# Assessing Surgical Innovation

## ALPPS: An IDEAL Example of Disruptive Innovation

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**Objective:** To assess the impact of the IDEAL (innovation, development, exploration, assessment and long-term) paradigm on the development of ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) in comparison to the evaluation of 2 other revolutionary innovations: laparoscopic cholecystectomy (LC) and robotic surgery.

**Background:** The assessment and development of disruptive procedures often follow a chaotic and unstructured approach. The IDEAL paradigm has offered a sequential 5-stage process to assess controversial surgical strategies like ALPPS, which was introduced in 2012 to expand liver surgery for primarily nonresectable disease.

**Results:** By October 2024, the international ALPPS registry collected 1349 cases from 146 centers in 46 countries. Early reports unveiled an alarming morbidity and perioperative mortality. Accumulating cases in the registry and a consensus conference enabled to reduce the initial 90-day mortality rates $>15\%$ to $<5\%$ in high-volume centers. Meta-analyses, long-term follow-up and a RCT were available through the growing data in the registry. In comparison, the development of LC was similarly marked by technical advances and a registry to highlight safety (especially bile duct injuries). A small multicenter RCT (and a larger one later) supported an unstoppable wave of rapid adoption by patients and surgeons. Robotic surgery is currently going through close scrutinization by many stakeholders in view of the massive promotion by the industry, but a compelling registry is still missing.

**Conclusions:** ALPPS has now reached a high-level of evaluation with clear guidelines for use thanks to international collaborations and the IDEAL paradigm. This may serve as template for future evaluations of surgical innovations.

**Key Words:** ALPPS: associating liver partition and portal vein ligation for staged hepatectomy, CRLM: colorectal liver metastases, IDEAL: innovation, development, exploration, assessment, and long-term, PVE: portal vein embolization, PVL: portal vein ligation

(*Ann Surg* 2025;282:678–689)

Improvement of surgical care of patients usually relies on innovation including new, often called "disruptive", procedures. The evaluation and implementation in clinical practice of these novel procedures have most often followed a chaotic and unstructured approach, thereby leading to unconvincing evidence triggering never-ending controversies.[1]

Recognizing these shortcomings, a group of surgeons as well as experts in evidence-based medicine held a few meetings in Oxford between 2007 and 2009 proposing 5 sequential stages of development and dissemination of new operative techniques; ranging from case reports to randomized clinical trials (RCTs), and registries. This landmark work was published in 2009 in a series of 3 articles[2–4] leading to the currently well-established and widely accepted IDEAL paradigm recommendations and framework. This has been well summarized in an editorial calling for standardization in the evaluation of new procedures (Table 1).[5] Importantly, it became clear that disruptive interventions cannot be evaluated within the existing paradigms of drug treatments.

The aim of the current study was to critically explore the assessment of 3 disruptive surgical procedures through the eye of the IDEAL paradigm. First, our focus turned on a highly debated technique of hepatectomy known as the ALPPS (Associating Liver Partition and Portal vein ligation for Staged Hepatectomy) procedure. It was introduced in 2012 by a German group of surgeons reporting on 25 cases, allowing liver surgery in primarily nonresectable liver tumors[6,7] by using a 2-stage procedure. The initial accompanying editorial called it a "revolution in liver surgery".[6,7] This provocative statement, signed by 2 authors of the current special lecture, has triggered antagonistic comments from a number of liver experts, but conclusive data have now emerged after evaluation using the IDEAL paradigm.[7]

Received for publication February 25, 2025; accepted May 9, 2025.
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Submission: special lecture ESA, Geneva May 1-2,2025.
This study is supported by the Liver and Gastrointestinal Disease (LGID) Foundation, the Yvonne Jakob Foundation and the FZ-Healthcare Foundation.
J.B. and P.A.C. were members of the Balliol consortium and authors of the original reports. J.B. was the President of the robot4HPB consensus conference Paris, December 2024. E.d.S., H.L., and P.A.C. were the founders of the ALPPS registry. The remaining authors report no conflicts of interest.
Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.annalsofsurgery.com.

DOI: 10.1097/SLA.0000000000006865

**TABLE 1.** Stages of Development According to the IDEAL (Innovation, Development, Evaluation, Assessment, and Long-term) Framework[5]

| Stage | | Questions Related to Each Stage of the IDEAL Framework |
|---|---|---|
| 1 | Idea | What is the new treatment concept and why is it needed? |
| 2a | Development | Has the new intervention reached a state of stability sufficient to allow replication by others? |
| 2b | Exploration | Have the questions that might compromise the chance of conducting a successful Randomized Clinical Trial been addressed? |
| 3 | Assessment | How does the new intervention compare with current practice? |
| 4 | Long-term follow-up | Are there any long-term or rare adverse effects or changes in indications or delivery quality over time? |

Another procedure, which went through chaotic phases and virulent critics[8] was laparoscopic cholecystectomy (LC), which was considered in the 1990s as one of the most disruptive new surgical approaches ever introduced. This procedure was vehemently rejected in most academic centers at the same time as it was rapidly becoming the standard of care. The next current revolution in almost all fields of surgery lies in robot-assisted procedures, with a steadily growing use and skyrocketing clinical publications including a recent HPB consensus conference.[9] In contrast to ALPPS, robotic surgery is massively promoted by the industry, which likely impacts on the evaluation and adoption of this novel approach. The aims of this special lecture are to assess (a) the impact of the IDEAL paradigm on the development of ALPPS, and (b) the contribution of the ALPPS registry to refining indications, technical modifications and risks as well as long-term oncological outcomes, whereas (c) highlighting similarities in the evaluation process of ALPPS, LC, and robotic surgery.

