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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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Challenges to Liver Transplantation and Strategies to Improve Outcomes

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Liver transplantation (LT) is a highly successful treatment for many patients with nonmalignant and malignant liver diseases. However, there is a worldwide shortage of available organs; many patients deteriorate or die while on waiting lists. We review the important clinical challenges to LT and the best use of the scarce organs. We focus on changes in indications for LT and discuss scoring systems to best match donors with recipients and optimize outcomes, particularly for the sickest patients. We also cover controversial guidelines for the use of LT in patients with hepatocellular carcinoma and cholangiocarcinoma. Strategies to increase the number of functional donor organs involve techniques to perfuse the organs before implantation. Partial LT (living donor and split liver transplantation) techniques might help to overcome organ shortages, and we discuss small-for-size syndrome. Many new developments could increase the success of this procedure, which is already one of the major achievements in medicine during the second part of the 20th century.

Keywords: Liver Transplantation; HCC; Cholabgiocarcinoma; Machine Perfusion; Hepatitis C.

Approximately 6000 liver transplantations (LTs) are performed each year in the United States and Europe,[1] and more than 70% of recipients now survive for at least 5 years at most centers (Figure 1) compared with 20% in the mid-1980s.[2] This increase has occurred despite the fact that much sicker patients have undergone LT in recent years. Factors that contribute to increased survival include better control of disease in patients before LT, refined operative techniques, better organ preservation and immunosuppression,[3] and the availability of physicians specially trained in LT.[4] However, the success of LT has resulted in substantial organ shortages. To reduce the gap between the need and availability of donors, physicians are using organs previously considered unsuitable for transplantation, called extended criteria donor (ECD) organs. For example, in our centers, two-thirds of transplanted livers come from ECDs.[5] Organs can also be obtained from living donors, which are the only or main source of organs in Asian countries such as Japan or Korea.[6] However, living donation has failed to gain wide acceptance in the West because of the level of risk for healthy donors; mortality is approximately 0.5%.

In this review, we discuss emerging trends in key indications for LT, such as nonalcoholic steatohepatitis (NASH), alcoholic liver disease, hepatitis C, and hepatobiliary cancers. We describe strategies to best match donors with recipients and review innovative concepts in liver preservation, such as machine perfusion, that can improve the quality of organs. We also review small partial liver transplants using livers obtained from living and cadaveric donors, which could greatly increase organ availability. It is important to consider small-for-size grafts and what we have learned about liver regeneration.

Trends in Indications for LT

Cirrhosis has been the leading indication for LT since it was developed, although the etiologies of cirrhosis have changed.[7,8] For example, malignancy as a primary indication for LT increased in the United States from 7.7% in 2002 to 22.4% in 2012,[9] with a similar trend in Europe.[10] Likewise, the percentage of patients with cirrhosis due to NASH increased from 1.2% in 2001 to 9.7% in 2009.[7] NASH now falls behind hepatitis C and alcoholic liver disease as the third most common indication for LT in the United States.[7] According to a large single-center study, the proportions of LTs performed for NASH have increased from 3% to 19%

Abbreviations used in this paper: **AASLD, American Association for the Study of Liver Diseases; BAR, balance of risk; D-MELD, donor age × recipient Model of End-Stage Liver Disease; DCC, distal cholangiocarcinoma; DCD, donation after cardiac death; DDLT, deceased donor liver transplantation; DRI, donor risk index; EASL, European Association for the Study of the Liver; ECD, extended criteria donor; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HOPE, hypothermic oxygenated perfusion; ICC, intrahepatic cholangiocarcinoma; IFN, interferon; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model of End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PHC, perihilar cholangiocarcinoma; SFSS, small-for-size syndrome; SOFT, survival outcome following liver transplantation; SVR, sustained virologic response; UCSF, University of California San Francisco.**

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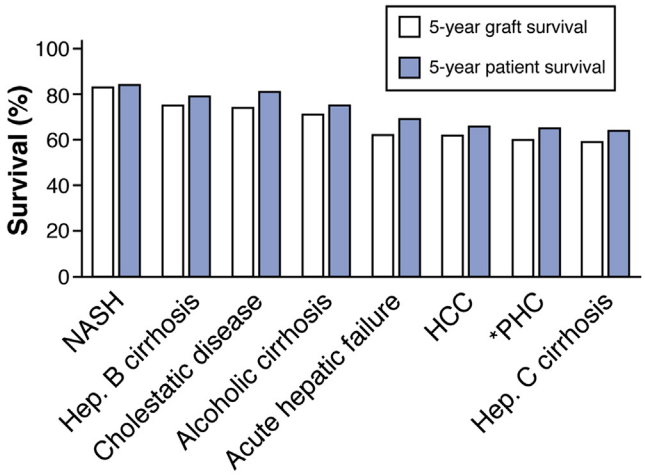

*Neoadjuvant chemoradiation, followed by LT

Figure 1. Five-year patient - and graft survival for the most common indications for LT as reported by the European Transplant registry (ELTR).[2] Data for perihilar carcinoma (PHC) is obtained from 12 US centers.[58]

over the past decade, making it the second most common indication for LT.[8] In addition, NASH-associated hepatocellular carcinoma (HCC) is the most rapidly growing indication for LT in patients with HCC.[11] The incidence of hepatitis C–associated cirrhosis is expected to decrease with new effective treatment options, so NASH will probably become the leading indication for LT in the near future.[7] It is important to develop strategies to prevent NASH and associated metabolic disorders and to avoid recurrence of NASH after LT.

