Centralization of Biliary Atresia: Has Germany Learned Its Lessons?

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Abstract

Introduction The majority of pediatric surgeons and hepatologists recommend the centralization of biliary atresia (BA) treatment within experienced liver units. We aimed to investigate whether voluntary self-restriction and acceptance of the need for this change in practice changed the BA referral policy in Germany during the last decade.

Materials and Methods In cooperation with pediatric surgeons, gastroenterologists or hepatologists, and pediatric liver transplant units, the 2-year follow-up data of infants with BA born in Germany between 2010 and 2014 were collected using www.bard-online.com or pseudonymized data transfer. Results were compared with our previous analysis of the outcome data of infants with BA born between 2001 and 2005 in Germany.

Result Overall, 173 infants with BA were identified, of whom 160 underwent Kasai portoenterostomy (KPE; 92.5%) and 13 (7.5%) underwent primary liver transplantation at 21 German centers. At 2-year follow-up, overall survival was 87.7% (vs. 81.9% in 2001–2005 [$p = 0.19$]), survival with native liver post-KPE was 29.2% (vs. 22.8% in 2001–2005 [$p = 0.24$]), and jaundice-free survival with native liver post-KPE was 24.0% (vs. 20.1% in 2001–2005 [$p = 0.5$]). Compared with the 2001–2005 analysis, all criteria showed improvement but the differences are statistically not significant.

Conclusion Our observation shows that KPE management requires improvement in Germany. Centralization of BA patients to German reference liver units is not yet mandatory. However, European and national efforts with regard to the centralization of rare diseases support our common endeavor in this direction.

Keywords
- biliary atresia
- Germany
- centralization
- liver transplantation
- registry

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Introduction

Despite extensive clinical and basic research, we know very little about the etiology and pathomechanism of biliary atresia (BA).[1,2] Nevertheless, in our joint efforts to solve the puzzle of this enigmatic disease, variables in perioperative management, among others, have been the subject of many clinical trials.[3–5] Some of these variables address preferred surgical technique and adjuvant therapy, while others have to do with prognostic factors related to the outcome of the Kasai portoenterostomy (KPE).[6,7] However, it is a matter of common sense that early diagnosis (screening programs), sequential surgical treatment (the KPE and optional liver transplantation), and thorough follow-up in pediatric liver units improve survival rates among BA patients with native livers.[8–11]

Another controversial and much discussed issue concerns a causal link between the caseload of a center and its post-Kasai outcomes.[12,13] Debate about this crucial point has been ongoing since Davenport and colleagues demonstrated that "seamless management of biliary atresia in England and Wales" improves post-Kasai outcomes.[14] To date, most, if not all, European pediatric hepatologists and surgeons agree that centralization of BA patients in pediatric liver units should be mandatory. In some countries, this is already a reality but in others, a change is overdue.[15–18]

In Germany, the nationwide coverage given by pediatric surgical departments is different to that in other European countries. Every institution operates autonomously; there are no professional prerequisites and neither the health care system nor insurance companies impose any restrictions.[19] To evaluate and describe the pediatric surgical care for BA in Germany, we performed a retrospective analysis for the period between 2001 and 2005.[20] At the time of this survey, 29 pediatric surgical departments had reported their results following KPE or primary liver transplantation (pLTx), respectively. The main finding of this survey was that the experience of the center emerged as the only significant predictor for jaundice-free survival with a native liver.[20] Since the survey was performed, there has been extensive discussion of the need for centralization of BA patients within experienced liver units, as recommended by most opinion leaders in pediatric hepatology and surgery. However, the German health care system is not bound by governmental regulations, and no agreement between the 100-plus German health insurance companies can be expected. Hence, the question has been raised whether voluntary self-restriction and acceptance of the need for this change in practice could change the BA referral policy. For this purpose, we repeated the Germany-wide BA study by reaching out to all clinics which had participated in the first one and requesting data on their caseload over the previous 5 years, as well as data on the 10-year outcomes of BA patients.