## ALPPS PROCEDURE

This prospective observational study on the development of ALPPS focuses on the IDEAL paradigm and compares its implementation to LC and robotic surgery. We conducted a comprehensive literature review encompassing all studies reporting on ALPPS in PubMed/MEDLINE (Supplemental figure 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F581). All English retro and prospective original articles from database inception (first record: March 1, 2012) until July 31, 2024, were eligible for inclusion. All non-original articles, experimental studies on animals, and studies not reporting surgical outcome data were excluded. Systematic screening and data extraction were performed by 2 independent reviewers (M.L. and M. P.). Besides basic study characteristics (ie, year of publication, study type, sample size), qualitative data on indication, definition of interventional and control groups, as well as quantitative data on postoperative mortality were extracted. CADIMA (www.cadima.info, Quedlinburg, Germany) was utilized for study selection and data extraction.

The inaugural report of ALPPS[6] and its accompanying editorial[7] published in 2012 were the starting point of the evaluation of ALPPS (IDEAL stage 1). Although different groups were already gaining experience with this procedure, an international ALPPS registry was launched at the 2012 annual world International Hepato-Pancreato-Biliary Association (IHPBA) meeting in Paris, at the initiative of 3 ALPPS early adopters (E.d.S., H.L., and P.A.C.), thereby progressing into the development phase (stage 2a). The early initiative for a voluntary international registry was hosted by the University of Zurich (UZH) and endorsed by the IHPBA (www.alpps.net). To maximize quality and compliance of the entered data and promote real-time assistance to centers, coordinators (initially Dr. Erik Schadde and subsequently Dr. Michael Linecker) were hired, operating in concert with an active scientific committee consisting of 9 members from 8 different countries (Table 1, Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F581). By October 2024, the registry had collected 1349 cases of ALPPS from 146 centers in 46 countries (Supplemental figure 2, Supplemental Digital Content 1, http://links.lww.com/SLA/F581). The scientific committee approved over time a total of 44 registry-based observational projects leading to 29 original publications.

The major early issues and criticisms opined by several experts[10–13] were related to the high perioperative mortality associated with ALPPS, as highlighted by a 12% mortality among the 25 patients presented in the inaugural report.[6] Numerous subsequent reports have also reported high morbidity and mortality (>15%) calling for caution in offering ALPPS to patients with complex scenarios of primary liver tumors or metastases.[14–18] Several studies, mostly arising not only from the registry,[19–21] but also from other sources,[18] have focused on evaluating risk adjustments and thereby narrowing the indications with novel patient selection as well as optimizing technical modifications to achieve more favorable outcomes.[20–25] This information led in high-volume centers to a drop of 90-day mortality rates from >15%[14–18] to consistently around <5% mimicking benchmark values after conventional major liver surgery.[21,26,27]

The comprehensive literature review for the purpose of the current publication screened 655 articles, which showed a decrease in mortality from 13% in 2013 to 6% in 2024 in experienced centers reporting a minimum of 30 patients (Fig. 1, Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F581).

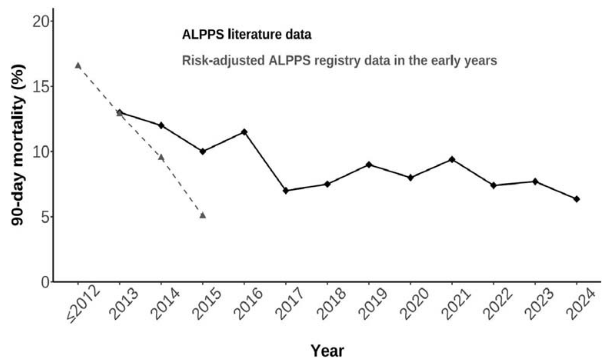


**FIGURE 1.** Ninety-day mortality rates from risk-adjusted ALPPS registry data from ≤2012 to 2015 respecting the variables age, tumor entity, interstage complications Clavien-Dindo ≥3b, and pre-stage 2 serum bilirubin and creatinine (dashed line).[21] A comprehensive literature review and analysis of the registry on ALPPS revealed a drop in median 90-day mortality rates to a median of 6% in 2024 in studies reporting on ≥30 patients (solid line).



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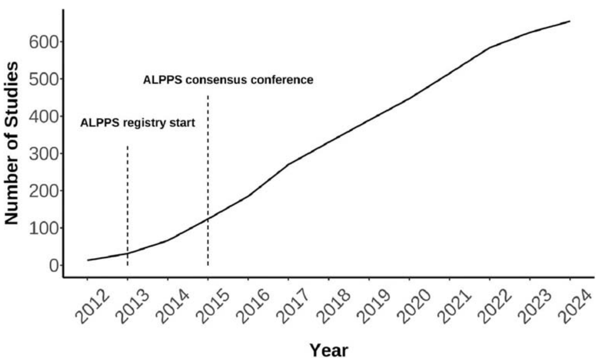


**FIGURE 2.** Total published articles on ALPPS from 2012 to 2024.

A significant next step to advance ALPPS into the exploration phase (2b) was the advent of an international consensus conference held in February 2015 in Hamburg, Germany[28] (Supplemental table 2, Supplemental Digital Content 1, http://links.lww.com/SLA/F581). This early call for consensus meeting was driven by "early adopters" consisting of 55 international experts with a larger attendance of general surgeons. Eight working groups were active 6 months before the actual conference and were asked to review the available data as well as their own experience on different aspects, including, respectively: indications, technical considerations, morbidity, and mortality to long-term outcome data. The main source of data was the ALPPS registry, which was made available to each panel member for their own analysis. The consensus conference led not only to 8 recommendations,[28] but also provided an impressive academic stimulus as the number of publications increased explosively thereafter cumulating in 655 publications (Fig. 2). Another benefit of the consensus process was the establishment of a uniform terminology around the acronym ALPPS to prevent the confusing neologisms.[29]