NASH

Although patients with NASH have higher mortality from cardiovascular events or sepsis after LT than patients without NASH,[12] rates of long-term survival are no different than for other indications.[7,12] Recurrence of steatosis (at least grade 2) is observed in 60% after 1 year, and approximately 60% develop frank NASH after 2 years. Nevertheless, only 5% of patients will develop cirrhosis with follow-up to 10 years.[13] Accordingly, graft failure in patients with NASH is less frequent compared with patients without NASH.[12] However, patients with NASH are at increased risk for cardiovascular morbidity in the perioperative period.[14] The best approach to improve patient outcomes is to prevent recurrence of NASH with a focus on its associated cardiovascular and metabolic complications. This can be done by controlling the weight of patients after LT, such as through bariatric surgery.[15] Although bariatric surgery is feasible before LT and recommended for patients with early stages of liver disease,[16] it is too risky for patients with decompensated cirrhosis.[17] Bariatric surgery is still an option after LT; however, this requires a second surgical procedure. A strategy combining LT with sleeve gastrectomy for obese patients who failed to lose weight in the pretransplant period has been proposed.[18] The procedure seems to be safe because none of the patients died and no grafts were lost; more importantly, no patients developed post-LT diabetes mellitus and all significantly lost weight (mean body mass index, 29 kg/m^2). Because only patients with a sleeve gastrectomy achieved a sustained weight loss after LT, such a one-operation approach may gain wider acceptance.[18]

Alcoholic Liver Disease

Alcoholic liver disease is the second most common indication for LT in many areas.[9,19] Although patients who undergo LT for alcoholic cirrhosis have significantly longer survival times than those who undergo the procedure for viral or cryptogenic cirrhosis,[19] the public and many health professionals have negative perceptions about providing livers to patients with alcoholic liver cirrhosis.

Many transplant centers use the 6-month rule of abstinence to determine whether patients with alcoholic cirrhosis should receive livers, although there is only a weak association between sobriety and outcome after LT.[20,21] Strict adherence to the 6-month rule of abstinence might unnecessarily exclude some patients in high need of LT from the waiting list[22]; consequently, the European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), and UK guidelines no longer adhere to this policy,[23] instead recommending a balanced analysis of each patient.[24] However, a period of abstinence from alcohol can significantly improve liver function, and immediate listing of patients with Child B cirrhosis is not associated with a survival benefit.[25] Therefore, a 6-month rule of abstinence is still useful to avoid unnecessary LT in these patients.[26]

Patients with a combination of alcohol-associated cirrhosis and hepatitis deteriorate rapidly, especially those who do not respond to corticosteroid therapy.[27] They are usually excluded from the LT waiting list; alcoholic hepatitis is considered a clear contraindication in the UK guidelines.[28] In contrast, the EASL guidelines support future evaluation for LT in carefully selected patients with severe alcoholic hepatitis who do not respond to medical therapy.[26] The EASL guideline incorporated the results of a study by Mathurin et al,[29] who evaluated the effects of immediate LT for 26 highly selected patients with a first episode of severe alcoholic hepatitis who did not respond to 7 days of daily treatment with 40 mg of prednisolone.[30] In this study, 78% of the patients who received liver transplants survived for at least 6 months compared with 24% of a historic control group of patients who did not respond to corticosteroids. Interestingly, 85% of a historic control group of patients who responded to corticosteroids survived for 6 months (Lille score <0.45). A total of 2.9% of all LTs and 8.3% of all LTs for alcoholic liver disease were performed in patients with severe alcoholic hepatitis during the study period. During the follow-up period, 3 patients resumed drinking (24, 25, and 38 months after LT) and 2 patients remained daily consumers despite counseling, so far without evidence for graft dysfunction. Considering the significant increase in survival among patients with

alcoholic hepatitis who undergo LT, it seems difficult to refuse the procedure to selective patients who do not respond to standard medical care.

Hepatitis C

Hepatitis C virus (HCV) infection is one of the leading causes of end-stage liver disease and the main indication for LT in most countries.[31] Overall, patient and graft survival after LT for HCV-associated cirrhosis is inferior compared with other indications.[32] However, successful pretransplant or posttransplant antiviral therapy has been associated with increased graft and overall survival.[33]

Until recently, the combination of pegylated interferon (IFN)-α and ribavirin was the standard of care for the treatment of patients with chronic hepatitis C. Highly active antiviral compounds have been developed over the past decade, thanks to new in vitro systems to study HCV entry, replication, assembly, and release. Elucidation of the 3-dimensional structures of viral proteins such as the NS3-4A serine protease, the NS5A (involved in RNA replication and infectious virus assembly), and the NS5B (an RNA-dependent RNA polymerase) also made important contributions to drug development.[34]

In 2011, the first-generation NS3-4A protease inhibitors, telaprevir and boceprevir, were approved for treatment of patients with HCV genotype 1 infection, in combination with pegylated IFN-α and ribavirin. This combination increased the rate of sustained virologic response (SVR) by 25% from approximately 50% to 75%.[35] However, because of the serious adverse effects, this treatment is not recommended for most patients on the waiting list for a liver or after LT.[36,37]

The ultimate goal is to eliminate IFN from hepatitis C treatment regimens. The first IFN-free regimen, comprising ribavirin in combination with the nucleotide polymerase inhibitor sofosbuvir,[38,39] has been tested in patients with Child A cirrhosis and HCC to prevent graft reinfection.[40] Of the patients who underwent LT, 93% were negative for HCV RNA at the time of transplantation and 64% remained negative 12 weeks after LT. On multivariate analysis, the factor most strongly associated with absence of HCV recurrence was the length of time that HCV RNA was undetectable before transplantation. Therefore, the current AASLD, Infectious Diseases Society of America, International Antiviral Society–USA, and EASL guidelines strongly recommend (A1) treating patients on the waiting list with sofosbuvir and ribavirin daily until LT.[41,42] No findings have been published on the efficacy and safety of this regimen for patients with decompensated cirrhosis Child B or C, but the AASLD and EASL suggest treating these patients at experienced centers with sofosbuvir and ribavirin.[41,42]

Findings have been reported using the same regimen to treat patients with recurrent hepatitis C. In one study, 70% achieved an SVR 12 weeks after the end of therapy.[43] Importantly, no graft loss, rejection episodes, or relevant interactions with the immunosuppressive drugs were observed. A sofosbuvir-based regimen that includes ribavirin, with or without pegylated IFN-α, for 24 to 48 weeks was evaluated in a compassionate use program for patients with severe recurrent hepatitis C and a life expectancy <1 year.[44] Overall treatment was well tolerated; 87% of these patients who completed treatment were HCV RNA negative at the end of treatment, and 62% achieved an SVR 12. Even more importantly, in regard to clinical condition, 70% of the patients improved, 13% remained stable, and 17% deteriorated.