Materials and Methods

The aim of the present study was to identify all BA patients who were born and treated in Germany between January 2010 and December 2014. Therefore, we contacted the pediatric surgery and gastroenterology or hepatology departments in those centers which had participated in the first study, performed 10 years ago. As the first preference, we recommended they enter patient data into the internet-based voluntary BA registry, accessible at www.bard-online.com. We asked for the following variables: gender, gestational age, presence of BA splenic malformation syndrome (BASM), and age at which the Kasai procedure was performed. With regard to the outcome, the following parameters were set at 2 years of the post-Kasai: survival overall (SOA), survival with native liver (SNL), jaundice-free SNL (JF-SNL), and bilirubin less than 20 µmol/L, LTx, and death.

Several centers which were unwilling to join the decentralized Biliary Atresia and Related Disorders (BARD) registry transferred pseudonymized data by mail or e-mail. Others complained that the increasing burden of administrative workload prevented them from active participation. However, they agreed to host one member of the researching team (D.F.) at their institution to collect data on site. A few centers referred to the restrictive German data protection regulations which are still inconsistently implemented by legal services. These centers refused to provide the above-mentioned variables, even in anonymized form. However, they reported the cumulative outcome data according to the schema shown in ►Fig. 1. Because of the incomplete dataset from these centers, cumulative Kaplan–Meier curves could not be calculated.

We were aware from our experience carrying out the first study that some BA patients bypassed pediatric surgical departments for the KPE and were directly forwarded to liver transplant centers. Therefore, we cross-checked our data collection and also asked all German pediatric transplant centers for primarily transplanted patients to prevent mismatch with the recorded cases.

When we asked centers to participate in the survey, we guaranteed the highest level of confidentiality, meaning that numbers and patient outcomes would not be traceable to any particular center. This implied that centers' locations and personnel would be regarded as confidential data; hence, no participants would be listed as authors or mentioned by way of acknowledgment.

Data Analysis

Statistical analysis was performed using GraphPad Prism software version 8.0 (GraphPad Software, San Diego, California, United States) to calculate the correlation coefficient, and an unpaired *t*-test. Data are displayed as means and standard deviation (SD). A p value of <0.05 was considered statistically significant.

Ethics

The study protocol is in accordance with the Helsinki Declaration and was approved by the ethics committee of Hannover Medical School.

Results

Centers and Patients

Of the 29 pediatric surgical departments who participated in the first survey, 21 confirmed that they still perform KPE. A

