The International Liver Transplant Society (ILTS) Living Donor Liver Transplant Recipient Guideline

Charles M. Miller, MD¹, Cristiano Quintini, MD¹, Anil Dhawan, MD², Francois Durand, MD³, Julie K. Heimbach, MD⁴, Leona Kim-Schluger, MD⁵, Eirini Kyrana, MD², Sung-Gyu Lee, MD⁶, Jan Lerut, MD, PhD⁷, Chung-Mau Lo, MD⁸, and Elizabeth Anne Pomfret, MD, PhD⁹

¹ Liver Transplantation Program, Cleveland Clinic, Cleveland, OH.
² Paediatric Liver, GI and Nutrition Centre, Kings College Hospital, London, UK
³ Service d'Hépatologie & Réanimation Hépatodigestive, Hepatology and Liver Intensive Care Unit, Université Paris VII Hôpital Beaujon, Paris, France.
⁴ William J. von Liebig Center for Transplantation and Clinical Regeneration, Mayo Clinic, Rochester, MN.
⁵ Department of Medicine, Mount Sinai Medical Center, New York, NY.
⁶ Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea.
⁷ Starzl Unit of Abdominal Transplantation, St. Luc University Hospital, Catholic University of Louvain, Brussels, Belgium.
⁸ Division of Surgery, The University of Hong Kong, Hong Kong, China.
⁹ Department of Transplantation and Hepatobiliary Diseases, Lahey Clinic Medical Center, Tufts University School of Medicine, Boston, MA.
All authors contributed equally

**ABBREVIATIONS:*** LDLT, living donor liver transplantation; ILTS, International Liver Transplantation Society; HCC, hepatocellular carcinoma; NIH, National Institutes of Health; SFSS, small for size syndrome; SLV, standard liver volume; GRBW, graft to recipient body weight; PR, portal vein; MHV, middle hepatic vein; RUQ, right upper quadrant; FLR, future liver remnant; LD, living donor; DD, deceased donor; DDLT, deceased donor liver transplantation; PNF, primary nonfunction; ERCP, endoscopic retrograde cholangiopancreatogram; HCV, hepatitis C virus; LT, liver transplant; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; NASH, nonalcoholic steatohepatitis; PNF, primary nonfunction; FLR, future liver remnant; PTC, percutaneous transhepatic cholangiogram; HAT, hepatic artery thrombosis

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PREAMBLE AND METHODS

Around the world, living donor liver transplantation (LDLT) has been increasingly embraced as an important strategy to address the shortage of deceased donor livers. However, compared to cadaveric liver transplantation, LDLT is challenged by ethical, medical and surgical considerations, many of which are still unresolved and understudied.

Aim of this guideline is to provide a collection of expert opinions, consensus, and best practices surrounding LDLT. With the leadership and guidance of the ILTS, this guideline will be updated regularly to accurately and effectively communicate newly gained experiences and advancements.

The following guideline has been approved by the International Liver Transplantation Society (ILTS) and represents the position of the Society. Review of evidence was based on relevant clinical questions and outcomes of importance to patients, proposed by the ILTS-designated writing group chair and approved by the ILTS Guidelines Committee and Council. Acknowledged experts from around the world were recruited to address these questions after obtaining appropriate disclosures to exclude any conflict of interest. Recommendations were developed from analysis of National Library of Medicine indexed literature on “living donor liver transplantation” [Medline search] using Grading of Recommendations Assessment, Development and Evaluation methodology\textsuperscript{1,2}. Writing was guided by the ILTS Policy on the Development and Use of Practice Guidelines (www.ilts.org).
Drafts of a full-length version (>20 000 words) were freely accessible for review and comment on the ILTSEducation.org website from June 2014 and were presented for discussion at the ILTS Annual Congress the same year. Presentations were also posted online, and over 900 ILTS members and many more nonmembers were invited to comment until submission of an abridged version to Transplantation in December 2015. All comments were taken into account by the writing group chair. Formal external peer review was then undertaken by the journal, reviewers also having declared no conflict of interest. Final drafts were approved by the ILTS Council.

