我が国の小児外科臨床研究の現況

- 少子化のため患者数は減少
- 多くの施設があり、施設の集約ができない
  - 小さな規模の施設も重症患者を扱う
  - 労務環境が悪くなり臨床研究のゆとりがない
  - 各施設の患者数が少なく前向き臨床研究ができない

現状を打破するためには
多施設共同研究
前向きコホートの研究
⇒
大規模臨床
データベース
の活用

図1

手術症例データベースで何を知り何をするか

- 我が国全体の外科医療の把握
  - 手術実施状況
  - 専門医制度の検証
- 医療水準評価
  - ベンチマークの設定
  - 個々の施設へのフィードバック
- 臨床研究
  - 前向き臨床研究
  - がん登録
  - 領域横断的研究など

図2

手術症例DBの階層構造

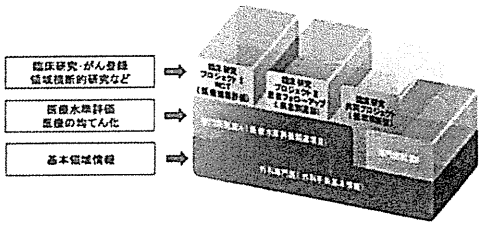

図3

NCDへの登録状況

2012年4月6日締め切り時点で
登録施設数　3,374施設
登録診療科数　4,916診療科
入力登録者数　16,073名
手術情報登録数　1,337,824件

2013年4月8日時点では
入力登録者数　22,407名
手術情報登録数　2,676,140件

これほど大規模に専門医制度と連動した臨床データベースは，国内外において前例がない

図4

NCDへの登録状況(小児外科領域　2011年)

新生児手術		新生児以降に対する手術	
食道閉鎖症	166	漏斗胸	317
横隔膜ヘルニア	113	横隔膜症	64
腸閉鎖症	351	肥厚性幽門狭窄症	417
腸回転異常症	235	腸重積イレウス	359
胆道拡張症	216	腸重積症	201
胆道閉鎖症	160	急性虫垂炎	11,772
ヒルシュスプルング病	250	副腎腫瘍	51
直腸肛門奇形	466	鼠径ヘルニア	22,056
仙尾部奇形腫	59	停留精巣	3,309

図5

小児外科手術の現状

- 食道閉鎖症根治術　N=166

	Number	Ratio
小児外科専門医が指導医	162	97.6%
小児外科専門医が術者	150	90.4%

- 小児鼠径ヘルニア手術　N=23,270

	Number	Ratio
小児外科専門医が指導医	17,018	73.1%
小児外科専門医が術者	6,981	30.0%

- 小児急性虫垂炎手術　N=11,772

	Number	Ratio
小児外科専門医が指導医or術者	2,997	25.5%
小児外科専門医が術者	1,274	10.8%

図6

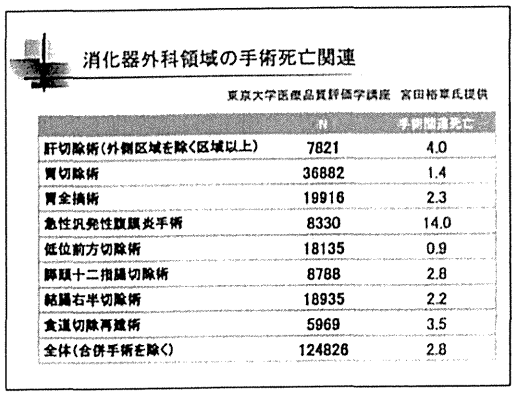

図7

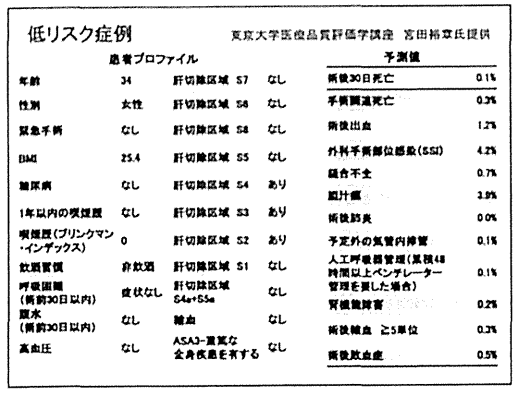

図8

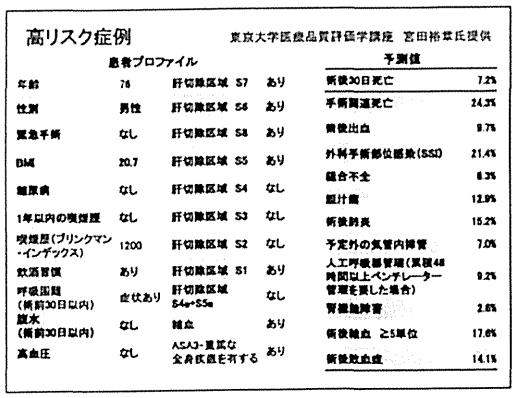

図9

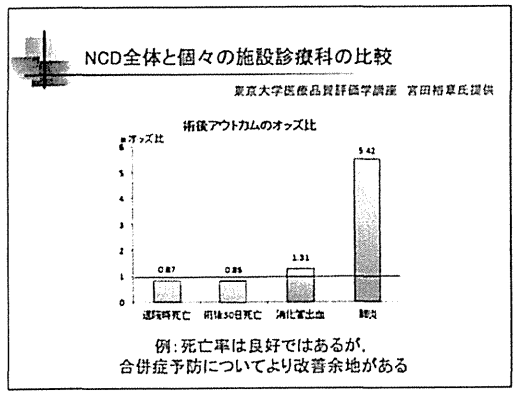

図10

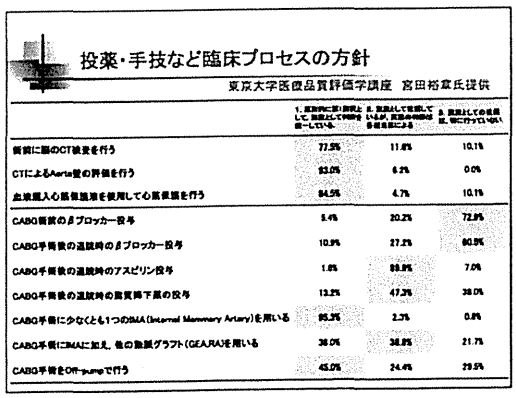

図11

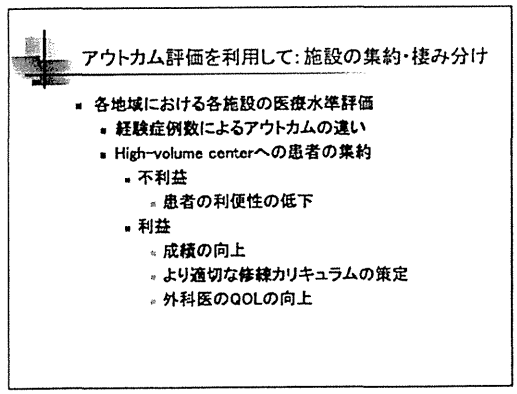

図12

小児外科領域は何をせねばならないのか？

- Risk-adjustされた入力フォーマットの作成
  - すべての手術をrisk-adjustする必要はない
  - 主たる一部の手術のみで可
  - 同じ定義で行うことが必要
    - たとえば心疾患の合併
      - 生後数日以内に心内修復術　ex TAPVC
      - 生後数日以内に姑息手術 ex PA banding
      - 生後数ヶ月以内に心内修復術 ex HLHS
      - 生後数ヶ月以内に姑息手術 ex BT shunt
      - 当面手術不要 ex ASD, VSD

図13

実際のフォーマットは？

- Format 1：主たる新生児疾患を数種類
  - 食道閉鎖症、横隔膜ヘルニア、臍帯ヘルニアなど
- Format 2：主たる後天性疾患を数種類
  - 胆道閉鎖症、腸重積症、GERDなど
- Format 3：小児がん
  - 神経芽腫、肝芽腫など

- あくまでも術後短期間の成績を評価
- 長期間の経過観察はマイナンバーがついてから可能

図14

3階部分のデータから

- 新しい医療機器・新薬の開発・効果判定
  - 早期の保険収載
  - 費用対効果分析への指標
- 複数の術式の優位性の検討
  - 限られた時間で大量のデータの収集
  - アウトカムと結合した臨床データ
- 新しい術式の工夫・開発
  - 短期間でのデータ収集による一流誌への発信
- 小児外科領域でどのようなことが可能か？