The main target of this conference was to improve perioperative morbidity and mortality rates. As a result, subsequent research efforts evolved around the identification of risk factors to improve patient selection. Analyses of multicentric cohorts and registry data pinpointed independent risk factors associated with poor postoperative outcome.[18,19,30,31] A comprehensive analysis from the ALPPS registry identified factors predictive of 90-day mortality after the first and second stages of ALPPS.[20] The pre-stage 1 score includes age older than or equal to 67 years, tumor site (biliary tumors vs others) as independent predictors for poor outcome. The pre-stage 2 score to predict the individual 90-day mortality included the development of major complications (Clavien-Dindo grade $\geq$ 3b) after stage 1, elevation in serum bilirubin, serum creatinine, and the pre-stage 1 risk score. A first longitudinal analysis of the registry revealed 2 predictive features with respect to long-term outcome: namely, (a) patient selection and (b) technical modifications, such as partial-ALPPS[23,24] or mini-[25]ALPPS.[25] This observation led to a dramatic decrease in early mortality and morbidity in most centers over the years as supported by a registry-based analysis of 437 patients from 16 high-volume liver centers having experience with at least 10 ALPPS cases over the past 3 years: they reported 90-day mortality rates $<4\%$.[21] This favorable outcome was associated with a proportionate increase in colorectal liver metastases (CRLM) as indication, combined with the increased use of less invasive ALPPS technical variants such as partial ALPPS.[21]

Although ALPPS did not benefit from preclinical laboratory work, translational research to deepen the understanding of specific mechanisms of liver regeneration in ALPPS accompanied the IDEAL paradigm from the first clinical description.[6,7] This started with the development of animal models, notably the first mouse model of ALPPS,[32] which led to the observation that the combination of amplified portal flow with systemic injury mediators released by the liver transection (or other types of injury) causes the accelerated regenerative process. The heterogenous models and approaches have precluded a unifying view of the underlying mechanisms. The combination of intensified portal flow changes with systemic injury mediators is meanwhile thought to underline the accelerated regeneration.[32] Besides an enhancement of known liver regeneration pathways, the unique release of a protein, the Indian Hedgehog (IHH), has enabled to identify the paracrine pathway JNK-IHH-GLI1-CCND1 signaling from stellate cells which is still the only ALPPS-specific pathway proven to accelerate liver growth in ALPPS.[33–35] Moreover, novel research in rodent models has shown that the acceleration of regeneration relies on the metabolic support from ligated lobes, which serve as auxiliary liver during the interstage phase. This observation demonstrates that the deportalized lobes maintain liver function, whereas the future liver remnant liver can undergo massive cell proliferation (unpublished data, JH Jang, PA Clavien, B Humar).

The availability of a RCT (LIGRO trial) enabled the ALPPS procedure to move to the assessment phase (stage 3) in the IDEAL paradigm (Comparative effectiveness testing). This trial from Scandinavia compared ALPPS to portal vein embolization (PVE)/portal vein ligation (PVL); the past gold standard to induce pre-emptive regeneration of the future liver remnant. One hundred patients were included, and primary endpoints were the volume increase of the future liver remnant as well as resectability. Secondary outcome measures focused on complications and oncological outcomes. The resectability rate was 92% in the ALPPS group (95% CI: 84%–100%) versus 57% (95% CI: 43%–72%) in PVE/PVL with similar 90-day mortality (8% vs 6%) and morbidity (Clavien-Dindo $\geq$3a) in both groups 43%.[36] These level-one study results were consistent with previously published data from the registry.[36] This has remained the only available RCT, and it convincingly favored ALPPS in patients with CRLM.

Shortly after the publication of this RCT, a benchmarking analysis, based on a total of 1036 patients from the ALPPS registry, established robust clinical outcomes as target references for the ALPPS procedure.[37] These benchmark values included: ability to complete stage 2: $\geq$96%, occurrence of liver failure (ISGLS-criteria) after stage 2: $\leq$5%, Intensive care unit stay after ALPPS stages 1 and 2: $\leq$1 and $\leq$2 days, acceptable interval between stages: $\leq$16 days, hospital stay after ALPPS stage 2: $\leq$10 days, cumulative morbidity rate combining both stage 1 and 2: $\leq$65%, and for major complications (grade $\geq$3a): $\leq$38% also 30-, 90-day, and 6-month mortality was $\leq$4%, $\leq$5%, and 6%, respectively. The short-term oncological results in patients with CRLM in this high-risk population were overall 1-year, recurrence-free, liver-tumor-free, and extrahepatic disease-free survival of respectively $\geq$86%, $\geq$50%, $\geq$57%, and $\geq$65%.[37]

The long-term follow-up phase (stage 4) relates mostly to robust long-term oncological outcome data in patients with CRLM, the premier indication of ALPPS (Fig. 3). The long-term analysis of the ALPPS registry covering 468 patients from 22 centers with a follow-up over a 10-year period disclosed a median overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS) of respectively 39, 42, and 15 months[38] (Fig. 3A). Multivariate analysis discovered tumor-characteristics (T4, right colon), biological features (K/N-RAS mutation), and response to chemotherapy as significant predictors for CSS.[38] Similarly, long-term follow-up from the LIGRO RCT[39] revealed a median OS of 46 months after ALPPS as opposed to a significantly inferior median OS of 26 months in patients randomized to PVE/PVL (Fig. 3B).[39]

## TWO OTHER DISRUPTIVE PROCEDURES WITH SIMILAR PATTERNS OF DEVELOPMENT: LC AND ROBOTIC HPB SURGERY

LC is a historical example of disruptive innovation introduced before the availability of the IDEAL paradigm. LC gained rapid acceptance by surgeons and patients, despite the absence of RCT or even high-level studies. In 1985, Erich Mühe performed the first laparoscopic cholecystectomy in Böblingen, Germany,[40] mainly inspired by Kurt Semm; a gynecologist, who described the "endoscopic" appendectomy (stage 1).[41] This innovation would qualify as stage 1 in the IDEAL paradigm. Concomitantly, 3 French surgeons, Philippe Mouret, Francois Dubois, and Jacques Perissat developed similar approaches for cholecystectomy, but Dubois eventually published the first small case series "Coelioscopic Cholecystectomy" in this journal.[42] This stage 2a milestone triggered harsh criticisms from colleagues coining this procedure "a futureless technique" and "circus surgery", which they predicted to be very dangerous for patients.[8] New instruments, essentially designed for gynecological procedures, enabled the first larger case series (stage 2b) publication.[43] The introduction of industry-sponsored teaching courses, particularly in the United States, convinced many surgeons to routinely offer this novel mini-invasive approach in their practice in the absence of controlled data. The first large case series of 1236 patients came from France supporting safety and effectiveness (stage 2b)[43] and finally in 1992, a RCT involving 70 patients from Canada suggested the superiority of laparoscopic cholecystectomy when compared with mini cholecystectomy, the gold standard at the time (stage 3).[44]