Recommendations have been based on information available at the time of final submission (March 2016). The lack of randomized controlled trials in this field to date is acknowledged and is reflected in the grading of evidence. Each recommendation (Table 1) has been classified as strong, conditional or not recommended\(^1,2\), depending on quality of evidence, balance of benefit versus harm, importance to patients, and cost-effectiveness. The quality of supporting evidence was rated as high, moderate, or low (A, B, or C) according to Grading of Recommendations Assessment, Development and Evaluation criteria. Intended for use by physicians, these recommendations support specific approaches to the diagnostic, therapeutic, and preventive aspects of care. However, they do not necessarily represent standards of care and should be applied only according to the best judgment of the treating team after full consideration of the circumstances relating to an individual patient.

**Evaluation**

As for cadaveric liver transplantation, evaluation and selection of adult LDLT recipients should involve a multi-disciplinary team. A LDLT candidate should also qualify as a candidate for a
deceased organ given the possibility of primary nonfunction and the need for immediate re-transplantation. Specifically related to living donor liver transplantation is the preoperative evaluation of recipient characteristics that could affect LDLT outcome. Preoperative work up should aim to establish the degree of the recipient portal hypertension (some programs routinely perform indirect measurement of the portal venous pressure and gradient), the existence of porto-pulmonary hypertension (which, if severe, could affect the outflow of the graft) and the degree of immunological compatibility between donor and recipient (preoperative cross-match)\(^3\)\(^-\)\(^8\). This information could not only help to select good candidate for living donor liver transplantation but also the type of graft to use (right vs. left lobe graft) as well as to implement strategies to optimize posttransplant outcomes (such as recipient desensitization in case of a positive cross match)\(^4\)\(^-\)\(^6\). Finally, the presence and extent of portal vein thrombosis should also be carefully assessed (see below).

Candidate selection in Asia differs quite significantly from candidate selection in Western countries. The root cause for this difference stems from the marked difference in deceased organ donation rates between the East and the West.

**Candidate Selection: The Eastern and Western perspectives**

Compared to other region of the world, in Asia there is a higher benefit and a stronger need for LDLT because of the critical shortage of deceased donor organs. Except for mainland China, LDLT in Asia accounts for over 80\% of all liver transplants compared to <5\% in the United States and Europe\(^9\). The most important differences in candidate selection between Eastern and
Western countries involve high-urgency patients, patients with hepatocellular carcinoma (HCC) and challenging surgical situations.

*High-urgency patients.* In contrast to several initial reports from Western countries that have shown inferior outcome of LDLT in high-urgency situations, several studies in Asia have demonstrated excellent outcomes for LDLT in high-urgency situations. Coercion of donors and the possible increase of donor risks are among identified concerns with LDLT, especially in high urgency situations. Experienced liver transplant programs in Asia have addressed these concerns by developing protocols and logistics for fast track evaluation of living donors, including, 24-hour radiology, endoscopy, clinical psychological assessment, and even legal support to assure the fulfillment of legal requirements. As a result, high-urgency patients with acute or acute-on-chronic liver failure are prime indications for LDLT in Asia. In western countries, LDLT is usually reserved to patients with a lower disease acuity, a practice supported by the A2ALL study. The NIH funded consortium showed that LDLT is beneficial even at lower MELD score by preventing liver transplant candidates from developing renal failure and malnutrition, key determinants for mortality on the waitlist and post-transplant complications. These findings are supported by another large national data base study showing that in more recent years (2012-2012) LDLT outcomes have improved dramatically. Furthermore data showed that the benefit of LDLT extends to late post-transplant outcomes, going beyond the benefit of earlier transplantation.

*Hepatocellular carcinoma.* HCC comprises over one third of the indications for liver transplantation in Asia, as compared to 10-20% in the United States and Europe. With a higher
demand for transplantation, yet a lower organ donation rate, these patients can rarely receive a
deceased donor liver graft in Asia. For these patients LDLT allows optimal timing of the
transplant and plays a key role in reducing the drop-out rate on the waiting list\textsuperscript{18}. As a result,
many Asian centers have adopted extended HCC criteria\textsuperscript{19-22} for LDLT because a graft from a
living donor is a dedicated gift and is not subjected to any allocation system/criteria (such as the
Milan criteria) to justify organ utilization. Consensus is lacking in the international liver
transplant community on how far these criteria should be extended. Transplant centers must
therefore balance donor risk with recipient benefit and determine a limit beyond which a
transplant becomes futile and ethically unjustifiable.