図15

まとめ

- NCDの登録データを利活用し、
  - 小児外科医療政策に応用できると思われる項目について検討した
  - 各施設・各医師の医療水準評価も可能
- 世界初の外科医情報とリンクした小児外科大規模手術データベースへ発展させましょう
  - 日本の医療技術の優秀さを発信する
    - ACS-NSQIPとの比較検討
  - 外国のように単一のhigh-volume centerの成績ではなく、日本の小児外科の標準医療の優秀さを発信する

図16

図17

図18

図19

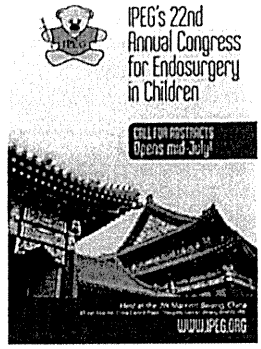
IPEG's 22nd
Annual Congress
for Endosurgery
in Children
CALL FOR ABSTRACTS
Opens mid-July!
WWW.IPEG.ORG

図20

Surg Today (2014) 44:1991–1999
DOI 10.1007/s00595-013-0802-3

REVIEW ARTICLE

Challenges and prospects of a clinical database linked to the board certification system

Hiroaki Miyata · Mitsukazu Gotoh · Hideki Hashimoto · Noboru Motomura · Arata Murakami · Ai Tomotaki · Norimichi Hirahara · Minoru Ono · Clifford Ko · Tadashi Iwanaka

Received: 12 June 2013 / Accepted: 30 September 2013 / Published online: 23 May 2014

Abstract In Japan, the National Clinical Database (NCD) was founded in April 2010 as the parent body of the database system linked to the board certification system. Registration began in 2011, and to date, more than 3,300 facilities have enrolled and more than one million cases are expected to enroll each year. Given the broad impact of this database initiative, considering the social implications of their activities is important. In this study, we identified and addressed issues arising from data collection and analysis, with a primary focus on providing high-quality healthcare to patients and the general public. Improvements resulting from NCD initiatives have been implemented in clinical settings throughout Japan. Clinical research using such database as well as evidence-based policy recommendations can impact businesses, the government and insurance companies. The NCD project is realistic in terms of effort and cost, and its activities are conducted lawfully and ethically with due consideration of its effects on society. Continuous evaluation on the whole system is essential. Such evaluation provides the validity of the framework of healthcare standards as well as ensures the reliability of collected data to guarantee the scientific quality in clinical databases.

Keywords Quality improvement · Database · General surgery · Cancer registry · Certification board for expert surgeons

H. Miyata · M. Gotoh · H. Hashimoto · N. Motomura · A. Murakami · T. Iwanaka
National Clinical Database, 1-8-3 Marunouchi, Chiyoda-ku, Tokyo, Japan

H. Miyata (✉) · H. Hashimoto · A. Tomotaki · N. Hirahara · M. Ono · T. Iwanaka
Department of Healthcare Quality Assessment, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: hqa.submission@gmail.com

C. Ko
American College of Surgeons National Surgical Quality Improvement Program, 633 North Saint Clair Street, Chicago, IL, USA

Introduction

When evaluating healthcare quality, it is important to consider the structure, process and outcome [1, 2]. However, Japan's healthcare policies have so far been evaluated mainly from the structural viewpoint of offering a system that provides plentiful medical care, i.e., on the number of institutions, physicians, specialists and nurses, on making sure that even a sparsely populated area has a medical facility and on ensuring that patients have access to specialists. This viewpoint of providing widespread medical care has a historical background [3]. In Japan, the fair distribution of medical resources has been politically emphasized in the context of universal health insurance. The equity of healthcare services in Japan is of international value, but when the service quality is referenced, it is important to systematically evaluate not only the structures of the services, but also their processes and outcomes.

To facilitate such evaluations, all surgical societies related to general surgery cooperated to establish the National Clinical Database (NCD), which systematically collects verified data in cooperation with various clinical fields so as to achieve the social responsibility of providing the highest quality healthcare possible in Japan [4, 5]. In order to evaluate the practices and performance of specialists, a committee for each specialty has been set up, and each of them identifies its framework for benchmarking.

As the surgical societies pay for all of the development and operating costs for the database, participating institutions can use the database system for free. Thus, it is mandatory for the institutions to participate in the benchmarking project when applying for the board certification system. Over 3,500 institutions were participating in the NCD in September 2012, and over 1,200,000 cases' data had been registered in 2011. The NCD, in cooperation with the specialist system, will provide important knowledge for future clinical database design and usage [6].

Without a systematic evaluation based on objective information, it is difficult for professionals to achieve social accountability. However, the Japanese healthcare system has been established through profit-sharing among specific groups, including the revision of the fee-for-service system, without fulfilling its social responsibility to weigh social advantage and costs objectively [7]. This system was formed on the basis of rapid economic growth after World War II and a pyramidal population structure.

With the slowdown in economic growth and the coming unprecedented aging society, it will not be possible to keep the current system anymore. Under these circumstances, reconfiguring the system only for a cost reduction will end up affecting its fair accessibility and the quality of the health care. First, whether the values of systematic evaluations based on verified data in the NCD will be suitable for the new society will be validated, and second, resource allocation and the development of a system structure to fulfill the values will be considered. The NCD was built as a platform not only for medical providers, but also for stakeholders, such as administrators, legislators and insurers, to allow them to provide better healthcare and to seek roles in collaboration. Using the nationwide platform, the collaboration among the stakeholders in Japan will also allow them to give useful suggestions to other countries that will face aging societies in the near future. We herein evaluate the significance and issues related to database initiatives that impact various aspects of society.

Social significance and issues related to the database initiatives

We herein evaluate the social impact of the clinical database initiatives from the perspectives of utility, feasibility and propriety standards [8]. The utility standard involves understanding the values of those involved in the initiatives, as well as those affected by it, determining their needs and evaluating whether services are offered that address these needs. The utility standard is assessed from the perspectives of (a) clarification of the central issue, (b) comprehension of the values of those involved, (c) comprehension of the process and outcomes and (d) consideration of the impact that the initiatives have. The feasibility standard relates to verifying whether the initiatives are realistic and economically reasonable. This standard is discussed herein from the perspectives of (a) political validity, (b) realistic progression, (c) project management and (d) resource use. The propriety standard relates to whether the initiatives are carried out lawfully and ethically and whether they pay due consideration to those affected by the results, as well as those involved in the initiatives. The propriety standard is assessed from the perspectives of (a) respect for basic human rights, (b) transparency and information disclosure and (c) maintaining balance.

The utility standard

The central issue

Just as the United States (US) Institute of Medicine identified the concept of "healthcare for the patient" as the chief provision of the twenty-first century medical revolution [9], patient-centric considerations are also an important aspect of future healthcare. Reducing medical costs is often a central policy issue in healthcare. However, the primary aim of healthcare should be to provide the best service to patients, rather than to curb medical costs [10]. High-quality healthcare services must be provided to patients, and considering how to design and coordinate practical approaches and the healthcare provision system, such as that for remuneration, is important to achieve this goal.

A key consideration when discussing the topic of improvements in healthcare quality is to define, understand and evaluate the quality that brings to fruition the values of the patients. The existence of "specialists" in various fields implies that a different result is expected when such specialists are involved in healthcare, compared with when non-specialists are involved. Thus, to fully grasp the quality of healthcare, the different effects that result from specialist involvement must be explained from the patient's perspective. Also important is the understanding of how each specialty is defined and the extent of their involvement. This can be achieved through continuous measurements and evaluations of the structure (e.g., human and material resources, organizational structure and operational management policy), the healthcare process (e.g., diagnosis/examinations, judging treatment indications, patient transport and admission and surgery/treatments) and healthcare outcomes (e.g., short-term mortality, complications, mid- and long-term prognoses and patient quality of life) for each specialty. In this context, the central goal of the NCD is to serve as the foundation for the development of a system that provides long-term, high-quality

healthcare by interfacing with the clinical setting in terms of systematic data collection and practical analyses.

The value of the NCD to stakeholders

Patients and the general public

The benefits of the NCD for patients and the general public include their ability to receive high-quality healthcare through the improvement of the healthcare service throughout Japan. This is achieved through directives by the NCD for improvement, with the clinical setting at the forefront. By reviewing the NCD data, patients can choose facilities that suit their preferences, whether it be the presence of board certified physicians of a relevant field, or the certification of a particular facility.

Health care providers

By unifying the standards of data management, health care providers in clinical settings can compare their approaches with peers throughout Japan and gain an understanding of where they stand. A risk-adjusted analysis based on nationwide data allows for one to determine and provide feedback on the information of the risks patients have beforehand. On the basis of these objective data, health care providers can then determine treatment indicators and obtain informed consent. Standardized information can be reformulated as case reports and shared at conferences. Moreover, the use of the NCD at individual facilities can reduce the burden of paperwork, for example, by providing clinical organizations with access to data for applications of certification, such as those required for board-certified physicians [11, 12]. By adding additional items and using data from one's own facility, clinical research may progress more efficiently.

