-line imaging modality for screening HCC. However, when B-mode US is used to screen patients with cirrhosis, small liver tumors are often overlooked because of coarse liver parenchyma. Although US is the only screening modality recommended in the guidelines issued by the AASLD [5], the EASL [6] and the Asian Pacific Association for the Study of the Liver (APASL) [23], in Japan, both sets of guidelines – the Evidence-based Clinical Practice Guidelines [24] and the Consensus-based Clinical Practice Guidelines [25] – recommend annual or semiannual computed tomography (CT) or magnetic resonance imaging (MRI) for type B or C cirrhotic patients, who have very high risk for liver cancer, due to the inherent limitations of B-mode US.

Challenges on HCC
Sonazoid-enhanced US, which is composed of the vascular phase and Kupffer phase, has recently been used proactively for screening as well as diagnosis of liver cancer [26, 27]. Perfusion defects can be detected easily in the Kupffer phase, which starts 10 min after venous injection. HCC can be accurately diagnosed by performing US after the re-injection of sonazoid [26, 28]. This was verified in a multicenter randomized clinical trial (NCT No. 00822991), and thus, it is highly likely that surveillance using Kupffer phase imaging in Sonazoid-enhanced US will be recommended in future editions of clinical practice guidelines for HCC.

Elastography is also now frequently performed to diagnose fibrosis in patients with diffuse liver disease. Elastography is simply classified by the measurement method used, namely, strain elastography or shear wave elastography (SWE). The representative strain method, real-time elastography (RTE), simplifies the diagnosis of fibrosis with the use of a liver fibrosis index [29]. Representative shear wave methods are FibroScan (transient elastography), virtual touch quantification and SWE, and they determine the stiffness of the liver by generating push pulses in order to measure the propagating shear waves. FibroScan is particularly well known for enabling liver cancer risk to be judged from liver stiffness measurements in patients with type B or C cirrhosis [30–32]. Consequently, FibroScan is a highly useful method for predicting the risk for cancer without an invasive biopsy, but it remains to be confirmed whether shear wave methods and RTE can produce results as good as FibroScan.

CT
Multidetector raw CT is the mainstream CT procedure that is in use today [33]. Further research is needed to reveal the utility of effective hepatic parenchymal blood flow by perfusion CT, as well as liver function assessment by dual energy CT.

MRI
A recent MRI-related topic attracting attention is the approval of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI (EOB-MRI). Early HCCs demonstrating hypovascularity on CT during hepatic arteriography (CTHA) or no decrease in portal flow on CT during arterial portography (CTAP) may be detected as hypointense signals on EOB-MRI [34, 35]. Such hypointense nodules are often diagnosed histopathologically as early HCCs [25, 36, 37]. Although there has been a report of dysplastic nodules occasionally displaying hypointensity even in the hepatocyte phase of EOB-MRI, such results were just based on a comparison with liver biopsy and EOB-MRI findings. In fact, a study that followed the natural course of hypointense hypovascular nodules has revealed that such nodules most likely develop into classical hypervascular HCC [38–56]. On the other hand, some early HCC nodules may not show hypointensity in the hepatocyte phase of EOB-MRI. More follow-up studies are needed to clarify this issue.

Another interesting topic concerning EOB-MRI is the role of transporters in HCC. The transporter that imports EOB into the hepatocytes is an organic anion transporting polypeptide 8 (OATP8 or OATP1B3) [57, 58]. Patients with typical moderately differentiated HCC that displays hyperintensity in the hepatocyte phase of EOB-MRI account for 5–10% of all HCC patients. Furthermore, OATP8-positive liver cancers are reported to be a subtype of HCC and exhibit a benign nature [59, 60]. In studies by Yoneda et al. [61] and Yamashita et al. [62], the expression of β-catenin is significantly upregulated in HCC expressing OATP8, suggesting that OATP8 is induced by Wnt/β-catenin signaling. Yamashita et al. [63] also recently revealed that the expression of OATP8 is inhibited by the transcription factor hepatocyte nuclear factor 4A and that OATP8-positive HCC is a subtype of HCC that expresses a specific group of genes. These findings suggest that EOB-MRI is a molecular imaging modality that acutely reflects the expression of OATP8 and will be useful for the assessment of multistep carcinogenesis in liver cancer [58] and the identification of benign HCC subtypes. Further studies are needed to confirm this proposal.