An important contribution towards safety came from a registry developed by the Southern Surgeons Club in the United States, which collected 1518 cases disclosing higher risk of biliary injuries of 0.5% at early follow-up[45] with a considerable morbidity on the long-term[46] which was considered to be "alarming" (stage 4). This newly identified risk of injury triggered awareness among the surgical community and other stakeholders including lawyers, who launched many lawsuits against surgeons, mostly in the United States. A new focus turned to the mechanisms of biliary injuries, avoidance strategy, classification, and repair of such injuries.[47] The description of the "critical view of safety" has significantly contributed to the decrease in frequency and severity of these injuries.[48] Altogether, it took less than 7 years for laparoscopic cholecystectomy to mature from a highly criticized "irresponsible" first case to what became the gold standard for treatment of symptomatic cholecystolithiasis. LC was undoubtedly the starting signal for the revolution of all minimally invasive abdominal surgery.

Robotic surgery progressed at a much slower pace through the IDEAL stages and has not yet fully completed its adoption curve possibly because of cautious industry credentialing. Initially introduced in the late 90s for cardiac surgery[49] (stage 1), robotic systems – most notably the DaVinci system (Intuitive Surgical) – have since been increasingly integrated across most surgical specialties. Abdominal surgery today, together with urology and gynecology, accounts for the largest number of procedures performed robotically worldwide.[50–52] The robotic approach offers several advantages over conventional open or laparoscopic surgery, such as enhanced dexterity, tremor reduction, motion scaling, and high-resolution 3D imaging.[53] These promising features have helped to defeat the skepticism of many surgeons regarding even highly complex minimally invasive procedures like hepato-pancreato-biliary (HPB) surgery, where the diffusion of laparoscopy has been somewhat modest.[54–57]

In HPB surgery, the robotic technology has reached the exploration phase (stage 2b), with industry still playing a significant role in its promotion. To critically assess its progression, an industry-independent initiative «ROBOT4HPB»,[9] endorsed by all major HPB societies, has recently proposed unbiased recommendations through an impartial multidisciplinary jury consensus exercise. The Jury was made up of a group of international stakeholders without conflict of interest in the robotic field. Beyond the critical review of the status of robotics HPB, an important goal of the initiative was to identify future research areas to guide further development and implementation of the technology based on the IDEAL paradigm. The conference

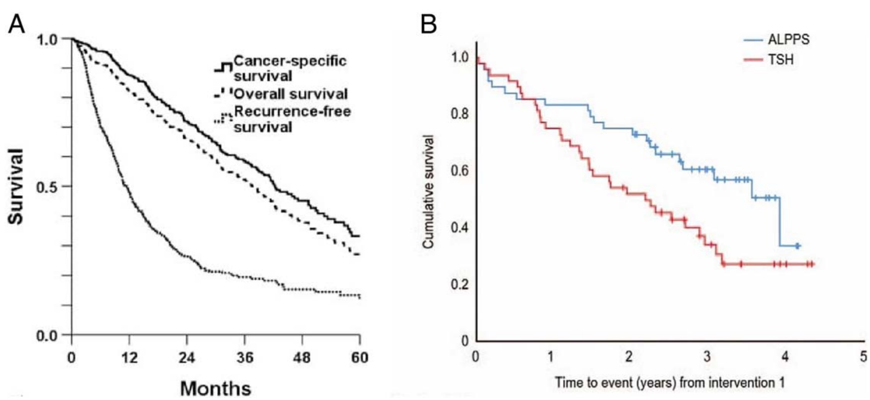


**FIGURE 3.** First long-term registry analysis of patients with colorectal liver metastases undergoing ALPPS (n = 468) (A).[38] Long-term data of the LIGRO RCT comparing n = 44 patients undergoing ALPPS to n = 27 patients undergoing conventional 2-stage hepatectomy (TSH) in the treatment of colorectal liver metastases (B).[39]



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recognized the revolutionary "disruptive" capacity of the robotic approach, predicting a continuous widespread diffusion with expanding indications. The adoption of robotic HPB surgery has undoubtedly reached a point of no return, although distinct trends of its evolution for liver and pancreatic procedures have been observed. Robotic pancreatic surgery, notably pancreatoduodenectomy, has being introduced with great caution, including data at a high-level of evidence including RCTs comparing it to the open approach (stage 3).[58,59] The evidence supporting robotic distal pancreatectomy over the open or laparoscopic approaches is mainly based on the favorable outcomes observed in RCTs comparing laparoscopic to open surgery, which demonstrated comparable oncologic outcomes and improved functional recovery.[60,61] Recent multicenter studies[62–64] – including 2 benchmark analyses[63,64] comparing matched robotic and laparoscopic cohorts confirmed the safety of the robotic approach, with even higher rates of spleen preservation and lower conversion rates.[63,65]

In contrast, the evidence on robotic liver surgery is more readily based on observational evidence,[66–69] mainly leveraging the experience and good results obtained from conventional laparoscopic techniques (stage 2b). When compared with laparoscopy in multicenter propensity-score matched studies,[66,68–75] robotic liver resection was consistently seen as feasible with reduced blood loss, conversion rates, and shorter learning curves; an observation consistently made across the entire spectrum of laparoscopic liver procedures. Benchmark values for robotic liver resection, however, are still lacking. There are challenging indications for laparoscopic HPB procedures, where the robot may be particularly suited given its technical advantages in meticulous dissection and reconstruction. One example is perihilar cholangiocarcinoma – where single center retrospective evidence from expert centers[76–78] demonstrated feasibility of the robotic approach (stage 2a). Similarly, live donor hepatectomy, another «attractive robotic indication», remains very promising in its early stage of development (stage 2a) and is restricted to very few expert centers.[79–82]

The jury of the robotic consensus conference pointed out a red flag in the safety of urgent robotic conversion[62,83,84] and pressed for implementation of regularly rehearsed standardized conversion protocols. Such recommendations from an independent Jury play a critical role in the safe adoption of new technology highlighting the value of this type of critical appraisal at stage 2b of the IDEAL paradigm. Continuous safety monitoring in the longer term through audited prospective databases and registries was identified as a critical and unmet need and has yet to be established.