\textit{Technical challenges}. Retransplantation, Budd-Chiari Syndrome, and portal vein thrombosis
especially with extension into the superior mesenteric vein had been regarded as
contraindications for LDLT in most centers. In western countries where there is a higher
availability of deceased donors, the use of a whole liver graft avoids the technical challenges of
LDLT. However, the increased experience and improved techniques that have been
demonstrated in some transplant centers in Asia, show that these technical hurdles can be
overcome and are not absolute contraindications for LDLT\textsuperscript{23}.

\textbf{Recommendations:}

1. The availability of cadaveric liver grafts in different areas of the world affects LDLT
recipient selection criteria. High-urgency LDLT represents a prime indication for LDLT
in Asia and can be performed with acceptable outcomes (Class I, Level B) whereas in
western countries LDLT is usually reserved for patients with a lower disease acuity.
2. LDLT significantly reduces the drop-out from the waiting list of patients with HCC (Class I, Level B). Although patients with more advanced HCC beyond Milan criteria may benefit from LDLT (Class I, Level B) there is no consensus on how far these criteria can be extended (Class II, Level C).

3. Retransplantation, Budd-Chiari Syndrome, and portal vein thrombosis are not absolute contraindications to LDLT in experienced LDLT centers (Class II, Level B).

**Hemodynamic and size considerations**

The most common factor limiting LDLT is represented by small for size syndrome SFSS. SFSS can be defined as functional impairment of a partial liver graft during the first postoperative week as evidenced by coagulopathy, cholestasis, encephalopathy and ascites after the exclusion of other causes (vascular, immunological etc.). The etiology of SFSS is multifactorial and consist of graft and patient factors. Graft factor include size and parenchymal quality. Based on the existing literature, most of the LDLT transplant centers would consider as safe a graft > 40% of the recipient’s standard liver volume (SLV) or > 0.8% of the recipient’s body weight (GRBW). With improved experience, skills and better patient selection, the safety limit for minimum graft-weight-to-standard-liver-volume ratio can be reduced to 35% and to <0.8% of GRBW. Importantly, the graft regeneration and size requirement has been shown to be higher when the donor age is > 50 years. Patient factors include the degree of portal hypertension and the overall clinical status. The severity of portal hypertension and the consequent graft hyperperfusion occurring after reperfusion have been object of intense animal and clinical research. Numerous studies have shown that modulation of portal vein pressure and flows are key in successful LDLT using small grafts. It is therefore important to carry out hemodynamic
monitoring during surgery (intraoperative arterial and portal venous flow measurement, PV pressure measurement) for the identification and management of patients at risk of developing SFSS. If the portal pressure exceeds 20 mmHg, portal inflow modulation can be achieved by performing splenic artery ligation, splenectomy, splenorenal shunting, hemiportocaval shunting, and mesocaval shunting. Various pharmacologic agents that may modulate portal flow and prevent SFSS have been tested in animal models but clinical studies are lacking. The importance of the outflow as a key factor to optimize graft function and prevent SFSS will be described in the following sections.

The degree of liver decompensation at the time of transplant has also been shown to affect graft and patient survival and should be kept into consideration when planning a LDLT with a small graft.

**Recommendations:**

1. Graft injury and dysfunction in SFSS is not only a reflection of the graft size but also related to graft quality and the degree of recipient portal hypertension causing graft hyperperfusion. (Class I, Level B).
2. Monitoring of the portal vein and hepatic artery hemodynamics are highly recommended for the early diagnosis, prevention and management of SFSS (Class 1, Level B).
3. Portal inflow modulation by splenic artery ligation/embolization or other porto-systemic shunts is effective in the prevention and treatment of SFSS (Class I, Level B).
4. The role of pharmacologic agents for the modulation of portal flow is unknown due to lack of clinical studies (Class 2, Level C).
Transplant Procedure

Left lobe LDLT

Due to donor safety concerns and better understanding of SFSS, adult-to-adult left lobe LDLT has been increasingly utilized around the world. Considering the relatively small-sized graft volume, large hepatic venous outflow is essential to optimize graft function and avoid SFSS. Hepatic venous outflow augmentation can be achieved with a number of surgical techniques and should always be considered. When the left lobe with a caudate lobe graft is used, revascularization of the caudate lobe may contribute to full graft regeneration and help preventing SFSS. Regarding arterial reconstruction, it is still controversial whether the routine reconstruction of multiple hepatic arteries of LD graft should be performed. Special attention should be given to the bile duct division site in order to avoid sizable, separate caudate ducts from the left hepatic duct.