Several large trials assessed 2 different IFN-free regimens for patients with HCV genotype 1 infection.[45–49] The first regimen, with a fixed-dose combination of sofosbuvir and ledipasvir without ribavirin for 12 weeks, was tested in patients with Child B cirrhosis.[50] All were HCV RNA negative at the end of treatment, but only 65% achieved SVR. These patients should probably be treated for a longer period or with an additional drug. Accordingly, the combination of sofosbuvir and ledipasvir with ribavirin, given for 12 or 24 weeks, is currently being tested in patients with Child B and C cirrhosis in two phase 2 studies as well as after LT (ClinicalTrials.gov; NCT01938430 and NCT02010255).

The second IFN-free regimen that has been evaluated in the posttransplant setting comprises a ritonavir-boosted NS3/4A protease, coformulated in a single tablet with the NS5A inhibitor ombitasvir, a non-nucleoside NS5B inhibitor, and ribavirin; the regimen is given for 24 weeks. This combination is only active against HCV genotype 1, so only patients with genotype 1 infection and mild recurrence of fibrosis (F0–F2) were included.[51] This combination increases blood levels of calcineurin inhibitors, requiring dose adjustments. At the end of treatment, all patients were negative for HCV RNA and the SVR 12 was 96% (with one relapse). Treatment was generally well tolerated. Finally, the combination of sofosbuvir and daclatasvir (an NS5A inhibitor), with or without ribavirin, has been used to successfully treat a small number of patients with severe recurrent hepatitis or cirrhosis after LT.[52,53]

In summary, NASH is likely to become the most frequent indication for LT in the West. Patients with corticosteroid-refractory alcoholic hepatitis may be considered for LT. The availability of IFN-free treatments for patients with chronic hepatitis C will change the care of patients on the waiting list and after LT (Table 1). Widespread use of these regimens will undoubtedly reduce the number of LTs needed for patients with hepatitis C.

Hepatobiliary Cancers

The success of LT as treatment for patients with liver cancer depends on the origin and extent of the disease.[2,54] Many researchers have studied the effects of LT in patients with HCC, an established indication at most centers, although criteria for transplantation vary.[55,56] Transplantation has gained acceptance for treatment of perihilar cholangiocarcinoma (PHC) at a few centers[57]; it is usually performed with institutional review board approval and multimodal approaches.[58] Transplantation for cancer, however, still faces many medical and ethical barriers due to the risk of cancer recurrence and organ scarcity.

Several comprehensive reviews have recently been published on treatment of HCC with LT,[55,56,59–63] along with

Table 1. IFN-free Therapy for Hepatitis C: Treatment Options for Patients With Decompensated Cirrhosis and Post-transplant

Treatment regimen	Duration (*wk*)	Setting	Previous treatment experience	n	Child–Pugh score/ MELD fibrosis score	Genotype, n (%)	Response at LT or end of treatment, n/N (%)	SVR 12 post-LT or SVR 12, n/N (%)
Decompensated cirrhosis (pretransplant)								
SOF 400 mg once daily + RBV (1000/1200mg)[40]	48 or up to transplant	Pretransplant, HCC within Milan criteria	75% treatment experienced	61, included 44 who underwent transplantation	CPS $\leq$ 8 MELD: 8 (6–14)	1a: 24 (39) 1b: 21 (34) 2: 8 (13) 3a: 7 (12) 4: 1 (2)	41/44 (93)	25/39 (64)
LDV/SOF (90/400 mg) once daily[50]	12	Child B		20	CPS: stage B	1a: 18 (90) 1b: 2 (10)	20/20 (100)	13/20 (65)
Posttransplant								
SOF 400 mg once daily + RBV low ascending dose starting at 400 mg[43]	24	Recurrent HCV CPS: $\leq$ 7 MELD: $\leq$ 17	88% treatment experienced	40	F0–F2: 5 (38%) F3: 9 (23%) F4: 6 (40%)	1a: 22 (55) 1b: 11 (28) 3: 6 (15) 4: 1 (3)	40/40 (100)	28/40 (70)
SOF 400 mg once daily + RBV ± pegylated IFN-α[44]	24–48	Severe recurrent HCV Life expectancy <1 y	NA	104	Severe acute hepatitis (n = 48) Fibrosing cholestatic hepatitis (n = 56)	1: 88 (85) 2: 1 (1) 3: 7 (7) 4: 8 (8)	81/93 (87)	53/85 (62)
ABT-450/r-ombitasvir (150/100/25) + dasabuvir (250 mg twice daily) + RBV[51]	24	Recurrent HCV F0–F2	NA	34	F0–F1: 8 (53%) F2: 6 (47%)	1a: 29 (85) 1b: 5 (15)	34/34 (100)	25/26 (92)

SOF, sofosbuvir; RBV, ribavirin; CPS, Child–Pugh score; LDV, ledipasvir; NA, not applicable.

a report from an international consensus conference.[64] The Milan criteria provide the benchmark requirements for transplantation (a single tumor <5 cm or up to 3 tumors <3 cm).[65] More than 70% of patients with HCC who underwent LT survive for at least 5 years, with rates of cancer recurrence ranging from 5% to 15%.[66,67]

Researchers have attempted to extend the Milan criteria (Table 2). Although the size of the larger lesion or total volume of the tumor burden do not change, revised criteria include factors such as risk of tumor progression or recurrence, based on levels of tumor differentiation or other markers.[68,69]

There is no convincing genetic signature that can aid in the decision process for LT.[64] The University of California San Francisco (UCSF)[70] criteria (a single tumor up to 6.5 cm, 2 tumors ≤4.5 cm, or total tumor diameter ≤8 cm) are also frequently used and have been validated[71–73]; 5-year rates of overall survival are comparable to those for the Milan criteria. Yao et al have also proposed down-staging protocols for HCC, beyond the Milan criteria, using transarterial chemoembolization or radiofrequency ablation. These approaches have rates of success of approximately 70% and impressive 4-year posttransplant rates of survival of 92%.[74]

Furthermore, the up-to-seven,[6,75] Tokyo,[76] Hangzhou,[77] Kyoto,[78] Asan,[79] and Toronto criteria[68] (see Table 2) have challenged the conservative approaches of the Milan or UCSF criteria. However, in the absence of validation, these criteria are risky in that too many grafts could be given to recipients likely to have poorer outcomes; this penalizes other patients on the waiting list. Mazzaferro et al[66] and Llovet et al[80] stated at a consensus conference that "modest expansion of criteria should consider the dynamics of the waiting list and worse prognosis could be tolerated, if there is no prejudice for patients without HCC."[64]