## DISCUSSION

Novel disruptive procedures generated by "out of the box" individuals are unavoidable and likely desirable, but their evaluation remains a true challenge to separate great ideas from disasters as early as possible! The development of the IDEAL paradigm has helped with such a task.[2–4] ALPPS, initially one of the most controversial procedures proposed by liver surgeons, is a prime example of the swift development and assessment through the IDEAL stages within its first decade. In our view this achievement could be reached by the recognition of a "great idea"[6] followed by 3 critical features including (1) the creation of an international registry by early adopters, (2) a timely consensus conference,

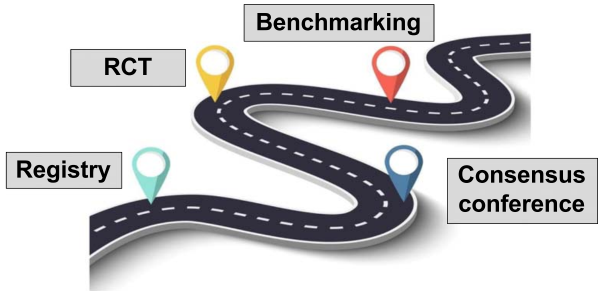


**FIGURE 4.** Critical elements to be considered in the evaluation of novel surgical procedures are: registry, consensus conference, RCT, and benchmarking.

and (3) the iterative designation of benchmark values (Fig. 4).

Both ALPPS and LC showed a similar swift transition through all IDEAL stages: 7 years for LC[44] versus 9 years for ALPPS.[39] In contrast to LC where a non-surgeon run consensus conference had very limited impact,[85] an effective, surgeon-led early consensus conference was initiated in ALPPS, only 3 years after the inaugural publication, clearly marking the start of the exploration phase 2b.[28] This event involving most experts of the time dramatically enhanced the academic interest and systematically tackled safety issues leading to a number of studies targeting risk adjustment and technical refinements.[18–21] Experienced centers (eg, ≥ 10 cases) performing ALPPS were able to reduce 90-day mortality to 4% due to the identification of risk factors leading to superior patient selection.[21] This was solely possible due to the availability of an international ALPPS registry: the only source of data with sufficient numbers of patients to yield meaningful analyses. In addition, the registry provided long-term results including oncological results[38] along with the longitudinal analysis of the LIGRO RCT.[39] While climbing the IDEAL stages and the availability of a RCT, the motivation to enter new cases in the registry waned and there was a drop registry patient accrual to less than 10 patients 2020 and 2021. With this observation, the founding members of the ALPPS registry decided to close it, even though ongoing long-term surveillance is a desirable for IDEAL stage 4. Given the waning interest and the ever present logistical challenges of an ALPPS registry at this time, future research will mostly rely on single or multicenter initiatives and may focus on comparing ALPPS to competitive approaches like the percutaneous right portal and hepatic vein deprivation[86] or expansion of the concept in transplantation like the RAPID procedure; another probable disruptive innovation.[87] The well-established benchmarking approach for surgical outcomes will be essential for meaningful comparisons and performance improvement of surgical techniques as evidenced by the growing number of published international benchmarks in liver surgery and transplantation.[27,88,89]

Translational research is still not well developed in the IDEAL framework except for the mention of a stage 0 related to preclinical achievements. ALPPS cases were reported without any relevant preclinical data. But the observation of this newly unmatched speed in liver regeneration has triggered ongoing interest in several laboratory scientists. For example, the JNK-IHH-GLI1-CCND1 signaling from stellate cells has been identified as a unique pathway to accelerate liver growth during ALPPS.[33–35] Moreover, unpublished data from the Zurich group as shown the separation of labor during the critical interstage phase, where the deportalized lobes maintain metabolic function, whereas the FLR can undergo massive cell proliferation.

Robotic surgery, unlike ALPPS, is going through close scrutinization by many stakeholders in view of the massive promotion by industry and expansion of technologies. Because of this significant push by the medical device industry to promote robotic surgery, health care providers, payers, and regulatory bodies must critically evaluate the actual benefits and effectiveness of robotic surgery. Such possible biases have raised questions about whether the technology delivers sufficient value in terms of patient outcomes, cost-effectiveness, and long-term benefits.[90,91] This process is largely akin to the advent of LC, where industry played a crucial role in meeting the expanding needs of novel instruments and devices. Also, similarly to early LC courses, credentialing in robotics remains a key point of discussion and was discussed at length in the recent Jury-based Paris consensus conference on HPB procedures.[92] The jury emphasized the importance of an industry-independent evaluation approach rather than industry-driven development alone.[9]

The 4-staged IDEAL paradigm provides a robust path to assess a new surgical procedure through its introduction and uptake but needs to be continuously reassessed. The 2019[93] IDEAL update emphasizes the importance of comprehensive data collection through registries. The example of ALPPS and LC underline the importance of beginning a registry-based data collection at an early stage. Such information would not be available in small-scaled single center studies. A large multicentric cohort analysis of homogeneous data provided by a registry is also the only way to detect unexpected low incidence complications, but with dramatic consequences such as biliary injury during at and after LC.[45] In robotic HPB surgery, such a compelling international registry is still missing but highly desired as recommended in the Paris consensus conference.[9]

Another key feature in objectively assessing disruptive procedures and identifying priorities for future development is the early organization of a well-prepared consensus conference, optimally including an independent Jury to adjudicate and phrase the final recommendations.[94] The timing of such a conference, however, must allow for sufficient published evidence and the availability of experts with experience with the new procedure. In ALPPS, the initial high morbidity and mortality in small series and single surgeon experiences triggered the initiation of a consensus conference[28] only 3 years after the inaugural publication in the exploration phase (stage 2b).[6,7] Although there was no independent Jury, crucial issues were reviewed and discussed triggering new studies and the design of a safer procedure.