Recommendations:

1. In selected donor/recipient combinations left lobe adult-to-adult LDLT can be carried out successfully (Class I, Level B).
2. Hepatic venous outflow augmentation is essential to optimize graft function and can be achieved with a number of surgical techniques (Class I, Level B).
3. Caudate lobe inclusion and revascularization in left lobe graft LDLT may help preventing SFSS (Class II, Level C).
4. There is no consensus whether reconstruction of multiple hepatic arteries of LD grafts should be considered on a case by case basis or represent a routine (Class II, Level C).
5. Special attention should be given to the bile duct division site in order to avoid multiple bile duct anastomosis (Class I, Level C).

**Right LDLT**

Because of its size, right liver LDLT is the graft most commonly utilized in adult LDLT\(^9,15\). Nonetheless, even a right liver graft can be subject to the catastrophic consequences of SFSS.

As for the left lobe, optimal hepatic venous outflow is key for a successful outcome\(^55,56\).

The issue of whether or not to include the middle hepatic vein (MHV) in right lobe liver grafts remains controversial and has been partly addressed in the previously published ILTS guideline on Living Liver Donation\(^57\). When the MHV is not included in the graft, it is advisable to preserve and reconstruct sizable (> 5mm) right inferior hepatic veins and segment 5 and 8 hepatic venous branches (V5, V8). Different reconstructive techniques can be used to achieve this goal\(^56,58-60\). If the MHV is included in the graft, a venoplasty that converts the right hepatic vein and MHV to a triangular cuff\(^61\) will facilitate a single, direct venous anastomosis to the recipient inferior vena cava. It is important to obtain a wide cavotomy to ensure optimal outflow.

Since there is a 10-35% chance of a portal vein anomaly in a right liver graft, surgeons performing this type of transplants should be familiar with various portal vein reconstructions techniques\(^62-64\). Operating microscope has been used successfully\(^65\) for complex arterial reconstruction in addition to loupe magnification\(^66,67\). Duct-to-duct anastomosis is currently the preferred technique for biliary reconstruction\(^54,68\) except in cases when the recipient bile duct is
not healthy. It is controversial whether the use of an external or internal biliary stent can reduce biliary complications, as the stent itself may result in complications\textsuperscript{68}. When the graft has more than 1 right hepatic duct and they are close together, approximation of the adjacent ductal orifices to form a single cuff may be done and a single duct-to-duct anastomosis should be performed incorporating the hilar plate\textsuperscript{69,70}.

**Recommendations:**

1. Right liver LDLT can overcome the restriction imposed by donor-recipient size matching and is the most common graft used in centers active in adult LDLT. (Class I, Level B)

2. Optimal hepatic venous outflow is key for a successful outcome. It is recommended to preserve and reconstruct major venous branches larger than 5 mm in diameter that drain a right liver graft (Class I, Level B).

3. Surgical field magnification (either by operating microscope or surgical loops) should be used for hepatic artery anastomosis. (Class I, Level B)

4. Duct-to-duct anastomosis is the preferred technique for bile duct reconstruction. (Class I, Level B)

5. The role of external or internal biliary stents to reduce biliary complications is unclear (Class II, Level B)

**Dual Graft LDLT**

Dual graft LDLT can be used as an alternative approach to prevent SFSS and to improve donor safety whenever a partial liver graft is unlikely to meet the metabolic demand of the recipient.
Dual-graft LDLT has been performed since 2000 by the Asan group and recently at many other hospitals as well. The hepatectomy follows the same principle of distal hilar dissection used in single graft LDLT. Engraftment procedures and anastomosis sequence depends on the type of graft used (2 left grafts vs 1 right + 1 left grafts) as the anatomical 3-D orientation of the hilar structures changes when a left graft is rotated 180 degrees and placed on the RUQ. Engraftment procedures using both right and left liver grafts are a combination of 2 single-graft LDLTs using right and left liver grafts respectively, because both grafts are positioned orthotopically.