The ethical issue related to LT might be less relevant with the availability of living donors, because there is no prejudice toward other patients on the waiting list. Many studies of living donor liver transplantation (LDLT), mostly from Asian countries,[81] showed comparable results with deceased donor liver transplantation (DDLT) for HCC within Milan criteria.[82–84] The question about offering a liver graft in patients otherwise not eligible for a cadaveric organ remains under debate.[69] The consensus conference report stated that "LDLT should be offered for patients with posttransplant 5-year survival similar to DDLT."[64] From an ethical perspective, the concept of "double equipoise" was proposed to balance the risk of a healthy donor versus the benefit for a high-risk recipient.[85,86] For example, in the setting of DDLT, the risk-benefit is restricted to the recipient, whereas the risk-benefit analysis for living donation includes not only the recipient but also a healthy, usually young, donor. This dual balancing should be defined and accepted by the recipient, donor, surgical team, ethical committee, and society.[86]

Due to the lack of high-level evidence, the recent consensus conference, endorsed by most liver and transplantation societies, made an attempt to provide recommendations that could be widely accepted regarding assessment of candidates, listing criteria in cirrhotic and noncirrhotic candidates, down-staging approaches for large HCC, management of patients on the waiting list, LDLT, posttransplantation management, and immunosuppression. An important focus of the conference was to prevent the overuse of grafts for this population of patients to the detriment of other patients awaiting a graft.[64]

Cholangiocarcinoma is commonly a fatal disease representing approximately 3% of all gastrointestinal tumors. Cholangiocarcinoma includes 3 different types on the basis of the location along the biliary tree: intrahepatic cholangiocarcinoma (ICC), PHC, and distal cholangiocarcinoma (DCC).[87,88] Resection remains the only option for a cure, but it can be offered to <20% of patients due to the presence of a too advanced stage, often with vascular invasion at the time of diagnosis.[87,89] A small proportion of these patients, however, may benefit from LT.

ICC is an absolute contraindication for LT in the majority of allocation systems, although one group[90,91] has reported results with a 5-year survival rate of 47%[94,95]; most series present poorer figures.[91–93] More recently, a multicentric study from Spain showed good outcomes with LT for ICC in cirrhotic patients with single tumors ≤2 cm.[94] The other variant of ICC, represented by mixed tumor (HCC-ICC), is also

Table 2. Different Criteria for LT for HCC

Criteria	Features	5-Year survival (%)
Milan[65]	Single tumor ≤5 cm Up to 3 tumors each ≤3 cm	>80
UCSF[70]	Single tumor ≤ 6.5 cm or 2 tumors ≤4.5 cm or total diameter ≤8 cm	75
Hangzhou[77]	Tumor <8 cm in total or tumor ≥8 cm and α-fetoprotein level ≤400 ng/mL and well differentiated	72
Toronto[68]	Any tumor size or number and no macrovascular invasion and no extrahepatic disease and well or moderate differentiated (when beyond Milan criteria)	70
Up-to-seven[66,75]	Largest tumor size ≤7 cm or tumor number ≤7	71
Asan Medical Center[79]	Largest tumor size ≤5 cm or tumor number ≤6 without macrovascular invasion	82
Kyoto[78]	Largest tumor diameter ≤5 cm or tumor number ≤10	87
Tokyo University[76]	Largest tumor size <5 cm or tumor number ≤5	75

associated with poorer outcomes after LT[95] and is considered an absolute contraindication for LT in most centers.

Historical data have shown poor short-term survival and high recurrence rates in patients undergoing LT for PHC.[96,97] The Mayo Clinic protocol has shed new light by combining neoadjuvant chemoradiation therapy with LT[98] (Figure 2). This concept was first introduced at the University of Nebraska[91,99] and subsequently developed by the Mayo group.[98] In January 2010, the availability of excellent long-term results with the Mayo Clinic protocol convinced the United Network for Organ Sharing to consider PHC to be an acceptable indication for LT (Figure 2).[58,100] Candidates can now be enrolled in the protocol if PHC is considered unresectable due to extensive infiltration of the biliovascular perihilar structures or in the presence of an underlying liver disease such as primary sclerosing cholangitis. Of importance, tumor masses exceeding 3 cm, positive regional lymph nodes, or other metastases remain absolute contraindications.[101]

An important limitation in the comparability of the various therapies, including LT, has been the lack of a widely accepted staging system. For this purpose, a new PHC staging system was proposed by an international group of experts[102] with a focus on collecting information in a uniform way to enable analysis of large collectives of patients to identify criteria for resectability and LT associated with better outcomes. The PHC International Registry records infiltration of the bile duct tumoral and vascular structures (both portal vein and hepatic artery), lymph node status, tumor size, underlying liver disease, and predicted size of the future remnant liver. The feasibility of recording all patients with PHC was successfully assessed by registering all patients with PHC who underwent transplantation (DDLT and LDLT) at the Mayo Clinic.

In summary, HCC is an acceptable indication for LT, providing that long-term survival matches the whole population of patients on the waiting list. LT for PHC with neoadjuvant chemoradiation therapy used to produce poor outcomes but now produces acceptable results. However, only selected patients, those meeting United Network for Organ Sharing or Mayo Clinic organ procurement and transplantation network criteria, should be considered for LT.

Organ Allocation: Matching Donor and Recipient

There is a worldwide shortage of available livers. Transplant centers are increasingly confronted with difficult decisions due to policies of allocating organs to the sickest patients. Recipients are frequently selected using Model for End-Stage Liver Disease (MELD) scores, which are based on levels of creatinine and bilirubin as well as prothrombin time.[103,104] There is debate about whether suboptimal organs might be offered to patients at the top of the waiting list (ie, the sickest candidates). Some studies have found that patients with high MELD scores have poorer outcomes after LT compared with those with lower MELD scores. These findings have led to questions about offering organs to high-risk patients (a concept of futile allocation).[105] However, intention-to-treat analyses have reported that LT, without restriction to the type of graft, prolongs the survival of patients with high MELD scores.[106]

Some researchers have proposed offering livers to patients with increasing MELD scores to achieve the greatest survival benefit.[107] From a clinical perspective, there is no upper limit on MELD score for individual survival benefit due to an increasing difference between survival with and without LT along with increasing MELD score.[108,109] However, analyses of individual survival benefit concepts have not considered the maximum gain to the entire waiting list population, which occurs only when patients most likely to benefit receive organs. Currently, there is no reliable model for calculating or estimating collective survival benefit.[62,110]