Participating institutions

Facility reports, in which the severity-adjusted clinical performance of a facility is contrasted with nationwide data, are periodically sent to the participating institutions. These reports can describe the characteristics of each institution and elucidate the issues that require solution. Moreover, knowing one's position among peers allows for strategic planning and proper staff management. The mere fact that a facility participates in a benchmarking project that uses NCD data is in itself a means to ensure stable quality as a facility [13, 14].

Clinical organizations

Maintaining a clinical database as per the unified standards and definitions allows clinical organizations to improve their understanding of the actual performance of various fields, particularly when unified standards and definitions exist. Not only do unified standards increase the reproducibility of the collected data, they also ensure scientific accuracy. The large sample size offered by the database further paves the way for various types of research designs. Moreover, accurate information, as well as insight into the implementation status of various treatments and their effects, allows clinical organizations to provide policies and recommendations on the evidence-based board certification of physicians, their effective placement, improvement of their work environments and setting remuneration schedules. By serving as the driving force for efforts to improve the quality of healthcare, clinical organizations, as groups of specialists, can broadly appeal to the utility of certified facilities and the significance of board certified physicians to society, and at the same time, achieve accountability to society.

International collaboration is important to evaluate the quality of healthcare and produce meaningful results. The aim of the collaboration is to compare the incidence rates of diseases, the treatment trends and the outcomes and to identify factors that explain the differences. The NCD was developed in collaboration with the leadership of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), which adopted a similar goal of developing a standardized surgery database for quality improvement and investigation. The core members of the NCD joined the meetings and seminars of the ACS NSQIP to discuss various issues related to a large clinical database, including the data collection methods, data feedback and public relations. In addition, the NCD implemented the same variables as those of the ACS NSQIP to facilitate future international cooperative studies. This collaboration is expected to lead to potential global benchmarking and further collaborative efforts to evaluate and improve clinical practices.

Pharmaceutical/medical device companies

Research collaborations with clinical organizations will allow pharmaceutical and medical device companies to more rapidly carry out trials and post-marketing surveillance of pharmaceutical products and medical devices. Trials based on the NCD will decrease the costs associated with clinical trials and provide opportunities to obtain information on unregistered patients, thereby improving the scientific quality of the research. Moreover, when randomization is ethically difficult, data from the cases in the clinical database can be used to generate a control group, making it easier to determine the effects of interventions. For post-marketing surveillance, information on the effects and use of medical devices and drugs is valuable

for the development and promotion of more effective drugs and devices.

Government and insurance companies

A lack of understanding regarding healthcare quality indicators may result in the provision of low-quality care that increases the overall costs because it results in expensive postoperative adverse effects and higher rates of complications and mortality. Previous studies have reported that decreases in the mortality rates and incidence of adverse events through benchmarking activities can help cut down medical costs [15, 16]. Therefore, taken together, the coordinated efforts of the NCD, which carries out clinically led benchmarking activities, may benefit the government and insurers.

Processing and reporting results

Benchmarking reports

As discussed above, a report is periodically distributed to participating facilities and provides data on each facility's severity-adjusted clinical performance in comparison with the national data. The report is formatted in a way that makes the patient characteristics evident. In the cardiac surgery field, a web-based program already provides feedback on severity-adjusted clinical performance [17]. Real-time feedback through the web provides an opportunity to observe changes within facilities and shifts in clinical performance instantaneously.

NCD and the board certification system

Data registered with the NCD can be used to design evidence-based board certification systems. In addition to easy tracking of clinical performance, source data acquisition will also become easier, as the system streamlines the need to apply for source data and its usage. Through appropriate data registration, it will also be easier for facilities to become certified or considered an "associated facility" by achieving stable performance. With an effective certification system, the clinical performance data required for the certification process can be readily obtained, and performance comparison and on-site audits using source data can be conducted. For the most part, the current Japanese system focuses on the clinical experience of board-certified physicians. Coordinating with the NCD may enable these organizations to operate on the basis of the parameters that better reflect the clinical reality, including the severity-adjusted clinical performance and the rate of use of appropriate clinical treatments.

Communication within the clinical settings

From various perspectives, including reporting the results of the data analyses, status of database operations, policy measures through the NCD, improvements in entry items and interfaces and supporting each facility's efforts, the NCD and facilities of various fields will need to share information and communicate to operate at an advanced level. Periodic meetings, such as symposia and scientific conferences, in addition to the use of the web and e-mail, provide opportunities to share information and increase awareness. Furthermore, the formation of region- or topic-specific groups will promote NCD-related activities. These activities will enable organizations to introduce and share the best practice recommendations in the participating clinical departments.

Progress reports to patients and the government

Periodic reports for patients and government officials will ensure the impartiality of NCD-related activities. To this end, the NCD has established a group of outside experts (e.g., patients and specialists of law and information) to provide such reports. Moreover, when outside organizations provide funding, conflicts of interest must be considered. When institutional support is required to provide high-quality healthcare, policy recommendations must be coordinated among the members of the government, legislature and patients.

Considering various influences

In addition to prioritizing and appropriately designing NCD benchmarking efforts in various disciplines, an understanding of the overall clinical performance and the temporal transition of clinical processes is important. For instance, when a new treatment is widely used, the database must be kept current to understand and follow the impact of this treatment. For clinical performance evaluations, if inter-facility differences in perioperative mortality become small, the focus will need to be placed on a different complication with a larger disparity between facilities, and initiatives that consider this new area of investigation will be needed. Negative influences must be considered as well. In other countries, different benchmarking stances have had a major impact on patient selection, for example, the treatment of critically ill patients may be avoided, or patients may be discharged early or transferred to different departments [18, 19]. Continuous assessment of the impact of the NCD may help to prevent such occurrences in Japan. When clinical organizations offer recommendations to the government or other institutions, the consequences and effects of these recommendations must be monitored. This would allow for

before-and-after comparisons of certified facilities with regard to patient transfer and the impact of certification on the clinical performance [20, 21].

The feasibility standard

Political validity

The NCD was established in April 2010 as a general incorporated association in partnership with several clinical organizations (http://www.ncd.or.jp). By participating as members of various NCD divisions, leaders of various organizations and those in charge of the board certification system can continuously guarantee partnerships with the leadership of various disciplines and the board certification system. However, NCD operations are free from the influence of other stakeholders, such as the government and businesses. Although donations from businesses and government research grants can help fund NCD-related activities, these are used in a manner that secures the independence of NCD operations.

Realistic progression

In order for NCD operations to continue successfully, it may be beneficial for the various specialty divisions to divide roles among themselves and to collaborate in performing the day-to-day operations. Independent NCD divisions are already in place for continuous coordination with the board certification system in each field. The data management and analysis secures the scientific quality of the data and analysis, systems management ensures the continuity and security of information systems and investigation of the legality and ethicality of activities aids in securing resources and preparing budget plans.

Particularly important is the development of a system that allows for easy data entry and reduces the burden on those entering the data. To this end, case registration in the NCD is based on an easy-to-use web system. The results of a questionnaire survey of various clinical departments registered with the NCD indicated that 63 % of respondents entered information directly via the web while referring to medical records (i.e., source data: Table 1), and 52 % entered information in real-time or immediately upon finalization of the information without delay (Table 2). Moreover, the survey revealed that data entry was performed at common hospital computer terminals or on individuals' personal computers in most cases. In 3.1 % of clinical departments, data entry was performed at an operating room computer terminal (Table 3); however, entering data onto the web while referring to source data was difficult for some departments. Therefore, information was written on paper first and entered into the system later (Table 1). The Case Report Form developed by the NCD is useful in such situations.