Angiography
Recent advances in CT, contrast-US and EOB-MRI have meant that angiography is no longer necessary diagnostically as it was in the past. However, CTHA and CTAP still play extremely important roles in the detection of small HCC and in the differentiation from liver shunt. An extremely important angiographic finding is that when patients with hypervascular HCC undergo single-level dynamic CTHA, the contrast agent injected via the hepatic artery stains hypervascular HCC intensely and then drains from the tumor capsule to stain the surrounding liver tissue in a corona-like fashion [64]. Such corona-like staining is also observed in dynamic CT after careful examination, making this dynamic CT finding important for differentiating HCC from other tumors [65]. It is anticipated that CTHA and CTAP will be used more often in treatment to monitor the degree of lipiodol retention during transcatheter arterial chemoemboliza
Ablation (RFA). Today, RFA accounts for approximately 99% of all locoregional therapies that are being undertaken. The latest development in RFA treatments for HCC is the application of Celon electrodes that allows for expansion of the ablation area, owing to the bipolar needle electrodes used. Treatment is possible without touching the tumor because 2 needle punctures are made. Since the bipolar electrodes require no return electrode, they are also associated with low risks of burn and damage to surrounding organs. Clear advantages of using needle electrodes are, therefore, the non-touch ablation of tumor tissue due to the placement of 2 electrodes and also, unlike conventional overlapping ablation, the ability to avoid reduced puncture accuracy because the tumor is punctured with multiple electrodes prior to thermal coagulation. Consequently, this method of locoregional therapy is expected to become popular, although it remains to be seen whether bipolar needle electrodes replace the conventional Cool-tip® needles used.

Other developments in RFA include the application of contrast-enhanced US, fusion imaging using volume data from CT, MRI and US and fusion imaging combined with contrast-enhanced US to treat lesions that are not detectable with B-mode US. Although any of these imaging options can be used to help localize tumors precisely and insert needle electrodes, fusion imaging is particularly useful for the determination of accurate ablative margins [69].

The injection of lipiodol before RFA is extremely useful in confirming the ablative margins. Without lipiodol injection, it is impossible to determine accurate ablative margins by simple comparison of pre- and post-ablation images placed side by side in the display. This is why the pre-treatment injection of lipiodol was mandatory in the past, even though it requires an angiographic procedure before RFA. Today, fusion images before and after RFA can be overlaid using an extracted overlay method [74]. However, the method needs to be improved further because it currently involves cumbersome procedures including using the workstation.

TACE

Recent advances in TACE include the development of microsphere embolic agents. In Japan, conventional TACE (cTACE) [75, 76] is routinely performed to inject a liquid containing an antitumor agent via the hepatic artery, which is followed by embolization with gelatin sponge particles. However, the introduction of microspheres such as DC Beads®, HepaSphere and Embosphere in 2014 has increased the treatment options related to TACE. Therefore, the challenge today is in the selection of different beads for TACE, also known as drug elut-
ing beads TACE (DEB-TACE) and cTACE. Microsphere beads of exactly the same size embolize blood vessels of a certain diameter, and their advantages are their non-absorbent property and excellent biocompatibility, thus rarely causing inflammatory reactions in the body. The microsphere beads come in different sizes, and those 75–250 μm in size are frequently used for the treatment of liver cancer. This size range is far smaller than the size of Gelpart embolic agents (1,000 μm). Accordingly, the goal of arterial embolization in liver cancer today is to fill the blood vessels inside the tumor and the nearby tissues with embolic materials, instead of performing proximal embolization to block blood supply to the tumor as in the conventional embolization method. As shown in the PRECISION V randomized clinical study in 2010 [77, 78], treatment outcomes are similar between DEB-TACE and cTACE, but DEB-TACE is associated with fewer side effects. However, if a similar comparative trial were conducted in Japan, where cTACE is performed, using super-selective techniques, cTACE may turn out to be superior in terms of validity. Regardless of such a study’s results, there are a number of issues with DEB-TACE that need to be addressed. Well-organized clinical trials are necessary to answer questions regarding the selection DEB-TACE over cTACE and the effectiveness of DEB-TACE in patients who do not respond to cTACE.