In the Eurotransplant region, livers that have been offered and turned down multiple times can be offered to

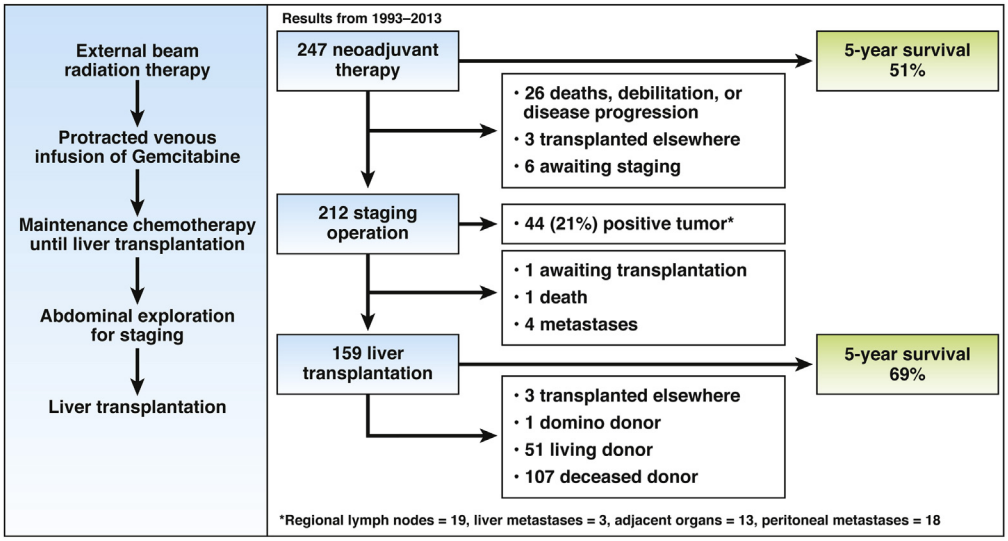

Figure 2. Mayo clinic treatment scheme and outcome of patients receiving neoadjuvant treatment followed by LT for PHC. Of the 247 patients with neoadjuvant treatment, 64% could proceed to LT resulting in a five-year survival of 69%. Figure courtesy Prof. C. Rosen.

patients selected by the center (to "rescue" the organ) rather than to the next sickest patient on the waiting list.[111] Rescue allocation policies have been shown to be effective; more than 50% of the ECD organs that had been rejected could ultimately be allocated. However, one significant drawback is extended cold ischemia.

Many researchers have attempted to define thresholds at which poor or unacceptable results are most likely to occur based on features of donors and recipients. Features include donor age older than 70 years,[112] duration of cold storage >12 hours,[113] presence of macrosteatosis >30%[114–116] or mixed steatosis >60%,[115] donation after cardiac death (DCD), and donor warm ischemia that exceeds 30 minutes.[117,118] Strategies that combine donor and recipient risk are likely to best predict outcomes of LT; several predictive combinations have been formulated.

The donor risk index (DRI) was introduced in 2006[119] to objectively calculate chances of graft survival based on 8 donor variables. The DRI, as well as its modification for Europe (the European DRI),[120] does not consider recipient factors. This might account for its weak ability to predict which patients will have the best versus the worst outcomes.[119,120] Another shortcoming of the DRI is that donor age is the main determinant, and 5 of 8 of the determinants do not vary largely in most countries (DCD, race, partial transplant, cause of death, and allocation [national vs regional]).

The D-MELD, a product of 2 continuous variables (donor age × recipient MELD), was developed in 2006 to predict postoperative mortality and length of hospital stay.[121] The D-MELD model was subsequently validated in an Italian population.[122] The shortcoming of this simple system is the absence of cofactors that obviously affect outcome.[110] As a result of this system, conservative use of grafts associated with D-MELD scores >1600 results in the refusal of a graft from a donor older than 45 years by a recipient with a MELD score of ≥35. However, in countries with a low frequency of donations, an offer of another organ from a younger donor might not come in time for the sickest candidates.

The survival outcome following LT (SOFT) score was introduced in 2008 and includes 18 features of donors and recipients.[123,124] However, several factors are subjective (eg, encephalopathy, ascites, portal vein thrombosis) and there is no real cutoff value that predicts poor patient outcome; posttransplant mortality increases linearly with increasing SOFT score. Therefore, it remains difficult to set thresholds for wasteful liver transplants based on the SOFT score alone.[106]

A new simple prediction model was developed that includes 6 factors of established systems[1,125] (donor age, recipient MELD score, recipient age, retransplant status, the need for mechanical ventilation [life support], and cold ischemia time).[106] The formula was validated using the large United Network of Organ Sharing database, as well as in Europe,[55,66,76] and aims to balance key features of donors and recipients to identify a cutoff point at which LT is most likely to be futile. This system, nicknamed the balance of risk (BAR) scoring system, identifies an exponential increase of mortality above a threshold of 18 points; mortality is relatively low (≤20%) below this threshold (Figure 3). The threshold was identified using categorical rather than continuous ranking of variables, in contrast to other prediction systems.[106]

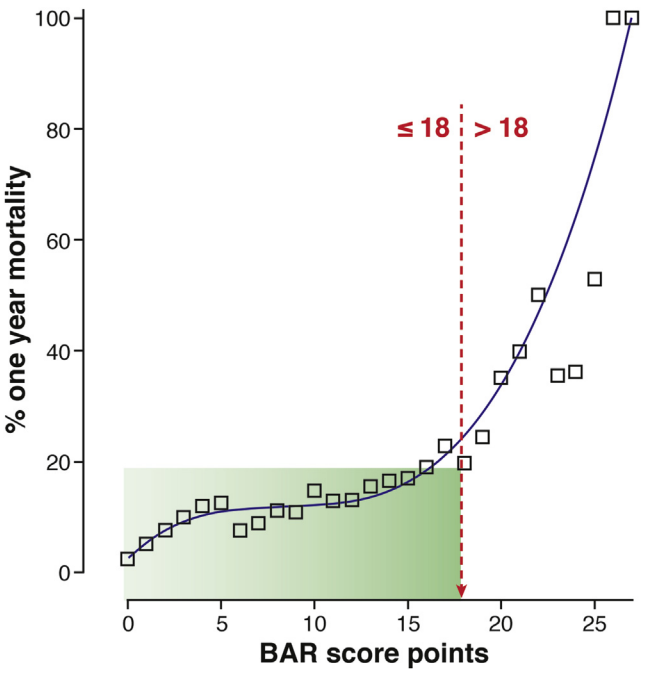

Figure 3. One year mortality after LT in relation to the balance of risk (BAR)-score.[116] While post-transplant mortality remains below or equal 20% up to BAR score of 18, the risk to die after LT increases exponentially above BAR 18.