Table 1 The input method (multiple answers allowed, $n = 2,123$)

	n	%
Direct data entry via the Web while referencing medical records	1,344	63.3
Data entry after first accumulating data in the department's database (e.g., FileMaker, Access)	458	21.6
Data are first written on case report forms (CRFs; data entry manuals) and then registered	438	20.6
Departmental information systems, such as electronic medical charts, are first revised to be compatible with the NCD before data entry	175	8.2
Others	37	1.7

Table 2 Timing of data entry ($n = 2,123$; as of January 13, 2012)

	n	%
Register case information in real-time to the extent possible	503	24
Register case information upon finalization of information	598	28
Case information is collected and entered periodically	1,022	48

Table 3 Location of data entry (multiple answers allowed, $n = 2,123$)

	n	%
Common terminal other than a hospital terminal	1,156	54.5
Personal computer	1,081	50.9
Hospital terminal outside the operating room	325	15.3
Operating room terminal	65	3.1
Others	50	2.4

In order to avoid the burden on physicians, the NCD allows data entry by various medical staff members in each department. NCD data entry privileges allow people other than physicians to enter the data. Table 4 lists the data entry workers utilizing the NCD as of January 13, 2012. Although the department chair entered information in 58 % of the departments, a medical information manager entered information in 10.2 % and a medical administrative assistant did so in 35.1 % of departments. Importantly, either the department chair or a physician designated by the department chair must approve each case for data entry when somebody other than a physician enters the data to secure the data accuracy. Before the initiation of the database, tests were conducted in various relevant areas to determine the user needs. As a result, an easy-to-use

Table 4 Data enterer (multiple answers allowed, $n = 2,123$)

	n	%
Department chair	1,125	53.0
Department-affiliated physician (other than department chair)	1,232	58.0
Department-affiliated resident	113	5.3
Physician affiliated with different department	7	0.3
Nurse	13	0.6
Medical information manager	216	10.2
Medical administrative assistant	745	35.1
Others	60	2.8

system with an error identification component was developed. Efforts to improve the system continue today in the form of a questionnaire on the web that solicits comments on how to improve the system.

Management plan

A database cannot operate on its own if no data are entered, regardless of whether the system is ready for operation. As its name suggests, a clinical database requires the entry of technical and clinical information, which can be time-consuming. Securing funds for labor costs associated with data entry for each department is no simple task in Japan. Therefore, consistent with this, data are often entered by the physicians themselves. In the NCD, data entry is performed by workers of various backgrounds (Table 4). Continuous sharing of high-quality data requires the securing of funding and personnel to enter the data. In addition, the data must be verified. To address this issue, NCD-registered hospitals throughout Japan have been requested to provide continuous support and understanding of the processes involved in maintaining such a huge database. For example, large hospitals may perform examinations that might not be carried out at small-scale facilities. Therefore, data from such examinations cannot be included as entry items in the database. Thus, an important consideration is the verification of whether entry items and the entry system are realistic for each participating institution. Moreover, because the clinical database documents medical treatments, database items and options inevitably change with advances in surgery and changes in treatment. Depending on when the entry items are revised, the entered data may no longer be used; therefore, frequent revisions without careful planning must be avoided. This underscores the importance of entry item management.

Resource use

By unifying the standards and digitizing the medical record systems in each participating facility, the costs related to data collection may be minimized. In addition, incorporating a program that extracts clinical information other than that requiring a physician's judgment into the database would decrease the burden associated with data entry. In this way, the clinical database may be most efficiently developed in conjunction with developments in medical record systems.

The propriety standard

Respecting basic human rights and consensus building

Ethical guidelines and study types

The NCD is grounded on the framework of observational studies. Therefore, no additional tests or surgery, or even a prolonged length of stay, are required for the institution to participate, and the registration of patient information does not influence the treatments. Projects that do not involve documenting actual events are bound by the Ethical Guidelines for Epidemiological Research developed by the Japanese Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour and Welfare [22]. For interventional studies, such as randomized-controlled trials, comprehensive registration in the NCD may be desirable [23]. In such cases, a new review based on the Ethical Guidelines for Clinical Research must be conducted [24]. Even within the framework of observational studies, broadening registration details and targeting certain disorders can change the nature of the management and operation of clinical databases. Changes that are particularly pronounced may warrant further ethical review, and project implementation may be reconsidered in light of independent valuations.

Patient consent

The patient intentions must be respected when considering the pros and cons of data registration. This can involve obtaining explicit verbal or written consent from participants (opt-in) [23], or not obtaining consent, but accepting a patient's explicit refusal to participate (opt-out) [25]. Only when these conditions are satisfied can clinical databases adopt the opt-out system. A few points are worth noting in this regard. First, clinical databases operate for the purpose of medical and public health research [26]. Second, clinical databases operate under the principle that the risk to participating patients is minimal [27]. Finally, clinical databases must guarantee that patients are given the opportunity to learn about the purpose of registration and the type of information registered [28]. The NCD has adopted the opt-out system and broadly discloses the

purpose of registration and the type of registered information. Moreover, to support the efforts of various clinical departments, the NCD provides web-based templates and explanatory material. However, when interventional studies (e.g., clinical trials) are conducted using the NCD infrastructure, a sufficient explanation must be provided to patients, and their explicit consent must be obtained.

Information security

The NCD data entry system is managed and operated via the web. Occasionally, a tradeoff may exist between the benefits of using the web and the associated risks, such as information leakage. The NCD data entry system uses an ID and password system, and the department chair of every participating facility has the authority to issue IDs. Users are notified about the password management policy; however, given that desirable security standards change as technology advances, the possibility that the evaluation standards at one point may not necessarily be valid in the future must be considered. In such situations, clearly articulating new policies on information management and operations is important. By complying with the disclosed policies, and the contents and measures therein, when issues arise, information system managers and operators can achieve a certain degree of accountability.

Use of personal information

Clinical databases must adhere to laws related to the protection of personal information. Various types of personal information, including (1) identifiable non-anonymous data, (2) identifiable anonymous data and (3) non-identifiable anonymous data require different considerations. In addition to patient information, the NCD includes information on participating facilities, as well as the health care providers involved in the treatment. Thus, the data management system and data use must be carefully considered. The American Association of Thoracic Surgery accepts analysis plans from applicants, and rather than source data, it principally feeds back the results of the analyses [29]. The Japanese Association of Thoracic Surgery has adopted a similar policy.

In view of the sensitivity of such information, the parent operating body of the NCD has established an ethics committee comprising outside experts. This committee includes members of the Japanese Surgical Society ethics board, lawyers, patient representatives and experts on information security. This ethics committee was requested to consider the ethical propriety of the entire initiative, and the progress of the review process was made public on the Japan Surgical Society website [30]. Thus, rather than merely undergoing a review, the contents of the discussion were made public, clarifying for the public the measures taken to address ethical issues. In addition, the NCD requested that the participating facilities undergo a review of ethical propriety regarding case registration in the form of facility director approval or a review from the facility's ethics committee. Because some participating facilities may not have ethics committees, the NCD made it possible to submit to a review by the NCD ethics committee. Since the review of ethical propriety must occur without delay, an application template was designed for ethics committee review and is available on the NCD website. As of January 2012, most participating facilities had received approval from a facility director.

Transparency and disclosure

Data usage

It becomes necessary to accept/adopt a fair stance for data usage. For example, in particular, covering up information that would be disadvantageous for certain facilities or businesses, or disclosing only advantageous information, may lead to conflicts of interest. Transparency must be guaranteed. Therefore, disclosure of information regarding the standards for data usage and rule of publication are important.

Publicizing the results of the data analyses

Further, the standards for publicizing the results of the data analyses need to be established. When performing severity adjustments, as in the US, where additional remuneration is provided on the basis of a department's clinical performance, the details and how severity adjustment is carried out must be disclosed [31]. In some cases, applicants who wish to use data may retain the results as internal documents without publicizing them. It is difficult to determine whether such decisions are made because secrecy would be advantageous, or whether the results are simply not worthy of public disclosure. However, certain standards need to be in place from the perspective of fairness.

Maintaining balance

Unifying the standards for evaluating clinical performance

Standards must be applied for evaluating the clinical performance of departments whose data are registered with the NCD. For instance, when choosing "mortality rate" as a clinical performance indicator, one facility may narrowly define the mortality rate as intraoperative mortality, whereas others may broadly define it as the 30-day postoperative mortality. Some facilities may even exclude periods in which an abnormally high number of deaths

Table 5 Participating facilities/number of departments (as of April 5, 2012)

	Facilities	
	n	%
Hokkaido/Tohoku	437	13.0
Kanto	942	27.9
Chubu	495	14.7
Kinki	650	19.3
Chugoku	252	7.5
Shikoku	142	4.2
Kyushu/Okinawa	454	13.5
Total	3,372	

occur. Even with raw mortality rates, the meaning differs between facilities that treat severe illnesses and those that only treat mild ailments. Therefore, the clinical performance must be fairly evaluated to avoid distrust among the participating facilities. Balanced information sharing can achieve this goal.