The availability of clinical benchmark values is another key step in promoting safe dissemination of a novel procedure by establishing real-world desirable outcome targets. This allows for comparisons of single surgeon or hospital practices to the best results available. Therefore, after the stages of idea (stage 1) and development/exploration (stage 2) of the IDEAL framework, establishing benchmarks can be seen as a critical step in a procedure's life cycle.[9,95,96] Benchmarking has been a widely recognized tool for quality improvement in business and manufacturing. It is now increasingly being used in many surgical procedures, including liver transplantation,[89,97–99] major liver surgery,[26,88] bariatric[100] and colorectal[101] procedures.[95] Benchmarking also allows for a more objective comparisons to alternative treatments outside of a controlled trial. or may even provide a sense of a procedure's results compared with different procedures in other fields. For instance, having benchmark standards available for major liver resections may give a "real world" perspective benchmark value for ALPPS. Today, best-achievable results are also available for ALPPS.[37] Similarly, benchmark analyses in robotic distal pancreatectomy[63,64] may be the best tool for a safe adoption of the evolving robotic approach. Establishing benchmarks for robotic pancreatoduodenectomy and robotic liver surgery has been identified as a primary research priority by the recent international consensus.[9]

With the increasing amount of data becoming available in near real-time throughout the adoption of a novel procedure or technology, machine learning and artificial intelligence (AI) is expected to substantially shape future data analyses and assessment. Anticipating the exponential increased impact of AI in surgery and science in the next few years,[102,103] generating validated source data regarding demographics, comorbidity, procedure technique, and outcomes will be paramount to accurately track the performance and impact of new technologies and interventions. This highlights once more the critical importance of investing in large-scale international prospective registries and databases at an early stage as well as validating electronic health care–generated surgical outcomes data. Such data can then be used in emerging alternative study approaches, such as in silico (virtual) clinical trials using computer simulations based on real-world settings[103] to further streamline safe adoption. These will have to be incorporated judiciously in the IDEAL paradigm so that it remains pertinent in the era of big data and AI.

The Balliol group identified key landmarks defining the stage of a given surgical innovation's trajectory, guiding its path towards high-quality and meaningful RCTs.[104] in spite of this, it is widely acknowledged that robust hepatobiliary RCTs are relatively scarce, including those focused on robot-assisted surgery. Several factors may continue to explain this in the robotic era: First, robotic liver surgery is a relatively recent development, introduced well after the widespread adoption of this technique in fields like urology and colorectal surgery. In addition, liver procedures and related diseases are complex, possibly necessitating the design of more intricate technique-dependent RCTs. Also, the perceived variability in disease stages, comorbidities, and adjuvant treatment strategies further complicates the creation of consistent trial populations and the establishment of standardized outcomes. A good example is the development of PVE in the early 90s,[105] which sparked enthusiasm to pre-emptively enhance the volume of the FRL before surgery, reducing postoperative mortality related to liver failure.[105] This novel concept was smoothly adopted by many surgeons worldwide short of any RCT.

Recent experiences in comprehensively assessing such innovation – exemplified by ALPPS and robotic HPB surgery – highlight the importance of an early consensus meeting in line with other Balliol recommendations to align and provide unanimous guidance and direction for future development. This is particularly important in rare disease entities and indications, where RCTs as gold standard may neither be feasible nor efficient.



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In conclusion, ALPPS has now reached a high-level of evaluation with clear guidelines for use thanks to strong international collaborations and the IDEAL paradigm. This may serve as a template for future evaluations of surgical innovations.

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## DISCUSSANTS

### Andreas Schnitzbauer (Bochum, Germany)

Thank you very much for allowing me to be the first discussant of this paper. ALPPS becomes an adult this year. On September 3, it will be 18 years since the first ALPPS procedure was performed. From pure serendipity during the first procedure to a well-explored surgical procedure, it has been a long way. This paper shows that you must follow a transparent pathway exploring it with the right tools. To those who believed in it, ALPPS was first perceived as a holy grail, while those opposing it viewed it more as Russian roulette. By exploring it properly, it's a procedure that may find its place in the armamentarium of hepatic surgery.

I have 3 questions:

First, what are the 3 most important take-home messages to perform ALPPS procedures safely today?

Second, where do you see the realistic niche for ALPPS within the evolving armamentarium of regenerative liver surgery? Specifically, how do you see its role in experienced surgical hands compared with other strategies such as portal vein embolization (PVE), total venous deprivation, or even palliative chemotherapy?

Finally, in your view, what should be the essential elements required to make regenerative techniques, such as ALPPS, ideal, sustainable, and scalable, both for maximizing patient benefit and for guiding the development of future approaches?

### Response From Michael Linecker (Kiel, Germany)

Professor Schnitzbauer, thank you for your insightful comments and questions. Regarding your first question, 3 key factors must be considered: appropriate patient selection, the choice of optimal technical variants, and surgical expertise. In terms of patient selection, colorectal liver metastases have consistently emerged as the most favorable indication. In addition, patient age has been repeatedly identified as a significant predictor of outcomes in multivariate analyses. The technical aspects must focus on minimizing the impact of stage 1 surgery. There are many ways to do this: laparoscopically, robotically, using the tourniquet ALPPS, or a combination with PVE. As we know from the international ALPPS registry, the experience of the surgical team is another important factor to perform ALPPS safely. As such, I would say that these are the 3 most important things. By combining these factors, the ideal candidate would be a patient in their mid-40s with bilobar colorectal liver metastases, no significant comorbidities, and managed by a highly experienced surgical team.