BAR scores >18 identify poor outcomes with 98% specificity and a 2% false-positive rate. However, because of the low levels of sensitivity of the BAR system, a score of <18 does not guarantee survival. Additional donor factors associated with the use of ECD organs, such as hepatic macrosteatosis >30% or donor warm ischemia (due to DCD), require adjustments to BAR scores and can reduce the threshold for mortality from 18 points to 9 points.[106] Other recipient factors not included in the BAR score, such as cardiac risk, diabetes mellitus, chronic obstructive pulmonary disease, and connective tissue disorders, were recently shown to increase mortality in a large cohort of patients with high MELD scores.[126] Online calculators that use the BAR, DRI, and D-MELD systems are available at www.assesSurgery.com, www.gastro.cchmc.org/calculators/donor-risk-index, and www.D-MELD.com.

In summary, in the absence of donor-recipient matching systems, and in consideration of collective survival benefits, the BAR score may offer a readily available estimation of risk of postoperative mortality at the time of organ allocation.[106] Systems to estimate risk based on donor and recipient features will need to be updated as dynamic preservation technologies (eg, machine perfusion) or donor pretreatment strategies progress.

Machine Liver Perfusion

The term "machine perfusion" relates to dynamic preservation strategies of organs for transplantation, in contrast

to static cold storage preservation. Machine perfusion is applied ex vivo after organ procurement. There has been increasing interest in the use of machine perfusion to preserve ECD organs to improve graft viability and at the same time analyze graft function before implantation.[127] However, there has been debate over the optimal temperature for perfusion and the degree of oxygenation (normothermic, subnormothermic, or hypothermic perfusion). Normothermic machine liver perfusion simulates in vivo conditions and therefore requires dual perfusion, through the portal vein and the hepatic artery, at physiological flow and temperature with oxygenated diluted blood (full blood or erythrocyte concentrate), including nutritional compounds. In contrast, subnormothermic and hypothermic machine liver perfusion each rely on the physical dissolved oxygen, in a blood-free perfusate, at temperatures of 20°C to 25°C (subnormothermic) or 2°C to 10°C (hypothermic). Because there are several recent and comprehensive reviews on experimental aspects of machine liver perfusion,[128–130] we focus on clinical aspects in this report.

Although 9 studies have reported findings from ex vivo machine liver perfusion, only 2 report outcomes after LT. The other 7 studies were performed on discarded human livers that were not transplanted (Table 3).

Normothermic Machine Liver Perfusion

Op den Dries et al[131] perfused 4 DCD livers for 6 hours after 4 to 9 hours of cold storage. The livers were perfused at 37°C with diluted red blood cells via the hepatic artery and portal vein. Perfusate lactate decreased to normal values during perfusion, and bile flow remained stable. Histological analysis after 6 hours of normothermic perfusion confirmed well-preserved morphology of the liver.[131] Bellomo et al[132] described ex vivo normothermic perfusion of a discarded DCD liver, which functioned for 8 hours, based on bile production, paracetamol removal, and control of ammonia, bilirubin, and lactate levels.

Centers in the United Kingdom (Birmingham, London Kings College) are performing ex situ normothermic (37°C) perfusion of livers donated after brain death, which are then transplanted (unpublished data, Peter Friend, Oxford University, March 2013). The livers are perfused with oxygenated blood and nutrients (essential amino acids and lipids) (OrganOx, Oxford, UK) for up to 9 hours.[133] Findings on the outcomes of these transplants are awaited with great interest.

Fondevila et al have described in situ normothermic perfusion of uncontrolled DCD livers (Maastricht II category).[134] More than 290 normothermic extracorporeal membrane oxygenation procedures have been performed on DCD livers, and 82% of patients and 80% of grafts survive for 1 year.[134] Unfortunately, this approach is less practical; only 34 livers (12%) could be implanted due to graft microthrombosis, low venous return, increased levels of liver enzymes, and technical problems.[134]

Subnormothermic Machine Liver Perfusion

Bruinsma et al[135] perfused 7 discarded DCD livers at 22°C for 3 hours with phenol red Williams' medium E—a serum mixture without blood cells, enriched with amino acids, vitamins, inorganic salt, and glucose—through the portal vein and the hepatic artery. Liver levels of adenosine triphosphate increased along with increasing bile flow during perfusion. H&E staining after perfusion confirmed that hepatocytes and endothelial cells were not necrotic. However, no clinical data are available from the patients who received these livers.

Liver Perfusion With Hypothermic Machines

Guarrera et al perfused 10 discarded livers for 7 hours, via the portal vein and the hepatic artery without additional oxygenation, using relatively high flow rates ($0.7\ mL \cdot g\ liver^{-1} \cdot min^{-1}$). Liver quality was assessed based on the level of aspartate transaminase released into the perfusate.[136] In a subsequent study, machine-perfused livers donated after brain death were implanted into 20 patients. Early graft function improved, with lower levels of serum transaminase, and patients had shorter hospital stays compared with a historical group of patients receiving standard liver grafts (with cold storage).[137] The study follow-up, however, was limited to 3 months.