Fairness of participation

The NCD intends to improve the quality of healthcare throughout Japan. Because data registration is a condition for obtaining board certification, securing fairness is particularly important. In the US, many businesses pay millions of dollars each year to participate in clinical databases. However, in payment-based systems, the fairness of participation cannot be guaranteed, and coordination with board certification systems is difficult as well. Given the large number of small facilities in Japan, purchasing software for each department within a participating facility is not economically feasible. The NCD data entry software program was developed for use by all facilities and is distributed for free. Therefore, since the beginning of registration on January 1, 2011, more than 3,300 participating facilities have registered with the NCD as of April 2012 (Table 5).According to an administrative cross-country study of medical facilities by the Ministry of Health, Labour and Welfare, surgery under general anesthesia was conducted in 4,519 facilities in Japan [32]. The number of registered facilities by the Japan Surgical Society was 2,143 as of March 2012. [33] Therefore, a large proportion of the Japanese facilities in which surgeries are conducted participate in the NCD.

Conclusions

The coordination of a nation-wide clinical registry, such as the NCD in Japan, with board certification systems in various medical disciplines will positively impact society through their activities. The social implications of the activities must be considered. By identifying and addressing issues that arise from analyzing data, the clinical setting will drive improvements in healthcare quality. The central theme of clinical database activities is the provision of high-quality healthcare to patients and the general public. Clinical research and evidence-based policy recommendations based on the data from this database may positively impact businesses, the government and insurers. Initiatives may be evaluated to assess whether they are realistic and reasonably economical in comparison with the previous initiatives, in order to guarantee that they are conducted lawfully and ethically and to ensure that they pay due consideration to all the stakeholders involved. To ensure this, the continuity and responsibility of activities require continuous evaluation.

Acknowledgments The authors would like to express appreciation to all of the people and academies that cooperated in this project.

Conflict of interest None of the authors have any conflict of interest.

References

1. Donabedian A. The quality of care: how can it be assessed? JAMA. 1988;260:1743–8.
2. Glickman SW, Baggett KA, Krubert CG, Peterson ED, Schulman KA. Promoting quality: the health-care organization from a management perspective. Int J Qual Health Care. 2007;19:341–8.
3. Ikegami N, Yoo BK, Hashimoto H, Matsumoto M, Ogata H, et al. Japanese universal health coverage: evolution, achievements, and challenges. Lancet. 2011;378(9796):1106–15.
4. Iwanaka T, Miyata H, Okubo S. Significance of National Clinical Database. Japn J Clin Med: Nippon-Rinsho. 2011;69(Sup 3): 625–30 (in Japanese).
5. Iwanaka T, Miyata H, Okubo S, Tomotaki A. Principles of National Clinical Database. Clin Surg: Rinsho-Geka. 2012;67: 742–5 (in Japanese).
6. Okubo S, Miyata H, Hashimoto H, Gotoh M, Murakami A, et al. National Clinical Database, Japan (NCD): department registration and data entry. Clin Surg: Rinsho-Geka. 2012;67:746–51 (in Japanese).
7. Mori R, Takemi K, Fineberg HV. Science and consensus for health policy making in Japan. Lancet. 2012;379(9810):12–3.
8. Joint Committee on Educational Evaluation; Sanders JR (chair). The program evaluation standards: how to assess evaluations of educational programs, 2nd edn. Thousand Oaks: Sage Publications; 1994.
9. Institute of Medicine. Crossing the Quality Chasm: a New Health System for the 21st Century. Washington, DC: National Academy Press; 2001.
10. Porter ME, Teisberg EO. How physicians can change the future of health care. JAMA. 2007;297:1003–111.
11. Japan Surgical Society. The way to become a Board Certified Surgeon: start up, planning and requirements. http://www.jssoc.or.jp/procedure/specialist/mem_doc_senmon_online2003.html. Accessed 18 April 2012 (in Japanese).

12. Japanese Society of Gastroenterological Surgery. New system for Board Certified Surgeon in Gastroenterology. http://www.jsgs.or.jp/modules/senmon/index.php?content_id=93. Accessed 18 April 2012.
13. Jamtvedt G, Young JM, Kristoffersen DT, Thomson O'Brien MA, Oxman AD. Audit and feedback: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev. 2003; 3: CD00259.
14. Hall BL, Hamilton BH, Richards K, Bilimoria KY, Cohen ME, et al. Does surgical quality improve in the American college of surgeons national surgical quality improvement program. An evaluation of all participating hospitals. Ann Surg. 2009;250:363–76.
15. Berwick DM, James BC, Coye M. The connections between quality measurement and improvement. Med Care. 2003;41(1 suppl):I30–8.
16. Goetzel RZ, Ozminkowski RJ, Villagra VG, Duffy J. Return on investment in disease management: a review. Health Care Financ Rev. 2005;26:1–19.
17. Miyata H, Motomura N, Murakami A, Takamoto S, Japan Cardiovascular Surgery Database. Effect of benchmarking projects on outcomes of coronary artery bypass graft surgery: challenges and prospects regarding the quality improvement initiative. J Thorac Cardiovasc Surg. 2012;143:1364–9.
18. Landon BE, Normand SL, Blumenthal D, Daley J. Physician clinical performance assessment: prospects and barriers. JAMA. 2003;290:1183–9.
19. Schneider EC, Spstein AM. Influence of cardiac-surgery performance reports on referral practices and access to care-a survey of cardiovascular specialists. N Engl J Med. 1996;335:251–6.
20. Miyata H, Motomura N, Kondo MJ, Fushimi K, Ishikawa KB, et al. Toward quality improvement of cardiovascular surgery in Japan: An estimation of regionalization effects from a nationwide survey. Health Policy. 2009;91:246–51.
21. Vaughan-Sarrazin MS, Hannan EL, Gormley CJ, Rosenthal GE. Mortality in medicare beneficiaries following Coronary Artery Bypass Graft surgery in states with and without certificate of need regulation. JAMA. 2002;288:1859–66.
22. The Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor and Welfare. The Ethical Guidelines for Epidemiological Research. December 1, 2008. (Partial revision). http://www.niph.go.jp/wadai/ekigakurinri/H20_12_01_shishin-all.pdf. Accessed 18 April 2012 (in Japanese).
23. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360(10):961–72.
24. The Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor and Welfare. The Ethical Guidelines for Clinical Research; July 30, 2008. (Revision). http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/rinsyo/dl/shishin.pdf. Accessed 18 April 2012 (in Japanese).
25. Day M. Patients can opt out of controversial national records system. BMJ. 2007;334(7583):12.
26. The European Communities. Directive 95/46/EC; 1995. http://ec.europa.eu/justice/policies/privacy/law/index_en.htm. Accessed 18 April 2012.
27. National Institute of Health. 45 Code of Federal Regulations (CFR) Part 46; 2005. http://ohsr.od.nih.gov/guidelines/45cfr46.html. Accessed 18 April 2012.
28. The United States President's Commission. Final report of the ethical and legal problems in medicine and biomedical and behavioral research. Tokyo: Shinohara Publication; 1984 (in Japanese).
29. Society of Thoracic Surgeons. Guidelines on Use of STS National Database and Database-derived Information. 10th October 2004. http://www.ctsnet.org/file/STSNationalDatabasesGuidelines3FINAL.pdf. Accessed 18 April 2012.
30. Japan Surgical Society. Disclosure of the Result and the Process of Ethical Review about National Clinical Database. 2010. http://www.jssoc.or.jp/other/info/info20101117.html. Accessed 18 April 2012 (in Japanese).
31. Shahian DM, O'Brien SM, Filardo G, Filardo G, Ferraris VA, Haan CK, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1—coronary artery bypass grafting surgery. Ann Thorac Surg. 2009;88(1 Suppl):S2–22.
32. The Ministry of Health, Labour and Welfare. An Administrative Cross-Country Study of Medical Facilities in Japan (Iryo-shisetsu Tyousa). 2008. http://www.mhlw.go.jp/toukei/saikin/hw/iryosd/08/. Accessed 18 April 2012 (in Japanese).
33. Japan Surgical Society. About the Japan Surgical Society. 2012. http://www.jssoc.or.jp/aboutus/society/info.html. Accessed 18 April 2012 (in Japanese).

Stool Color Card Screening for Early Detection of Biliary Atresia and Long-Term Native Liver Survival: A 19-Year Cohort Study in Japan

Yan-Hong Gu, MD, MSc, PhD[1,2], Koji Yokoyama, MD[3], Koichi Mizuta, MD, PhD[4], Takashi Tsuchioka, MD, PhD[5], Toyoichiro Kudo, MD, PhD[6], Hideyuki Sasaki, MD, PhD[7], Masaki Nio, MD, PhD[7], Julian Tang, PhD[8], Takayoshi Ohkubo, MD, PhD[1], and Akira Matsui, MD, DMSci[6]

Objective To evaluate the sensitivity and specificity of a stool color card used for a mass screening of biliary atresia conducted over 19 years. In addition, the age at Kasai procedure and the long-term probabilities of native liver survival were investigated.