The most common complications in dual-graft recipients are biliary strictures (18%) and hepatic venous outflow obstruction of the heterotopic, right-sided left liver graft (13%). Hepatic vein obstruction infrequently occurs in orthotopically positioned, left-sided left liver and right-sided right liver grafts. This might be related to the progressive compression of the hepatic vein anastomosis by the regeneration of a heterotopically positioned left liver graft. The overall survival rate and the incidence and severity of long-term complications between dual-graft and single graft recipients are similar. From time to time, unilateral graft atrophy developed in recipients left lobes, but this did not affect their liver function or survival.

**Recommendations:**

1. Dual graft LDLT offers, in highly specialized LDLT centers, an important alternative to single graft LDLT when donor/recipient mismatch is prohibitive. (Class I, Level B).
2. Dual graft LDLT could enhance donor safety through avoidance of right lobe procurement in case of donors with borderline future liver remnant (FLR). (Class II, Level C)

3. When performed in highly specialized centers, there is no difference in the overall survival rate and the incidence and severity of long-term complications between dual-graft and single graft recipients (Class I, Level B).

The impact of LDLT transplant volume on outcomes

Several studies strongly support the concept that, as for many other complex surgical procedures, LDLT is characterized by a noticeable learning curve. After 15 to 20 cases, most LDLT centers reach a “steady state”. At this stage, most programs display comparable living donor and cadaveric post-transplant outcomes. This is an important factor to keep in mind for those liver transplant programs embarking on LDLT as well as for programs performing sporadic LDLT.

Recommendations:

1. Given the impact of volume on LDLT outcomes, transplant programs embarking on LDLT as well as programs performing LDLT sporadically should consider measures to mitigate the impact of the learning curve on patient outcomes (Class I, Level B).

Post-Transplant Care

Because of the increased technical complexity of the living donor allograft, the overall complication rates are higher in LD recipients compared to cadaveric liver transplantation. Common early postoperative complications following LDLT include bleeding and hepatic artery
thrombosis. Management of significant postoperative intra-abdominal bleeding is typically operative. Re-operation with attempted thrombectomy and revision of arterial anastomosis may also be successful in early HAT, especially if diagnosed via surveillance ultrasound. Primary nonfunction (PNF), an early postoperative complication which occurs in approximately 0.5-5% of DDLT, is not commonly reported in living donor liver transplantation, presumably due to the quality of the graft and relatively short cold ischemia time. Rejection, which is reported at similar rates compared to whole liver transplantation, is treated using a similar algorithm, with the use of steroid pulse and increased baseline immunosuppression followed by antibody treatment in case of refractory rejection. Overall, infection rates are higher following LDLT, likely related to higher rates of biliary complications leading to biloma and intra-abdominal abscess. Biliary leak rates track closely with center experience, and when the early cases are excluded, the reported incidence ranges from 15-30% for LDLT versus approximately 4-10% for DDLT. Management of a biliary leak includes biliary tract drainage via endoscopic retrograde cholangio-pancreatogram (ERCP), percutaneous trans-hepatic cholangiogram (PTC), or operative revision. SFSS represents another common complication in the early post-operative course. Treatment of SFSS is primarily supportive, with optimization of nutrition and physical therapy. Retransplantation should be considered if indicated and prior to development of systemic infection. Late biliary strictures are more common in LDLT (20-30%) than in cadaveric liver transplant and are more complex to manage due to the short length of an extra-hepatic duct as well as the high frequency of multiple donor ducts (50-60% in most series). Recurrent disease is a critical issue impacting long term outcomes for both LD and DD transplant recipients. While Initial reports suggested that outcomes for recipients undergoing LDLT for hepatitis C virus (HCV) may be inferior compared to DDLT recipients, others have
disputed this data\textsuperscript{91-93}. Hepatocellular carcinoma (HCC) is one of the most common indications for living donor liver transplant, particularly in Asia\textsuperscript{94}. Multiple authors have reported increased rates of HCC recurrence following LDLT. This is likely due to the reduced waiting time of living donor liver transplant candidates, a fact that prevents wait list drop out of those patients with a biologically unfavorable tumor\textsuperscript{95,96}. More recent series with closely matched patients undergoing LDLT or DDLT for HCC have demonstrated equivalent outcomes\textsuperscript{97-99}. Other diseases that may recur following LT include PSC, PBC, AIH, alcohol, and NASH. There is currently no evidence that recurrence is more likely following LDLT versus DDLT in these conditions.