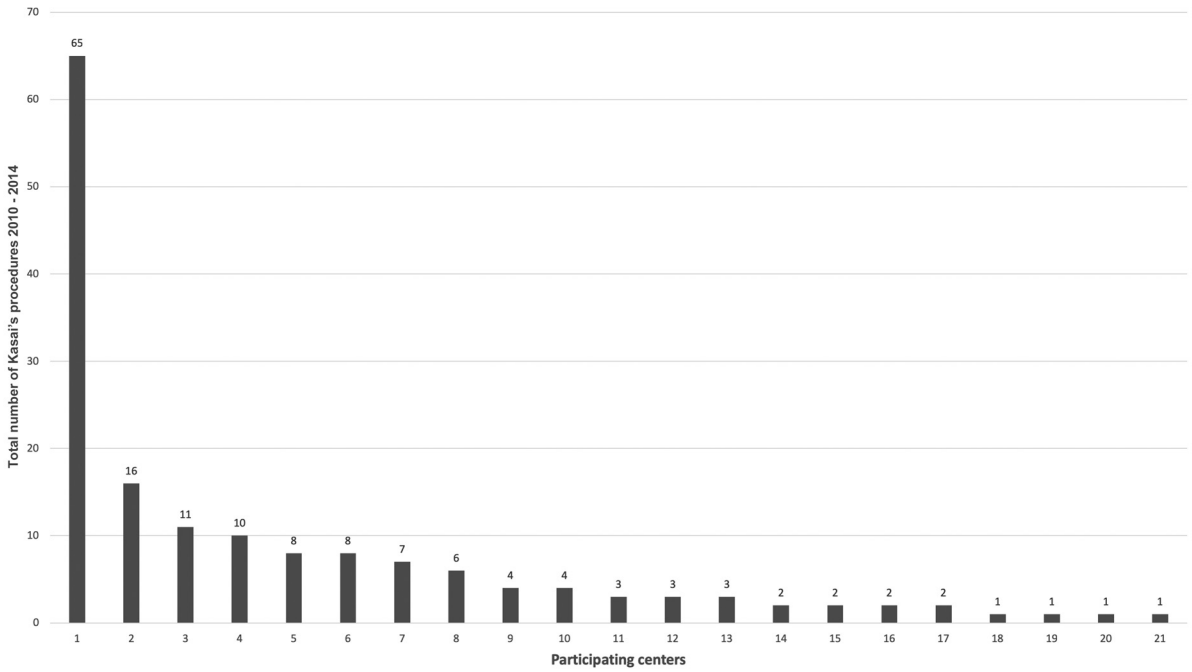

Fig. 1 Outcome data of 160 Kasai portoenterostomy (KPE) performed between 2010 and 2014 visualized in a flow chart, including information on the follow up data, the Kasai outcome stratified to jaundice-free survival with native liver (JF-SNL), survival with native liver (SNL), liver transplantation (LTx), and the pre- and posttransplant mortality.

total of 173 patients with BA was recorded in our second study, meaning that we captured approximately 94% given a BA incidence of 1:19,000 births (36 new patients per year; 180 over 5 years). One hundred and sixty infants (92.5%) underwent KPE, while in 13 cases (7.5%), pLTx was performed.

Stratifying the centers by case load, 8 (38%) reported more than one KPE per year, thus a total of 131 KPE was performed (82%; ►Fig. 1). Of these 131 operations, 65 infants (50%) underwent KPE at a single center, while the other seven departments operated on between 6 and 16 cases each. The remaining 29 KPE (18%) were undertaken by a total of 13 pediatric surgeons (62%) that corresponds to an average of two KPEs per center over a 5-year period.

With regard to the 13 pLTx, 10 cases were assigned to a single clinic, in which the KPE/pLTx ratio was 16:10, as compared with 10:2 and 4:1 in the two other clinics.

A few centers refused to provide all entry variables and follow-up information. Consequently, the dataset was incomplete and a more conclusive Germany-wide evaluation became senseless.

Outcome

Most centers whose data were extracted from the BARD or from their local registry agreed to data cumulation in a common spreadsheet for the purpose of further evaluation. Centers with a restrictive policy in terms of data exchange did not provide all the follow-up data required; instead, they entered the cumulative results of their own center into the schema, which we used for the evaluation of all centers shown in ►Fig. 1.

The SOA during this 5-year survey was 88.2%. Twelve patients died after LTx and three for other reasons. Across all centers, the KPE was performed on 160 of 173 BA patients, and follow-up data until the second year of the post-Kasai were available for 154 patients (96%). As shown in ►Fig. 2, 12 of these children died without any further surgery, presumably while on the waiting list. LTx within the first 2 years of life was performed in 63% of patients. Forty-five infants (29%) survived with their native liver, predominantly jaundice-free (24%). The latter group sets the benchmark for successful BA treatment and management which also depends on other factors (time the KPE was performed, concomitant congenital diseases, etc.), not least the competence of the respective liver unit. The survival rate at 2 years post-KPE was 88% (135/154).

In the present study, we primarily focus on whether the BA caseload per center still affects the outcome and what has changed over the 10 years which separate the two studies. For this purpose, and to maintain longitudinal, as well as horizontal comparability, we were forced to make one restriction and exclude one center from the final cumulative outcome evaluation. The reason is that in this center, during this particular period, more than 60% of the BA patients were primarily liver transplanted and the SNL of the remaining patients was zero. The reason for the unusual and dubious policy followed by this center will not be discussed here and we know that the situation has since changed.

When we look at the survival rate of all patients after KPE, we do not see any relation to caseload per se. The outcome after KPE or KPE and LTx is 88% in centers with more than five KPE over 5 years and 90% in centers with more than ten KPE over 5 years. The same is true for lower-volume departments (83%), because worse outcomes after KPE are compensated by secondary LTx. These differences are statistically not significant.