Study design From 1994 to 2011, the stool color card was distributed to all pregnant women in Tochigi Prefecture, Japan. Before or during the postnatal 1-month health checkup, the mothers returned the completed stool color card to the attending pediatrician or obstetrician. All suspected cases of biliary atresia were referred for further examination. Diagnosis was confirmed by laparotomy or operative cholangiography for high-risk cases before the Kasai procedure. Patients with biliary atresia were followed from the date of their Kasai procedure until liver transplantation, death, or October 31, 2013, whichever comes sooner.

Results A total of 313 230 live born infants were screened; 34 patients with biliary atresia were diagnosed. The sensitivity and specificity of stool color card screening at the 1-month check-up was 76.5% (95% CI 62.2-90.7) and 99.9% (95% CI 99.9-100.0), respectively. Mean age at the time of Kasai procedure was 59.7 days. According to Kaplan-Meier analysis, the native liver survival probability at 5, 10, and 15 years was 87.6%, 76.9%, and 48.5%, respectively.

Conclusions The sensitivity and specificity of the stool color card have been demonstrated by our 19-year cohort study. We found that the timing of Kasai procedure and long-term native liver survival probabilities were improved, suggesting the beneficial effect of stool color card screening. *(J Pediatr 2015; ■: ■-■).*

Biliary atresia is the most frequent hepatic cause of death in early childhood, with an incidence of 0.7 in 10 000, 0.6 in 10 000, and 0.5 in 10 000 live births in the US, UK, and France, respectively.[1-3] In Japan, the incidence is greater, affecting approximately 1.0 in 10 000 live births.[4] Biliary atresia is characterized by a complete inability to excrete bile as a result of sclerosing inflammation of the extra, and possibly intra, hepatic bile ducts.[5] Patients with biliary atresia have 3 main clinical features: pale-pigmented stools, prolonged jaundice, and dark urine. Pale-pigmented stools appears within the first month after birth for most patients, and 2-5 months for others.[4,6] Although there is strong evidence that biliary atresia develops before birth and progresses after birth, its etiology remains unclear. The Kasai procedure[7] commonly is used as a first-line treatment for all types of biliary atresia.[8,9]

Prognosis for patients with biliary atresia is primarily related to the patient's age at the time of Kasai procedure and the anatomy of the bile duct remnant.[8-10] It is generally acknowledged that a Kasai procedure performed early, especially one that is performed before the patient reaches 60 days of age, can improve the long-term native liver survival and reduces likelihood of liver transplantations.[10,11] In Japan, 66.1% of living-donor liver transplantations performed for recipients younger than 18 years of age were attributable to biliary atresia.[12]

Serinet et al[10] highlighted the importance of screening for biliary atresia. The concept of a stool color card for mass screening was introduced for the first time to the local population in Tochigi Prefecture by Matsui and Dodoriki in early 1994, which resulted in early Kasai procedure (<60 days of age) in 2 of 3 patients with biliary atresia.[13] Since then, the stool color card had been distributed in the prefecture until March 2011. Subsequently, the concept of stool color card for mass screening was adopted and used in Taiwan in 2002 and resulted in earlier referral of patients with biliary atresia nationwide.[14]

In this present study, we aimed to determine the sensitivity and specificity of stool color card screening during the 19-year period, as well as its effect on the

JBAR Japanese Biliary Atresia Registry

From the [1]Department of Hygiene and Public Health, Teikyo University School of Medicine; [2]Graduate School of Public Health, Teikyo University, Tokyo; Departments of [3]Pediatrics and [4]Transplant Surgery, Jichi Medical University; [5]Department of Surgery, Dokkyo Medical University, Tochigi; [6]Department of Hepatology, National Medical Center for Children and Mothers, National Center for Child Health and Development, Tokyo; [7]Department of Pediatric Surgery, Tohoku University School of Medicine, Miyagi; and [8]Department of Education for Clinical Research, National Center for Child Health and Development, Tokyo, Japan

Supported by the National Center for Child Health and Development of Japan (25-5 and 26-31). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.12.063

timing of Kasai procedure and long-term native liver survival in the Tochigi cohort.

Methods

Participants were all infants born to mothers living in Tochigi Prefecture, situated about 100 km north of Tokyo (**Figure 1**; available at www.jpeds.com), from August 1994 to March 2011. Infants born in Tochigi Prefecture to mothers who lived outside of the prefecture before giving birth were not included. Under the Maternal and Child Health Law in Japan acted since 1965, all children in the country go through the same postnatal health management.

The stool color card (3rd edition; **Figure 2**) was placed within the Maternal and Child Health Handbook that was given to all pregnant women by their respective local government according to the Maternal and Child Health Law in Japan. Before or during the infant's 1-month health checkup, the mothers were asked to fill in the corresponding number of the image on the stool color card (**Figure 2**) that most resembled the color of her infant's stool. The card was then submitted to the attending pediatrician or obstetrician. A positive result was defined as a stool color determined by the guardian that matched either image 1, 2, or 3 before or during the infant's 1-month health checkup.

The Department of Pediatrics at the Jichi Medical University in Tochigi Prefecture (as the stool color card office), Japan was notified of all positive cases as soon as possible by telephone or fax. All stool color cards were collected and sent to the stool color card office at Jichi Medical University on a weekly basis. At the office, the cards were rechecked to confirm whether all corresponding numbers were properly recorded and that positive cases had been properly attended to. At the initial phase (first 3 years), all staff was trained on how to manage positive cases detected by the stool color card.

Verbal informed consent was obtained from all participants. The study protocol was reviewed and approved by the Ethics Board of the National Center for Child Health and Development.

Patients with Biliary Atresia and Long-Term Follow-Up

For patients with positive stool color card results, the possibility of other types of infantile cholestasis was eliminated by a pediatric specialist or pediatric hepatologist through clinical, biochemical, radiologic, histologic, and genetic investigations when necessary. A final diagnosis for high-risk cases was determined by laparotomy and/or by operative cholangiography prior to Kasai procedure by a pediatric hepatologist or surgeon. None of the false positive cases underwent any invasive procedures. All patients with biliary atresia received Kasai procedure at the soonest possibility performed in accordance with the Japanese Society of Pediatric Surgeons classification.[15]

Patients with biliary atresia in Tochigi Prefecture received Kasai procedure and were followed up regularly by their respective hospital (across 8 medical centers). Long-term follow-up was possible because all Japanese residents are covered by at least 1 health insurance plan that allows access to any necessary procedures post-Kasai procedure.[16] In addition, pediatric patients with any of the 514 intractable chronic diseases (including biliary atresia), defined by Ministry of Health, Labour and Welfare of Japan, are supported by a medical aid program.[16] Postsurgical procedures in Tochigi Prefecture are consistent with those in other areas of Japan. To ensure that no patient with biliary atresia in Tochigi Prefecture was overlooked, the patient list in our study was compared with that of the medical aid program covering the 514 intractable chronic diseases.

For the investigation of native liver survival probabilities, patients with biliary atresia in this study were observed from the date of Kasai procedure until liver transplantations, death, or October 31, 2013, whichever occurred sooner.

Statistical Analyses

Four reference data sets were used: nationwide data during stool color card screening between 1994 and 2011 from the Japanese Biliary Atresia Registry (JBAR), nationwide data before stool color card screening between 1989 and 1994 from JBAR,[17] Tochigi Prefecture data before stool color card screening between 1987 and 1992,[4] and Tochigi Prefecture data before stool color card screening between 1989 and 1991[18] (**Table I**). To quantify uncertainty, 95% CIs were used. The records of approximately 80%-90% of nationwide patients with biliary atresia diagnosed in hospitals that are part of the Japanese Society of Pediatric Surgeons were documented in JBAR. All patients with biliary atresia in our study were registered in JBAR. According to the Act on the Protection of Personal Information, only statistical data and not individual data can be used. Student t test or one-sample t test was performed to compare age at Kasai procedure. Kaplan-Meier analysis and the log-rank test were used to estimate the native liver survival probabilities with age (in months) as the time scale. IBM SPSS Statistics 21 (IBM Corporation, Armonk, New York) was used for statistical analysis. $P < .05$ was considered statistically significant.

For analytical purposes, all 34 patients with biliary atresia were first considered as a whole (termed "all cases"), and then as 2 separate groups: patients identified using stool color chart and referred promptly (**Table I**).