Another technique that has been attracting attention is the balloon-occluded TACE (B-TACE) [79]. The principle of B-TACE is that when the blood pressure of the hepatic artery, which supplies normal liver parenchyma, drops distal to the balloon occlusion site, the flow of lipiodol declines quickly due to the narrow diameter of the arterial branches. In contrast, the amount of lipiodol flowing into the tumor increases because of the wide diameter of the vessels supplying the tumor. Subsequently, all the blood vessels supplying the tumor are blocked, and they become molded by continuously injecting embolic agents into them even after the flow in the tumor vessels is reduced to almost none and by moving the embolic agents into collateral blood vessels via the portal vein, which functions as a drainage vessel from the tumor. B-TACE is therefore a unique technique. Although it was reported to embolize target tumors effectively [79], further study is needed to verify this. Also, attracting attention is FlightPlan, which uses cone-beam CT to identify tumor vessels, but at present FlightPlan is limited to certain facilities because it requires special equipment and software.

Outside Japan, transarterial radioembolization is being frequently performed [80, 81]. Its introduction to Japan is eagerly awaited.

Hepatic Arterial Infusion Chemotherapy

From a global perspective, systemic chemotherapies using cytotoxic anticancer agents seldom offer survival benefits. In Japan, hepatic arterial infusion chemotherapy (HAIC) accounts for 90% of the chemotherapies for liver cancer. Two regimens are currently used in HAIC: low-dose 5-fluorouracil and cisplatin (FP) and IFN combined with 5-fluorouracil (IFN-5FU) [82]. It is difficult to compare the efficacy of each regimen because of the differences in the characteristics of patients and detailed protocols. According to Nousu et al. [83], a nationwide follow-up survey conducted by the Liver Cancer Study Group of Japan (LCSGI) revealed excellent treatment outcomes for HAIC with low-dose FP, with a 40.5% response rate and median survival time of 16 months. On the other hand, the complete and partial response rates ranged widely from 25 to 63% in HAIC with IFN-5FU.

In the United States and Europe, HAIC is practically not performed because no prospective comparative clinical trials of HAIC have ever been done to produce any evidence of its efficacy. In Japan, however, the main problem associated with HAIC is whether advanced liver cancer should be treated first with sorafenib or with HAIC. Although prospective clinical trials are needed to demonstrate clear-cut evidence for HAIC in Western countries, it is not ethically possible for Japanese physicians to conduct a clinical trial comparing HAIC with no therapy because of the obvious superiority of HAIC. Furthermore, it would likely be impossible to observe any differences in a head-to-head comparison of HAIC and sorafenib therapy given that such a clinical trial would need to be performed as a crossover study with overall survival as the end point because HAIC and sorafenib therapy are both standard treatment methods for HCC in Japan. For this reason, a research group supported by Japan’s Ministry of Health, Labour and Welfare is currently conducting the SILIUS clinical trial to compare the efficacy of the standard treatment method of sorafenib with that of sorafenib combined with HAIC (low-dose FP; NCT No. 00933816). This trial may be able to demonstrate, albeit indirectly, the survival benefits of HAIC. In addition to HAIC, radiation therapy is a treatment choice for patients with portal venous tumor thrombosis [84, 85].