**Recommendation:**

1. Close monitoring of LDLT recipients in the early perioperative stage for the development of intra-abdominal bleeding and HAT is recommended (serial liver vascular ultrasound). (Level 1, grade B).

2. Rejection rates are similar in LDLT and DDLT recipients, and therefore modification of immunosuppression protocols based on LD versus DD is not warranted. (Level I, grade B)

3. Biliary leaks are more common in LDLT recipients. Management is based on the clinical presentation and may include observation, percutaneous drain placement, biliary stenting, and/or operative intervention. (Level I, grade B).

4. Small-for-size syndrome is more common in LDLT. Allograft selection, potential use of inflow modification, and optimization of outflow are all strategies that should be utilized to decrease the incidence of SFSS. (Level I, grade B).
5. Anastomotic biliary strictures are more common following LDLT and may be successfully managed with endoscopic/percutaneous balloon dilation and stenting or operative revision. (Level I, grade B).

6. Recurrent disease (in particular HCC, HCV) does not appear to be more common in LDLT compared to DDLT recipients, which is useful in guiding donor and recipient selection criteria. (Level I, class B).

**Pediatric Considerations**

The most frequent LDLT used in the pediatric population is the left lateral segment\textsuperscript{100,101}, followed by left lobe, reduced left lateral segment, right lobe and posterior segments\textsuperscript{100}.

Overall outcomes for pediatric LDLT are good and generally better than for deceased donor liver transplantation\textsuperscript{102}. Surgical complications include biliary complications (14\% - 20.6\%)\textsuperscript{101,103}, hepatic artery thrombosis (6\% - 10.7\%)\textsuperscript{101,103,104} and portal vein complications (stenosis or thrombosis, 4\% - 9.1\%)\textsuperscript{101,103,105,106}. Acute cellular rejection is the most frequent histological abnormality (29.5\% - 48.7\%)\textsuperscript{102}. Chronic rejection has a lower incidence, at 2\% - 3.4\%\textsuperscript{102,107}, whereas in pediatric liver transplants overall rejection is reported at 5\%\textsuperscript{108}. Posttransplant lymphoproliferative disease has also been described with an incidence of 2.4\% - 11.3\%\textsuperscript{102}. In comparison to split organ transplantation, at least in the short term, LDLT is associated with better graft function, most probably because of decreased injury to the graft prior to transplantation\textsuperscript{109}. 
Living related liver transplant donation is accompanied by some ethical considerations mainly related to the small, but existing, donor mortality. In most pediatric cases, the donor is a parent of the patient and therefore 1 needs to take family dynamics into consideration (eg if the family may have more than 1 child or if the suitable donor is the family’s primary breadwinner).

**Recommendations**

1. Living related liver transplantation is an established form of liver transplantation in the pediatric population with excellent outcomes (Class I, Level B).

2. Living donor work up in pediatric LDLT should take into consideration family dynamics (eg if the family may have more than 1 child or if the suitable donor is the family’s primary breadwinner) (Class I, Level C).
References


Table 1.

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<tr>
<th>Grading system for recommendations and evidence</th>
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<td><strong>Class (strength) of recommendation</strong></td>
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<td>Class 1 (STRONG): There is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective</td>
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<td>Class 2 (CONDITIONAL): There is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment.</td>
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<td>Class 3 (NOT RECOMMENDED): There is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful</td>
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<th><strong>Level (Quality) of Evidence</strong></th>
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<td>Level A: Data derived from multiple randomized clinical trials or meta-analyses.</td>
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<td>Level B: data derived from a single randomized trial, or nonrandomized studies.</td>
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<td>Level C: Consensus of expert opinion, case studies, or standard-of-care statements.</td>
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