Results

There were 313 230 live births in Tochigi Prefecture from August 1994 to March 2011 (**Figure 1**). We collected the stool color cards of 264 071 infants, yielding a return rate of 84.3% at the 1-month health check-up; 2014 showed a positive result, and 26 of them were diagnosed with biliary atresia. Finally, a total of 34 patients were diagnosed with biliary atresia in Tochigi prefecture during the study period. A patient with Alagille syndrome detected by the stool color card (stool color corresponding to image 2) at

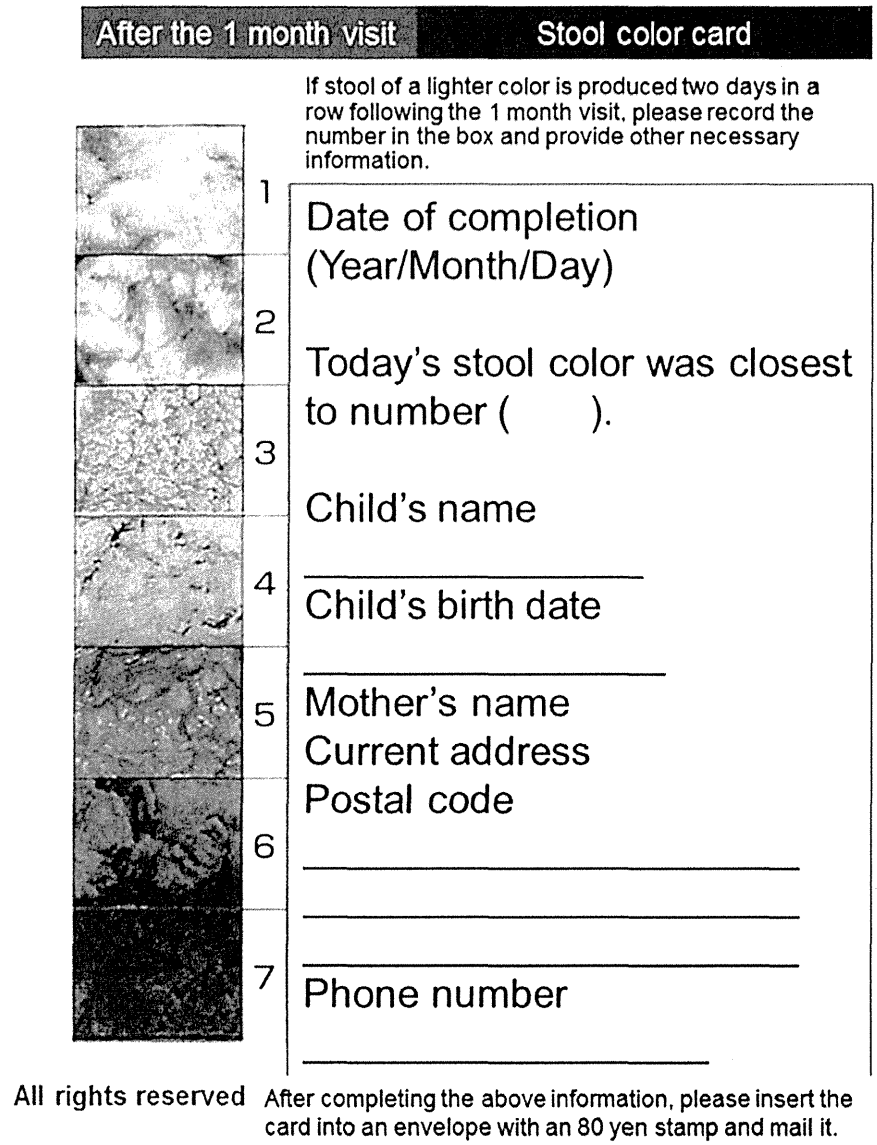

Figure 2. The 3rd edition stool color card used in Tochigi Prefecture from August 1994 to March 2011 consisted of 7 photographic images of stool color taken in both healthy infants and infants with biliary atresia. Images 1-3 denote abnormal stool color, whereas images 4-7 reflect normal stool color.

1-month health checkup was excluded. At the 1-month health checkup, the sensitivity, specificity, positive predictive value, and negative predictive value were 76.5% (26/34, 95% CI 62.2-90.7), 99.9% (313 018/313 196, 95% CI 99.9-100.0), 12.7% (26/204, 95% CI 8.2-17.3), and 99.9% (313 018/313 026, 95% CI 99.9-99.9), respectively. Incidence of biliary atresia was 1.1 in 10 000 infants (34/313 230, 95% CI: 0.7-1.5).

Among the 34 patients with biliary atresia, 8 were missed at the 1-month check-up (**Figure 1**). Of these patients, 2 (Patients 1 and 2) were in a neonatal intensive-care unit for more than a month after birth. Because their overall condition was poor, their guardians and the medical staff overlooked the presence of abnormal stool color. These 2 patients received Kasai procedure at 45 and 88 days of age, respectively. They did not undergo liver transplantations until October 2013. For 3 patients (Patients 3, 4, and 5), their guardians used the stool color card and reported pale-pigmented colored stool at the 1-month health checkup. However, no further examination was performed by their respective pediatricians because the infants did not present with visible jaundice. These 3 patients eventually underwent Kasai procedure at 62, 77, and 109 days after birth, respectively. Subsequently, Patients 3 and 5 underwent liver transplantations at 5 and 12 months of age, respectively. The guardian of 1 of the patients (Patient 6) failed to use the stool color card. The patient received Kasai procedure at 97 days of age and underwent liver transplantation at 72 months. One patient (Patient 7) did

Table I. Age at the time of the Kasai procedure in Tochigi cohort vs reference data, before and during stool color card screening

		Before stool color card screening		During stool color card screening	Tochigi stool color card cohort (August 1994-March 2011)		
	Year	Tochigi	JBAR	JBAR	All patients (N = 34)	Patients identified using stool color card and referred promptly (n = 30)	Patients with type III biliary atresia (n = 25)
Age at time of Kasai procedure, d							
Mean or mean ± SD	1987-1992[4]	70.3					
	1994-2011			67.7	59.7 ± 19.4*,†	56.2 ± 16.5‡,§	59.8 ± 19.1§,¶
	(1994-2002)			(67.8)			
	(2003-2011)			(67.6)			
Median (range)	1987-1992[4]	65.5					
	1994-2011			64.0	58.5 (18-109)	56.5 (18-88)	59.0 (18-109)
	(1994-2002)			(63.0)			
	(2003-2011)			(65.0)			
Number, % (95% CI)							
≤45	1989-1994[17]		18.9				
	1994-2011			20.4	8, 23.5 (9.3-37.8)	8, 26.6 (10.8-42.5)	6, 24.0 (7.3-40.7)
≤60	1989-1991[18]	34.0					
	1989-1994[17]		40.5				
	1994-2011			45.1	19, 55.9 (39.2-72.6)	19, 63.3 (46.1-80.6)**	14, 56.0 (36.5-75.5)
>80	1989-1994[17]		23.1				
	1994-2011			25.3	4, 11.8 (0.9-22.6)**,††	1, 3.4 (2.3-15.6)**,††	2, 8.0 (2.6-18.6)**,††
>90	1989-1991[18]	13.0					
	1989-1994[17]		15.1				
	1994-2011			16.2	2, 5.9 (2.0-13.8)**,††	0, 0.0**,††,‡‡	1, 4.0 (3.7-11.7)**,††,‡‡

*P = .023; †P = .001; ¶P = .000 vs JBAR data during screening (1994-2011), 1-sample t test.
†P = .003; §P = .000 vs Tochigi data before screening (1987-1992), 1-sample t test.
**P < .05 vs JBAR data during screening (1994-2011), ††P < .05 vs JBAR data before screening (1989-1994), and ‡‡P < .05 vs Tochigi data before screening (1987-1992).

not show abnormality at the 1-month health checkup. At 1.5 months of age, the patient's guardian noticed pale-pigmented stool and jaundice. The patient received Kasai procedure at 76 days of age and did not undergo liver transplantations. One patient (Patient 8) was not on our list but was later identified through the medical aid list. The patient received Kasai procedure at 66 days of age and did not undergo liver transplantations until October 2013. Therefore, with the exception of Patients 1, 2, 6, and 8, in which the usage of stool color card failed, 30 of the total 34 patients showed stool color changes around the time of the 1-month health checkup.

Demographic Data of Patients with Biliary Atresia

Among the 34 patients with biliary atresia, 11 (32.4%) were male and 23 (67.6%) were female. The numbers of patients who had type I, II, and III biliary atresia were 5 (14.7%), 1 (2.9%), and 25 (73.5%), respectively. The type of biliary atresia in 3 patients was unknown (8.8%). All patients with biliary atresia received Kasai procedure (1 patient with type I biliary atresia received hepaticojejunostomy, and all others received hepatoportoenterostomy).