With regard to your second question, ALPPS remains a valuable tool within the armamentarium of regenerative liver surgery. Although alternative approaches exist for certain cases, our previous work, presented at the ESA 5 years ago, highlighted that there is still no consensus among experts on the optimal treatment strategy for complex liver patients. This underscores the continued relevance of ALPPS in carefully selected scenarios. For many liver experts, a prime indication would be the scenario of bilobar colorectal liver metastases requiring a regenerative strategy and cleaning of the future remnant liver in a patient younger than 65 years of age without significant comorbidities. In the real world, the choice of therapeutic approach mostly depends on local expertise, and in the case of ALPPS, the availability of expert liver surgeons.

Regarding your third question on the essential elements for sustainability, several key steps are necessary. First, the establishment of an early and widely adopted international registry is crucial to ensure diligent case collection and continuous data monitoring. This should be followed by a multidisciplinary consensus conference to address safety concerns and evaluate early outcomes. Once the innovation reaches a more advanced stage, such as IDEAL stage D (development), randomized controlled trials become essential to investigate specific indications and technical refinements. Finally, the definition of benchmark values using standardized methodology is critical to outline expected, achievable outcomes and to guide broader adoption.

## Pål-Dag Line (Oslo, Norway)

Thank you for the excellent presentation on the development and validation of the ALPPS procedure. Your conclusion, which emphasizes the critical developmental stages, including innovation and proof of concept, formation of a registry, benchmarking, and randomized clinical trials, provides an excellent illustration of how surgical innovation can, and should be, conducted in line with the IDEAL principles.

All novel methods in surgery, however, rely on a range of previously developed concepts and principles. Thus, the evaluation of an innovation could also be broadened by examining the extent to which ALPPS has paved the way for, or inspired, other novel treatment strategies, helping to illustrate a more comprehensive longitudinal innovation timeline. The RAPID procedure, for example, is a clear example, and both techniques share the primary treatment indication of colorectal liver metastases. Viewed from this perspective, could it be argued that other developments in HPB surgery are, at least in part, a consequence of the introduction and evolution of the ALPPS procedure?

## Response From Pierre-Alain Clavien (Zurich, Switzerland)

Thank you, Professor Line, for your comments and I would like to acknowledge your important contribution to the development of the RAPID approach in liver transplantation, which derived from the ALPPS concept, as you mentioned. Surgery can be likened to a chest of drawers: the top drawer contains the first innovative, although sometimes imperfect, garments, whereas the drawers below offer increasingly refined variations – lighter, more elegant, and better suited for specific needs. ALPPS itself is not an isolated innovation, but rather a natural evolution stemming from foundational contributions: the introduction of portal vein embolization by Makuuchi in the late 1980s, the concept of staged hepatectomies by Henri Bismuth in the 1990s, and the 2-stage hepatectomy presented by Daniel Jaeck at this very meeting in 2004. More recent developments, such as minimally invasive techniques aimed at reducing the burden of stage 1, such as the robotic approach or liver vein deprivation, represent welcome incremental advancements. However, these innovations still require rigorous evaluation before they can be widely adopted.

Beyond prompting technical refinements and the integration of complementary approaches, ALPPS has emerged as a major catalyst for innovation in liver surgery. It has redefined the boundaries of what is both technically and biologically possible, inspiring the development of safer and more biologically informed alternatives. Perhaps most importantly, ALPPS has significantly deepened our fundamental understanding of liver biology and regeneration. It has laid the groundwork for breakthrough research in this field, with its principles of accelerated liver regeneration now being translated into a range of clinical and experimental applications, including ex situ liver regeneration through long-term machine perfusion. In this way, the influence of ALPPS extends far beyond its role as a single procedure for a specific group of patients.

## Laurence Chiche (Pessac, France)

I congratulate the authors for this excellent lecture. You demonstrated how ALPPS has followed all the steps of innovation in surgery and can be considered as a model of rigorous progress, following the IDEAL paradigm. You have demonstrated how a rigorous scientific process can not only improve the outcomes of innovations but also contribute meaningfully to our understanding of pathophysiology.

That said, I have a few comments. My first point concerns your comparison with laparoscopic cholecystectomy (LC). It's true that innovation often disrupts tradition and can be met with resistance, as was the case with LC in its early days, faced with scepticism, criticism, and doubt. However, LC was a different scenario: it involved a very common and straightforward procedure with low mortality, and laparoscopy was primarily a change in approach, not in concept. In contrast, ALPPS represents a rare and fundamentally new procedure aimed at expanding the boundaries of liver resection. It was understandably controversial in its early phase, due to relatively high mortality and the lack of proven benefit. Furthermore, although LC was ultimately supported by several randomized trials over time, this has not been the case for ALPPS, largely because such trials are far more challenging to conduct in this more complex and less frequent setting.

My second comment concerns your "milestone road" slide. Depicting innovation as a lone highway through a desert, with no side roads or crossroads, doesn't reflect reality. In practice, external developments can narrow, or even close, certain paths. For example, numerous surgical solutions for portal hypertension were sidelined once the TIPS (transjugular intrahepatic portosystemic shunt) emerged. Similarly, in the case of ALPPS, interventional radiology techniques, such as liver venous deprivation (or

RASPE), have entered the landscape. Although these approaches haven't "closed" the ALPPS route, they have certainly carved out their own niche. Each procedure could find its own indication, and this must be mentioned.

Finally, you emphasized the intense and sometimes vehement criticisms that often accompany surgical innovations. But don't you think such scrutiny is ultimately more beneficial than regrettable? After all, it can be a powerful stimulus, pushing innovators to refine their techniques and to rigorously demonstrate the scientific and clinical viability of their approach. That is exactly what happened with ALPPS, as perfectly illustrated by your lecture.