Molecular Targeted Therapy

At present, sorafenib is the only drug with proven survival benefits [86], based on the results of 2 large-scale RCTs: the sorafenib HCC assessment randomized protocol (SHARP) study [87] and a trial conducted in the Asia-Pacific region [88]. Although many clinical trials
have been conducted to investigate various first- and second-line treatments using molecular targeted drugs with or without a combination of TACE or in the adjuvant setting, they all failed [89]. Therefore, the results of currently ongoing trials – first-line treatment with lenvatinib, second-line treatment with regorafenib, tivantinib treatment in patients with a high expression of cMet, ramucirumab treatment in patients with a higher AFP level (≥400 ng/ml) and anti–PD-1 antibody – are eagerly awaited. Regardless of the results of these trials, there is an urgent need for us to have 1 or 2 more molecular targeted agents effective for HCC, beyond just sorafenib, to improve the survival of HCC patients. Biomarker for predicting the response of targeted therapy is another important issue [90].

The most promising treatment strategy for HCC is the combined use of a targeted agent with a locoregional therapy [91, 92]. The results of the STORM trial that is investigating sorafenib as an adjuvant therapy after hepatectomy or RFA (which has produced negative results), the TACTICS trial (NCT No. 01217034) that is investigating the combination of sorafenib with TACE and the SILIUS trial (NCT No. 01214343) that is investigating the combination of sorafenib with HAIC are keenly awaited. Prevention of HCC [93] is another important issue.

Response Evaluation Criteria for Liver Cancer
The Response Evaluation Criteria in Solid Tumors (RECIST), modified RECIST (mRECIST) [94, 95] and the LCSGJ’s Response Evaluation Criteria in Cancer of the Liver (RECICL) [10, 96] are available for treatment response evaluation in liver cancer. However, RECIST is not suitable for response evaluation of locoregional therapies such as ablation or TACE because the criteria were originally developed for evaluating tumor response to chemotherapy and because it is extremely rare for these locoregional therapies to reduce the size of HCC tumors [97]. Furthermore, even when a necrogenic effect is induced by chemotherapy, the effect cannot be evaluated using RECIST. Despite mRECIST having been developed to overcome the shortcomings of RECIST, mRECIST also utilizes 1-dimensional measurement and thus differs greatly from LCSGJ’s RECICL. However, RECICL also has its shortcomings because it was originally developed based on criteria established for the evaluation of direct treatment response to locoregional therapy, such as TACE or ablation, and not to chemotherapy. Therefore, the problem with RECICL, which was published in 2009, is that it does not take into account metastasis to other organs. Revision of the response evaluation criteria in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer developed by LCSGJ has been published [10, 98].

Treatment Algorithm

Treatment algorithms for HCC have been developed by the AASLD [5] and the EASL-European Organisation for Research and Treatment of Cancer (EORTC) [6]. Both algorithms fundamentally adhere to the Barcelona Clinic Liver Cancer (BCLC) treatment algorithm. Basically, the treatment algorithm issued by the APASL [23] is not very different from other treatment algorithms. The conciseness of the Evidence-based Treatment Algorithm from the Japan Society of Hepatology (JSH) [24] is appreciated, but it is somewhat unclear because of the placement in the footnotes of some descriptions, such as vascular invasion and distant metastasis. In JSH’s Consensus-based Treatment Algorithm [26], treatment options in line with evidence-based guidelines are provided in parallel with treatment choices based on expert consensus and are presented under separate topics such as extrhepatic spread, hepatic functional reserve, vascular invasion and the size and number of tumors. This consensus-based treatment algorithm is currently being used by experts in clinical practice, who also combine the evidence-based treatment algorithm with treatment methods without such evidence. Therefore, prospective clinical trials are needed to fill the gap between evidence-based and consensus-based treatment algorithms. While locoregional therapy is recommended in JSH’s consensus-based algorithm as an experimental treatment for Child-Pugh (CP) C liver cancer based on the previous publication [99, 100], best supportive care is recommended in the evidence-based treatment algorithm. For this reason, the Japan Liver Oncology Group is currently planning a clinical trial of patients with CP-C liver cancer (with a CP score of 10–11) and cancer stage meeting the Milan criteria in order to compare best supportive care and locoregional therapy (RFA or TACE).