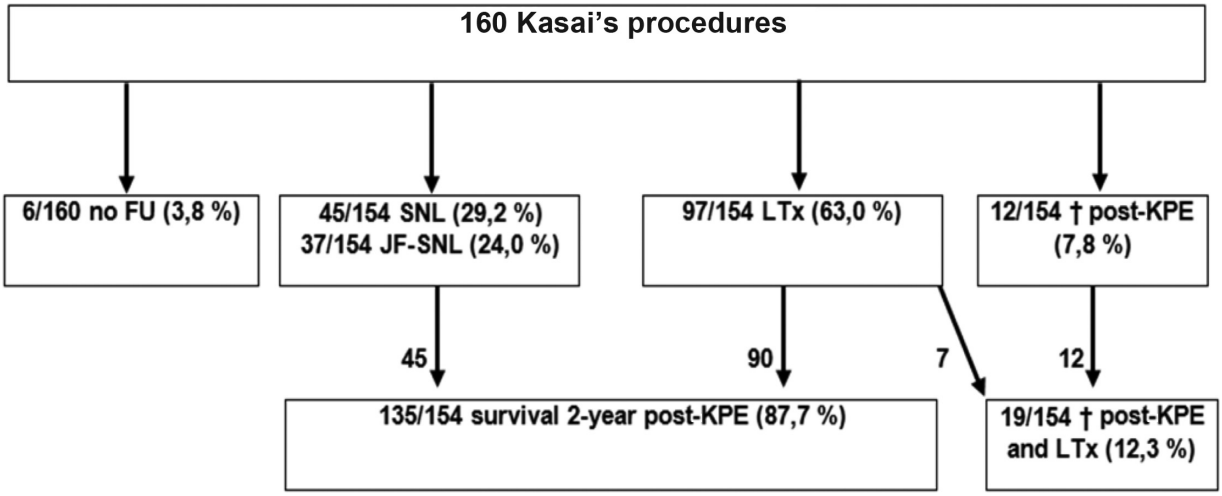

Fig. 2 Bar graph with the total patient numbers (*n*) of all infants undergoing the Kasai procedure between 2010 and 2014 at each of the 21 participating centers. FU, follow-up; JF-SNL, jaundice-free survival with native liver; KPE, Kasai portoenterostomy; LTx, liver transplantation.

The benchmark in evaluating the quality of care between centers with high and low caseloads is JF-SNL. In the recent study, centers performing more than ten KPE per 5 years reach an SNL of 40%, which is statistically and significantly different to the 21% achieved in pediatric surgical departments with lower caseloads ($p = 0.02$). The same is true for JF-SNL, where 33% remain jaundice-free versus 17% ($p = 0.05$).

Comparison of the 2001–2005 and 2010–2014 Studies

When comparing the two studies, the calculated number of expected BA cases per year dropped from 37 in the first to 36 in the second because the annual average birthrate in Germany also dropped from 709,800 in the period 2001 to 2005 to 681,660 in the period 2010 to 2014.[21] Therefore, the number of registered BA patients was 183 out of 185 calculated cases in the earlier study and 173 out of 180 calculated cases in the present one, which is slightly but not statistically different. A total of 10 patients (6.3%) could not be followed-up in the early survey and six (3.8%) in the second. Between the two study periods, the proportion of pLTx decreased from 21 (11.5%) to 13 (7.5%), while the number of centers performing the KPE with a caseload of five or more patients over 5 years rose by one, from seven to eight centers. However, the number of centers performing the KPE with a low caseload decreased from 22 to 14.

With regard to the identical outcome parameter in the two studies, set at 2 years after the KPE was performed, all criteria showed improvement but the differences are statistically not significant, as shown in ►Table 1.

Geographic Distribution of Centers and Cases in Germany

In the light of future developments and the centralization of rare diseases in Germany, the current state with regard to BA is of interest. Therefore, we divided the German territory into four approximately equal areas and calculated the estimated number of new BA patients per year on the basis of demographic information.[21] ►Fig. 3 shows a regionally uneven distribution of centers and cases, with a high BA incidence in the western and southern parts of Germany. In contrast, the current distribution of KPEs shows a high prevalence in the north, although the number of centers is low. Due to the guarantee that data would be handled confidentially, as mentioned above, the location and distribution of the 21 participating centers are not shown.

Table 1 Comparison of the Kasai outcome 2-year follow-up data between the observational period of 2010–2014 and the data of the previous analysis by Leonhardt et al, based on the data from 2001–2005[20]

The Kasai outcome	2001–2005 ($n = 159$)	2010–2014 ($n = 154$)	*p*-Value
SOA	118 (81.9%) 95% CI: 76–88	135 (87.7%) 95% CI: 82–93	0.19
SNL	34 (22.8%) 95% CI: 16–30	45 (29.2%) 95% CI: 22–36	0.24
JF-SNL	30 (20.1%) 95% CI: 14–27	37 (24.0%) 95% CI: 17–31	0.5

Abbreviations: CI, confidence interval; JF-SNL, jaundice-free survival with native liver; SOA, overall survival.
Note: The outcome is stratified into SOA, SNL, and the JF-SNL defined as native liver survival with total bilirubin <20 µmol/L.