In any case, this was not only a compelling defence of ALPPS, but more importantly, a powerful illustration of the right pathway to surgical progress. Congratulations.

## Response From Pierre-Alain Clavien (Zurich, Switzerland)

Many thanks, Professor Chiche, for your valuable and thought-provoking points. Although laparoscopic cholecystectomy (LC) is undeniably simpler than ALPPS, I vividly recall the early days of training when I assisted with the very first LC performed in Canada, a case that lasted over 5 hours and involved considerable stress for the entire team. In the following years, we witnessed numerous admissions for bile duct injuries, which led to poor quality of life for many patients and, in some cases, even mortality. In that context, the term "disruptive innovation" was entirely appropriate.

I fully agree with your second point as well. The "road" to innovation that we presented is, of course, a simplified representation, a deliberate shortcut meant to emphasize that a pathway does exist, albeit with associated, unexpected hurdles.

Finally, I wholeheartedly agree that rigorous debate and pointed questions are vital to challenge "out of the box" concepts. At the same time, our collective experience with ALPPS, LC, and other innovations shows that early innovators often face resistance that goes beyond healthy skepticism, sometimes bordering on ideological opposition. I remember respected chairs of surgery once declaring that LC would never be performed in their institutions. So, you can imagine the reactions ALPPS received until robust data from registries and RCTs began to change the narrative.

## Catherine SC Teh (Makati City, Philippines)

ALPPS: An IDEAL Example of Disruptive Innovation offers a timely and incisive view of how surgical innovations can evolve responsibly when guided by structured frameworks, such as IDEAL. Associating ALPPS with disruptive innovation is fitting, not only because it redefined resectability in liver surgery but also because it sparked early controversy, compelled global discourse, and eventually, matured through systematic data collection and evaluation.

From a low-middle-income country (LMIC) perspective, ALPPS reflects contextual innovation. In 2012, prompted by necessity, not trend, we performed ALPPS for a patient with advanced gallbladder cancer and bilobar liver metastases, who had an exceptional biochemical response and excellent functional status. Portal vein embolization (PVE) was financially inaccessible, and interventional radiology was limited. With full disclosure, ALPPS was a shared, goal-aligned decision offering quality of life and survival.

Our humble series – mostly successful, except one mortality in HCC – taught valuable lessons rooted in compassion, pragmatism, and resource-sensitive judgment. ALPPS provided a pathway for expanding resectability and refining surgical practices. Learning from every patient, we adapted criteria, improved patient selection, and enhanced perioperative care. After the HCC mortality, stricter selection and refined techniques became imperative. Patient-reported outcomes, therapy fatigue, and economic considerations were integral to the decision-making. Innovation must never outpace safety, and reflection remains essential.

Yet, even with frameworks like IDEAL, innovation faces hurdles: premature adoption, publication bias, learning curves, ethical dilemmas, and infrastructural gaps, especially in LMICs. Failures are costlier when systems are fragile. But, within these constraints, necessity drives meaningful progress. ALPPS not only restored life; it also restored dignity and hope.

As the registry closes, ALPPS stands as a model of responsible innovation. It reminds us that disruption must be coupled with deliberation and governance. Importantly, it underlines that innovation must remain grounded in humility, safety, and person-centered care.

## Response From Pierre-Alain Clavien (Zurich, Switzerland)

Professor Teh, many thanks for your valuable comments and for sharing a perspective on ALPPS from the context of a country that may have limited access to alternative approaches. This disparity in access to the full range of modalities for complex liver procedures is, in fact, a universal reality. Very few centers can offer equal levels of expertise across all subspecialties, and this inevitably influences therapeutic decision-making, sometimes subtly so, but even more markedly in low-income and middle-income countries.

Your institutional learning experience, though driven by necessity, is indeed a great example of the responsible, well-paced, and evidence-based adoption of innovation. It is of paramount importance that experiences like yours are shared with early adopters and the community, ideally through an early registry, which can then inform early consensus development. In this way, learning curves can be streamlined and learnings can benefit more patients.

## Albert Chan (Hong Kong, China)

This presentation provides a comprehensive appraisal of the ALPPS evolution through the IDEAL paradigm. Thanks to this process, ALPPS has become a well-recognized procedure within the metaverse of liver surgeons. In the East, ALPPS has been more frequently adopted for hepatitis-related hepatocellular carcinoma, owing to the prevalence of viral hepatitis. As such, the concern for the safety of ALPPS in cirrhosis was largely related to the risk of postoperative liver failure. For this reason, strict patient selection criteria were followed and only patients with Child A liver function were offered this procedure. To enhance the accuracy of the standard preoperative liver function assessments, an indocyanine green clearance (ICG) test was added with a clearance rate of $</=15\%$, regarded as a safe cut-off limit for ALPPS.

In addition, technical modifications have been adopted to mitigate the procedure risk. These include partial split with portal vein embolization, or laparoscopic ALPPS.



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Because of cases of hepatitis or cirrhosis, the degree of hypertrophy was less substantial compared with normal livers. After having performed 95 cases since 2014, our center observed an average of 50% future liver remnant volume gain over 7 days. Reciprocally, we witnessed a decline in the number of portal vein embolizations performed in the past decade, as ALPPS became the preferred liver augmentative approach due to its rapid hypertrophy effect. Finally, what we learned from the ALPPS procedure has advanced our knowledge in liver regeneration and transplant oncology, translating into novel derivatives, such as the RAPID procedure, and hopefully, more to follow in the future.

## Response From Pierre-Alain Clavien (Zurich, Switzerland)

Thank you, Professor Chan, for sharing your experience with ALPPS in cirrhotic patients with related HCC. In line with the previous comments, cooperation and learning among surgeons have benefited many patients. The registry, open to any investigators, has enabled a better understanding when it comes to applying ALPPS to many conditions.