Definition of TACE Failure/Refractoriness

JSH was the first to define HCC failure/refractoriness to TACE in 2010, in the Management of Hepatocellular Carcinoma in Japan: Consensus-Based Clinical Practice Manual [101] as well as in an article published in Digestive Diseases [102]. The definition was subsequently revised by LCSGJ in 2014 [25] as well as JSH clinical prac-
The modified JIS system, which replaces the CP classification, found LCSGJ’s criteria to be suitable for TACE treatment in Japan has been published and has received international awareness of the need to define TACE failure/ refractoriness. Conventionally, when no other options are available, TACE is performed repeatedly even when it is no longer effective. However, the benefit that patients receive from TACE is defined as a balance between the anticancer effect of TACE and the preservation of hepatic functional reserve. When TACE no longer offers an antitumor effect, its repeated use only needlessly reduces the functional reserve and, theoretically, it is time to switch to another treatment. Globally, the next treatment option would be sorafenib, but in Japan, HAIC may be another option. The revised definition of TACE failure/ refractoriness that LCSGJ issued in 2014 [25], although requiring verification in future studies, is believed to be superior to the EASL’s criteria, which recommend switching to sorafenib when HCC has not responded to TACE twice, or the criteria used in Korea, which define HCC as refractory when a second TACE is required within 6 months. Actually, a study investigating the validity of TACE treatment in Japan has been published and has found LCSGJ’s criteria to be suitable [104–107].

Prognostic Staging

Physicians treating liver cancer should be aware of the different staging systems used for liver cancer: those for deciding treatment strategy and those for prognostic prediction. Although BCLC stages [108] are sometimes compared with scores from the Cancer of the Liver Italian Program (CLIP) or the Japan Integrated Staging (JIS) system [109], the CLIP and the JIS scoring systems are staging systems for predicting prognosis, not for determining treatment strategies. In addition, BCLC staging involves just ordinary, common-sense treatment strategies, so to speak. In Japan, curative treatment is always selected for patients with the best TNM and liver function status, TACE is selected for patients with a moderate status and HAIC or sorafenib is selected for patients with advanced disease. It goes without saying that the survival analysis of these patients using the Kaplan–Meier estimation produces good stratification. On the other hand, the use of staging systems for prognostic prediction allows for the prognosis of patients to be determined using scores for prognostic factors in daily clinical practice and for groups of patients with the same prognostic scores to be compared between different institutions. Notably, the JIS scoring system is reported to be superior to the CLIP scoring system [109]. The modified JIS system, which replaces the CP classification with a classification of liver damage severity [110], and the biomarker combined JIS score (bm-JIS Score), which includes the tumor markers of AFP, PIVKA-II and AFP-L3 [111], have also been reported. It is understandable, then, that bm-JIS is theoretically superior to the conventional JIS score. The BALAD Scoring system has also been developed and uses albumin, bilirubin and the 3 tumor markers of AFP, PIVKA-II and AFP-L3, but not tumor staging or the CP classification [112]. This is an excellent staging system in that only blood sampling is required to predict prognosis in liver cancer. In the future, it will be necessary to determine which staging systems are most effective to apply in individual cases. Recently, the Hong Kong staging system has been introduced [113].

Subclassification of HCC

Molecular classification is a well-recognized system of HCC subclassification that classifies HCC based on the presence/absence of stem cell features [114–116]. This subclassification is also useful in determining future treatment targets and strategies. In addition, the finding that prognosis is good even when OATP8 is expressed in moderately differentiated liver cancer (i.e. shows hyperintensity in the hepatocyte phase of EOB-MRI) indicates a subclass of HCC. Also, because patients with CK19-positive HCC having stem cell features have shown poor prognosis [117], these tumors may be classified into a different subclass of HCC. Actually, even tumor markers may be important indicators of subtypes of HCC. Therefore, future challenges are the establishment of proper HCC subclassification methods and the respective treatment strategies for each subtype of HCC.

Conclusion

The current challenges and future prospects of clinical research on HCC have been reviewed. It is probably correct to say that, at the present, Japan greatly outperforms other countries in clinical practices for the disease, and emphasis should be placed on continuing to perform high-quality clinical studies such as multicenter, prospective comparative clinical trials in a straightforward manner.

Disclosure Statement

Authors declare no conflict of interest.
References


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