Discussion

Few reports on national health policy with regard to BA and overall outcomes can be found in the literature.[22–24] ►Table 2 presents a summary of studies from eight countries, most of which described a decentralized policy at the time of the survey. This summary is of interest, not least because it is the only one in existence; however, its informative value is limited. The outcome parameters diverged in terms of time points, periods, definitions (e.g., jaundice-free), and range of patient numbers. Little is known about the completeness and drop-off rate of patients.[24] Nevertheless, this table shows that the German results for SOA (87.7%) fall within the upper third of the list, while the SNL (29.2%) is last and LTx (63%) is in first

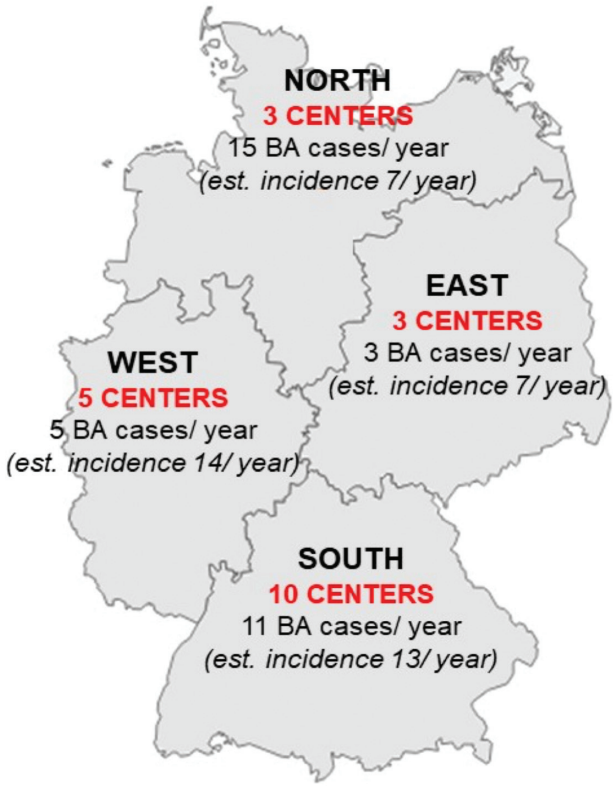

Fig. 3 Graphic of Germany, separated into the four regions North, South, West, and East. Visualization of the geographic distribution of centers and cases in Germany, based on the total numbers for each region between 2010 and 2014 and the estimated annual patient number per region, based on an incidence of 1:19,000 in Western Europe. The total center number per region is added in the figure. BA, biliary atresia.

place. This observation encourages the suspicion that the post-Kasai outcomes require improvement in Germany.

In light of this statement, the question posed by this paper, whether Germany has learned its lessons in terms of improving the outcome of BA patients, is meaningful. Unfortunately, the answer remains inconclusive, because there are arguments for answering both "yes" and "no." One positive development is represented by the decrease in pLTx and the increase in SOA and SNL. Besides this, a certain kind of unregulated centralization is taking place but the unidirectional shifting of cases to the north is not an option in the long term. Another positive signal is that eight centers with a low caseload have voluntarily ceased carrying out the Kasai procedures.

On the other hand, there are also strong arguments for answering "no." First, no therapeutic algorithms or protocols for BA have so far been launched where pTLx is an option, except for extremely late-referred patients with complete cirrhosis and sequelae of portal hypertension. From this point of view, it remains unacceptable that 7.5% of all BA patients became primarily liver transplanted during this period, as the criteria supporting this decision are nontransparent and the transplant teams themselves indicated the need for the procedure. Second, a 29% survival rate with native liver 2 years after the Kasai is far too low, when measured against the rates shown by competent liver units.[16,25]

What are the conflicting interests preventing the centralization of any rare diseases in Germany, and of BA in particular? The German health care system is characterized by allowing patients a free choice of hospitals and physicians, giving physicians the freedom to choose diagnostic and therapeutic procedures, and enabling free market competition among health insurances and hospitals.[26,27] From the patients' perspective, it is expected that competent medical