Jomaa et al[138] and Monbaliu et al[139] performed cold perfusion of discarded livers for up to 24 hours and assessed viability based on release of liver enzymes and morphology. In an additional study, discarded livers were randomly stored in the cold or perfused for 4 hours using the machine system (total preservation time of approximately 16 hours). The degree of reperfusion injury was tested through subsequent ex vivo perfusion of liver grafts at body temperature with diluted red blood cells for 2 hours showing reduced aspartate transaminase and lactate dehydrogenase release when compared with cold stored livers, but no morphological difference could be identified.[140]

Another technique of machine-mediated cold liver perfusion involves a hyperbaric oxygenated perfusate delivered through the portal vein only at low pressure 1 to 2 hours before implantation. It has been tested in DCD livers. The simple application of this hypothermic oxygenated perfusion technique, named HOPE, was the result of 15 years of studies in various animal models.[141–145] HOPE was performed because of the strict ethical regulations in Switzerland, which require asystolic warm ischemia for more than 10 minutes.[118] HOPE was initially applied to 8 DCD grafts with prolonged total warm ischemia periods of 40 minutes. The median age of the donors was 54 years, which is older than the maximum age for donors at most centers.[146] During a 6-month follow-up of the first group of recipients, no intrahepatic cholangiopathies were detected. Of note, this approach is less expensive and easier than all other perfusion strategies, which must begin at the site of procurement and require continuous pumping.

In summary, no outcome data have yet been published on patients who received livers oxygenated and perfused ex situ under normothermic or subnormothermic conditions. However, preliminary data from studies of discarded livers indicate the feasibility of each approach. There are promising initial results from analyses of livers processed by the

Table 3. Ex Vivo Machine Perfusion of Human Liver Grafts

Center	Year	Donor type	n	Cold storage (*h*)	Device	Perfusion (*h*)	Perfusion control	Perfusate	Temperature (°*C*)	Perfusion pressure (*mm Hg*)	Reperfusion	Protective (yes/no)
Hypothermic machine perfusion (discarded livers)												
Royal Free London[138]	2013	DBD	16	10.2	Life Port Kidney Transporter	1	Pressure	KPS-1	4–8	PV: 7 HA: 30	No	Yes
KU Leuven[a,139]	2012	DBD	17	3–24	Life Port Kidney Transporter	24	Pressure	UW	4–6	PV: 7 HA: 20–30	No	Yes
KU Leuven[140]	2011	DBD	13	15–17	Life Port Kidney Transporter	4	Pressure	KPS-1	5–8	PV: 3 HA: 20	2 h, RS-I solution + RBC, Hb 6.8	No
Columbia, New York[a,136]	2005	DBD	10	?	Medtronic Portable Bypass System	5–10	Flow	Vasosol	3–6	PV: 3–5 HA: 12–15	No	No control group
Hypothermic machine perfusion and transplantation												
Zurich[146]	2014	DCD and DBD	8× DCD, 8× DBD	2.4	ECOPS (Organ Assist)	2	Pressure	KPS-1	9–11	PV: 3	OLT	Yes
Columbia, New York[a,137]	2010	DBD	20	8–9	Medtronic Analog Life Port Transporter	3–7	Flow	Vasosol	4–8	PV: 4 HA: 6	OLT	Yes
Subnormothermic machine perfusion (discarded livers)												
Boston, Groningen[135]	2013	DCD and DBD	5× DCD, 2× DBD	4.9–19	Own device	3	Flow	Phenol red Williams' medium E	20	PV: 4–7 HA: 50–80	No	No control group
Normothermic machine perfusion (discarded livers)												
Melbourne[132]	2013	DCD	1	?	?	?	?	?	?	?	?	No control group
Groningen[131]	2013	DCD	4	4–9	Liver Assist (Organ Assist)	6	Pressure, flow	RBC, fresh frozen plasma, albumin, saline	37	PV: ? HA: ?	No	No control group

DBD, donation after brain death; PV, portal vein; HA: hepatic artery; RBC, red blood cell; Hb, hemoglobin; OLT, orthotopic LT.
[a]No active oxygenation.

HOPE technique, but further evaluation in randomized trials with different types of grafts is required.

Types of Partial Liver Grafts

Techniques to use partial grafts gathered from either living or deceased donors (split transplantation) have been developed to minimize organ shortage. However, the use of these grafts implies precise recipient selection to prevent technical complications and liver failure due to an inadequate liver mass. The number of living donor or split LTs remained low throughout the past decade, accounting for only 6% of all LTs in Europe[2] and 5% in the United States.[147] However, in Asian countries, where the use of cadaveric grafts is limited, the proportion of LDLTs continues to grow, comprising more than 90% of LT activity.[148]

Livers From Living Donors

The large proportion of LDLTs in Asia can, on the one hand, be attributed to cultural, religious, and traditional reasons. On the other hand, the endemicity of hepatitis B virus– and HCV-related diseases, including HCC, leads to an increased demand for organs, and LDLT is a highly effective strategy to overcome organ shortage.[6] In the United States, the Adult-to-Adult Living Donor Liver Transplantation Study (A2ALL), a prospective cohort of 9 centers, documented overall 1-year and 3-year patient survival of 94% and 78%, respectively.[149] Recipients of LDLTs in Europe have an overall 5-year graft survival rate of 69%, and survival is better for children than for adults (78% vs 63%).[2] In Japan, where most of the current experience with LDLT was developed,[150] 1-year and 5-year survival rates for adults are 90% and 83%, respectively.[151] Although the number of LDLTs increased worldwide until 2001, it slightly decreased thereafter in the United States and Europe, mostly due to reports on donor mortality.[3] The European Liver Transplant Registry documented a donor surgical mortality rate of 0.18%.[2] In the United States, early postoperative deaths, defined as up to 3 months after LDLT, accounted for 0.2% ($n = 4111$).[152] In this cohort, donor liver failure occurred in 0.12% ($n = 5$), all in right hemiliver donors; 3 of them could be rescued by cadaveric LT. The worldwide donor death rates have been estimated to range between 0.1% and 0.3%, possibly reaching 0.5% when using the right hemiliver for adult-to-adult LDLT.[153]

Splitting Livers

Split LT involves the potential benefit of splitting a cadaveric organ for 2 recipients. Although initially believed to rescue donor scarcity, its application has remained limited due to greater technical and logistic complexities.[154] In addition, graft and patient survival rates as well as biliary and vascular complication rates with split LT are significantly worse compared with whole organ deceased donor transplantation, especially in donors older than 40 years,[155] and in critically ill recipients.[156] As reported by the European Liver Transplant Registry, overall 10-year survival rates, including pediatric and adult split LT, are 56%.[2]

The success of any partial LT relies on the ability of the liver to regenerate. An adequate liver mass is known to be decisive for proper regeneration. In LDLT, a liver graft to body weight ratio of 0.8% is widely accepted as the cutoff for minimizing the risk of liver failure in the recipient.[157] Several centers, including ours, routinely perform liver biopsy as part of the evaluation process of a living donor graft to rule out hepatic steatosis and other liver diseases. Understanding of the mechanisms of graft injury and what options are available to preserve graft function or promote liver regeneration are central for the future use of a partial graft for transplantation.