Table 2 The Kasai outcome data of 10 publications from eight different countries, including follow-up information on the SOA, SNL, JF-SNL, liver transplantation numbers, following the Kasai procedure, and pLTx numbers

Study	Country	Observational period	Patient numbers	Centralized/ decentralized	Overall survival	SNL	JF-SNL	LTx	pLTx (%)
Davenport et al[16]	England and Wales	1999—2009	443	Centralized	90% (5 y)	46% (5 y)		42.2% (10 y)	15 (3.4)
Wildhaber et al[29]	Switzerland	1994–2004	48	Decentralized	91.5% (2 y)	43.4% (2 y)	32.6%(2 y)	51.2% (2 y)	5 (11.6)
De Vries et al[30]	Netherland	1987–2008	214	Decentralized	73% (4 y)	46% (4 y)	38% (4 y)	35.5%	6 (2.8)
Serinet et al[31]	France	1986–1996 1997–2002	472 271	Decentralized Combination	72% (5 y) 87% (5 y)	40.1% (4 y) 42.7% (4 y)		54.4% 47.6%	20 (4.2) 15 (5.5
Chardot et al[25]	France	1986–2009	1.107	Decentralized	81% (5 y)	40% (5 y)	38% (after the Kasai)	52%	46 (4.2)
Hukkinen et al[17]	Finland	1987–2004 2005–2016	25 36	Decentralized Centralized	68.0% (2 y) 93.7% (2 y)	37.5% (2 y) 77.6% (2 y)	32% (3 mo) 65% (3 mo)	42% (2 y) 29% (2 y)	1 (4.0) 1 (2.8)
Tiao et al[32]	Taiwan	1996–2003	327	Decentralized	70.2% (5 y)	45.1% (5 y)		19%	27 (8.3)
Nio et al[33]	Japan	1989–1999	1.381	Decentralized	75.3% (5 y)	59.7% (5 y)	57%		2 (0.1)
Leonhardt et al[20]	Germany	2001–2005	183	Decentralized	83.3% (2 y)	20.3% (2 y)	18% (2 y)	63% (2 y)	21 (11.5)
Madadi-Sanjani et al[3]	Germany	2010–2014	173	Decentralized	87.7% (2 y)	29.2% (2 y)	24% (2 y)	63% (2 y)	13 (7.5)

Abbreviations: CI, confidence interval; JF-SNL, jaundice-free survival with native liver; LTx, liver transplantation; pLTx, primary LTx; SOA, overall survival.
Note: Information on the regional Kasai management (centralization vs. decentralized care) is included.

care in every respect will be available close by. Hospital administrations and medical staff share the same motivation, namely, to attract and retain patients with medically demanding and profitable diagnoses. This is particularly the case in regard to patients who are candidates for organ transplantation. The principal interest of health insurance is to save money, which is congruent with the patients' requirement to be cured as quickly and effectively as possible.

At this point, we have to ask ourselves why we are not able to turn this unsatisfying situation around. The answer is as simple as it is embarrassing. The health system, as described above, is legally protected from unilateral governmental directives. This situation offers many advantages but it also means that the governmental regulation seen in other countries is not an option in Germany. However, it is not acceptable that responsible persons and medical professional associations close their eyes to these facts.

A potential solution has now appeared on the horizon. Driven by patients' initiatives, in 2017, the European Commission (EC) launched the "European Reference Network" (ERN) to promote better care for rare diseases.[28] Herein, the "ERN-rare-liver" covers pediatric liver diseases, of which BA is a key diagnosis (https://rare-liver.eu). The aim of this network is, among other matters to centralize patients with rare diseases and ensure interdisciplinary communication, particularly in complicated cases. All participating health care providers are obliged to enter all patients and their follow-up data into a common registry, and quality of care is another crucial issue.

In parallel with this EC initiative, the German societies for pediatric surgery and gastroenterology, hepatology, and nutrition together with the German society of pediatrics are promoting the process of centralization. A recently taken decision provides a plan for a rationally oriented assignment of five liver units for regional coverage.

Conclusion

Our new survey demonstrates that in Germany, centralization of BA patients to a limited number of reference liver units is not yet mandatory. However, European and national efforts with regard to the centralization of rare diseases support our common endeavor in this direction.

Conflict of Interest

None declared.

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