Mechanisms of Graft Injury

In healthy livers, regeneration is triggered by resections as well as transplantation of partial grafts. The mechanisms behind this have been covered in a number of comprehensive reviews.[158–160]

Liver failure after transplantation of a small amount of liver tissue (in the absence of technical or immune problems or infection) is called small-for-size syndrome (SFSS), which is characterized by coagulopathy, hyperbilirubinemia, and encephalopathy.[161] The combination of liver injury along with a primary regeneration defect are believed to initiate SFSS, but donor- and recipient-related factors often aggravate the condition.[161]

Liver injury typically results from reperfusion of a small partial graft. The initial portal hyperperfusion is often related to a hyperdynamic splanchnic circulation as it occurs in end-stage liver disease.[162] Those changes are also observed after extensive hepatectomies in patients without cirrhosis.[163] Portal hyperperfusion causes endothelial denudation in medium-sized portal vein branches along with arterial vasospasm.[164] Arterial flow reacts in a reciprocal manner to the increased portal flow (ie, dramatic decrease in flow), which aggravates damage.[165,166]

A primary regeneration defect initiates the development of SFSS[165] in animal models. Removal of more than 80% of the liver in mice, in the absence of any other type of injury, strongly impairs hepatocyte proliferation due to p21-dependent cell cycle arrest.[165]

Preserving Graft Function

In LT, it is of utmost importance to minimize injury to the partial graft, such as by optimizing the surgical technique and keeping short times of cold and warm ischemia. Prevention of portal hyperperfusion, such as by prophylactic placement of a mesocaval shunt or splenic artery ligature, can save lives by decreasing portal pressure in small liver grafts.[167] A retrospective study of 566 adult LDLTs revealed that keeping the portal pressure less than 15 mm Hg increased survival by 20% compared with patients who did not receive portal pressure control.[168] This pressure control was mainly achieved by creation of a portosystemic shunt and concurrent splenectomy. This

strategy may provide a benefit only in the absence of outflow obstruction.[161]

Most pharmacological and other interventions to prevent the release of inflammatory mediators at the time of graft reperfusion, including ischemic preconditioning,[169] intermittent clamping[170] or remote ischemic preconditioning,[171] the use of free oxygen radical scavengers,[172] volatile anesthetics,[173] and HOPE, also belong in this category.[143–146]

Promoting Liver Regeneration

Drugs that act on proliferation signaling pathways might induce liver hyperplasia by promoting hepatocytes to enter the cell cycle or even reverse p21-dependent cell cycle arrest.[165]

Pentoxifylline improved liver regeneration in humans after partial hepatectomy with beneficial effects on regeneration in small liver remnants, possibly mediated by interleukin-6.[174] However, this compound could not be used in clinical practice because of its adverse effects.[174] Other factors that could promote liver regeneration include triiodothyronine,[175] prostaglandin E_1,[176] somatostatin,[177] and granulocyte colony-stimulating factor,[178] increasing survival in animal models of partial liver grafts.

Despite encouraging experimental data in the growing field of liver stem/progenitor cell research, clinical use of these and many other compounds has not been yet established. Promising studies are under way to reverse p21-dependent cell cycle arrest.[165] For example, the constitutive androstane receptor, a nuclear receptor that regulates xenobiotic and endobiotic liver metabolism via cytochrome P450 enzymes, is another good target. Constitutive androstane receptor agonists can induce spontaneous liver enlargement by inducing progression of the hepatocyte cell cycle during liver regeneration.[179]

Although partial LT could minimize organ scarcity, the risks of death of a healthy donor or the development of SFSS in both donors and recipients and technical complexity limit its applicability. Except for the use of shunts, no pharmacological strategy has been moved into the routine clinical setting. Compounds that interfere with signaling pathways that regulate proliferation are receiving increased attention and might be used to prevent or reverse SFSS.

Conclusion and Future Directions

Over the past 3 decades, LT has evolved from an experimental approach with major skepticism from most to a well-established and accepted therapy worldwide to cure many liver diseases, saving many lives. There are, however, a number of challenges ahead, often related to the success of LT with the resulting lack of organs. This review focuses on changing indications for LT, including those diseases that may vanish, such as hepatitis C, and the increasing need for transplantation in the presence of NASH or a variety of cancers. A main challenge ahead will be to offer a particular organ to the most adequate recipient on the waiting list. New algorithms to allocate liver grafts to recipients will primarily have to consider collective instead of individual benefits, including waiting list mortality and posttransplant survival and quality of life.

Modern antiviral-targeted drugs are in the pipeline, with the hope of eradicating hepatitis C within a decade. Up to one-third of recipients currently receive a graft for liver cancer, but this figure may well increase with better immunosuppressants or drugs offering concomitant antirejection and antitumor properties, such as the family of mammalian target of rapamycin (mTOR) inhibitors.

Immune tolerance remains an objective in the field of transplantation, but the clinical success with various protocols is still lacking. With a recipient 1-year survival rate greater than 80%, the focus of many groups has turned to long-term end points such as chronic renal failure or skin cancer. This review could target only a few topics, and the novelties of immunosuppression or long-term results could not be covered. However, excellent reviews in this field are available.[180–182]

Efforts are directed to identify strategies to increase the number of available organs or provide better-quality organs. Dynamic preservation methods will likewise replace static cold storage, with the advantages of predicting organ function before implantation and improving organ quality, allowing the safe use of organs that were previously discarded. The best type of dynamic preservation method (eg, temperature of the perfusion), however, is still under investigation. An important source of organs is living donors, particularly in Asian countries, and donor safety has emerged as one of the highest priorities in many programs. The lower the liver mass retrieved in a healthy donor, the lower the risk of postoperative complications or even mortality. Therefore, another major interest has turned to better understanding of liver regeneration with the aim of boosting growth and improving function of a small liver graft. Thus, LT has already enjoyed a laborious and glorious past, but many challenges lie ahead for this procedure, which may gain even further popularity and wider indications.

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