Age at the Time of Kasai Procedure

The mean age at the time of Kasai procedure was 59.7 days in the 34 patients with biliary atresia (Table I). The percentage of Kasai procedure performed before 60 days of age was greater in patients with biliary atresia who were referred promptly after reporting of positive colors. The percentage of Kasai procedure performed after 80 days of age was significantly lower in the Tochigi cohort (Table I). The mean age ± SD of Kasai procedure for the 8 patients with biliary atresia who were missed at the 1-month checkup was significantly later compared with the other patients with biliary atresia (n = 26; 77.5 ± 20.4 days vs 54.3 ± 15.8 days; P = .002).

Long-Term Native Liver Survival Probabilities of Patients with Biliary Atresia

As of October 2013, 17 patients received liver transplants and 17 did not. One female patient died at 13 months without receiving a liver transplant. Kaplan-Meier survival analysis with the end point defined as liver transplant, death, or alive as of October 31, 2013, showed the native liver survival probability at 5, 10, and 15 years to be 87.6%, 76.9%, and 48.5%, respectively (Table II). The median survival estimated by Kaplan-Meier analysis is the earliest time at when the cumulative survival probability reached 50% or lower. In this study, the median native liver survival was 197.2 (95% CI 136.0-258.4), 207.9 (95% CI 184.6-231.3), and 212.5 (95% CI 146.7-278.4) months in all patients, patients who were referred promptly upon reporting of positive color, and patients with type III biliary atresia, respectively. There was no significant

Table II. Kaplan-Meier analysis of native liver survival at 5, 10, 15, and 20 years in the present study and previous reports

Countries	No. teams/ medical centers	Stool color card	Period	Study design	No. patients	Rate of native liver survival % (SE), y			
						5	10	15	20
Yokohama, Japan[19]	1	No	1970-1986	RCR	80	63.0	54.0	-	44.0
Sendai, Japan[20]	1	No	1975-1980	RCR	60	60.0	60.0	58.0	-
			1981-1986		50	68.0	60.0	51.0	-
US[21]	2	No	1972-1996	RCR	266	49.0	-	-	-
UK[22]	3	No	1999-2009	RCR	443	46.0 (95% CI 41-51)	40.0 (95% CI 34-46)	-	-
France[23]	45	No	1986-2009	RCR	1044	40.0 (1.6)	35.8 (1.6)	32.1 (1.7)	29.6 (2.0)
France[10]	27/45	No	1986-2002	RCR	695	37.9 (2.0)	32.4 (2.0)	28.5 (2.3)	-
Present study	8	Yes	1994-2011	Cohort study					
All patients with biliary atresia					34	87.6 (0.06)	76.9 (0.08)	48.5 (0.11)	-
Patients identified using the stool color card and referred promptly					30	89.6 (0.06)	77.6 (0.08)	55.5 (11.1)	-
Patients with type III biliary atresia					25	86.8 (0.07)	70.5 (0.10)	50.4 (0.12)	-

RCR, retrospective chart review in medical center(s).
In this study, the period of native liver survival was from the point of Kasai procedure until liver transplantation, death, or October 31, 2013, whichever occurred sooner.

difference across the 3 aforementioned groups mentioned on the basis of the log-rank test ($P > .05$).

Discussion

We have conducted a 19-year Japanese cohort study for screening of biliary atresia using the stool color card. The high stool color card sensitivity and specificity achieved are likely to have contributed to more patients with biliary atresia being diagnosed earlier, leading to a timely Kasai procedure. Accordingly, long-term native liver survival probabilities were improved. Serinet et al[10] reported that if every patient with biliary atresia were to undergo the Kasai procedure before 46 days of age, 5.7% of all liver transplantations performed annually in France in patients younger than 16 years could be spared.

In our cohort, the 5-, 10-, and 15-year native liver survival probabilities (Table II) were greater compared with studies conducted in US,[21] the UK,[22] and France,[10,23] where stool color card was not used. Notably, the 5- and 10-year native liver survival probabilities increased by more than 20% during 1994-2011 compared with studies conducted in the Japanese cities of Yokohama and Sendai where stool color card was not used (Table II).[19,20] The 15-year native liver survival probability estimated by Kaplan-Meier analysis in the Sendai patients was 51%-58% between 1975 and 1986[20] (Table II), which is greater than what we found in this study. It might be attributable to the data being collected from a single, highly specialized center, whereas our data were collected from 8 centers.

There are 2 other reports of long-term native liver survival rates in Japanese patients with biliary atresia. Notably, the method for the calculation of native liver survival and/or subjects selected in those studies was different from this study. In our case, we did not consider whether jaundice appeared or not after Kasai procedure. On the basis of JBAR data of 1989, Nio et al[24] reported the 5-year native liver survival rate was 62.0% in 735 patients who did not undergo liver transplantations, and 19 (2.6%) of patients were lost to follow-up. The 10-year native liver survival rate was 52.8% (57/108). The authors also found that when the Kasai procedure was performed at age of <60, 61-90, 91-120, and >120 days among patients with type III biliary atresia registered between 1953 and 2009 whose jaundice disappeared after Kasai procedure, the 10-year native liver survival rate was 74.4% (32/43), 74.5% (41/55), 100.0% (6/6), and 33.3% (1/3), respectively.[11]

Although the stool color card has been adopted and used in Taiwan,[14] Argentina,[25] and Switzerland,[26] the outcome was only reported in Taiwan, where the 5-year native liver survival rate (without jaundice) was 64.3% (18/28).[27]

According to JBAR data, the mean and median age at Kasai procedure was not significantly different between the periods of 1994-2002 and 2003-2011 (Table I), suggesting that the management of patients with biliary atresia did not change drastically over the years. Hence, the improvement of the probability of native liver survival revealed in this study is likely to be attributable to the younger age at Kasai procedure as a result of stool color card usage.

Although data of patients who did not use stool color card were available in JBAR, we could not access them because of the restriction imposed by the Act on the Protection of Personal Information. As such, the associations between stool color card usage/early Kasai procedure and the probability of long-term native liver survival cannot be statistically analyzed.

On the basis of our results in Tochigi Prefecture, the stool color card was gradually introduced to 16 other autonomous administrative divisions in Japan between 1999 and 2010. However, only patients from 2 of the regions were followed up. Nonetheless, the mean age of Kasai procedure after the introduction of stool color card was found to be significantly younger in those regions,[28,29] demonstrating excellent reproducibility and effectiveness of the stool color card.

In April 2012, a nationwide biliary atresia screening using an updated edition of the stool color card was initiated. In addition, a pilot study was launched in October 2013 in Beijing, China. The new edition of stool color card consists of digital photographic images to ensure quality control and

greater reproducibility. A modified screening protocol has also been devised. Instead of a single inspection point, the stool color card is now being inspected at 3 intervals; 2 weeks, 1 month, and 1-4 months after birth, allowing us to identify more patients with biliary atresia.

On the basis of our 19-year experience of stool color card usage in the Tochigi Prefecture cohort, the effectiveness of the stool color card, a non-invasive technique, was demonstrated. In particular, the stool color card was beneficial for patients with biliary atresia whose jaundice was not obvious. However, we are aware that the distribution of the stool color card in the community alone is not sufficient to achieve earlier detection of biliary atresia. Proper usage of the stool color card by guardians coupled with a sound knowledge of biliary atresia among healthcare personnel is essential. ■

We thank all patients and their families for participating in this study, as well as to all pediatricians who participated in our screening program. We are grateful to Hideki Yamamoto, MD (Gunma Children's Medical Center), Minoru Kuroiwa, MD (Children Medical Center of Toho University), and Wada Hiroki (University of Tsukuba), for their cooperation in the follow-up of patients. We would also like to thank Kevin Urayama (Tokyo Medical and Dental University), for his valuable comments.

Submitted for publication Jul 16, 2014; last revision received Dec 1, 2014; accepted Dec 19, 2014.

References

1. Yoon PW, Bresee JS, Olney RS, James LM, Khoury MJ. Epidemiology of biliary atresia: a population-based study. Pediatrics 1997;99:376-82.
2. McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. Lancet 2000;355:25-9.
3. Chardot C, Carton M, Spire-Bendelac N, Le Pommelet C, Golmard JL, Auvert B. Epidemiology of biliary atresia in France: a national study 1986-96. J Hepatol 1999;31:1006-13.
4. Matsui A, Sasakia N, Arakawa Y, Ishikawa T, Momoya T, Kasano Y, et al. Neonatal mass screening for biliary atresia, a pilot study in Tochigi Prefecture, Japan. Screening 1993;2:201-9.
5. Ohi R, Nio M. The jaundice infant: biliary atresia and other obstructions. In: O'Neill JA, Rowe MI, Grosfeld JL, eds. Pediatric surgery. St Louis (MO): Mosby-Year Book; 1998. p. 1465-82.
6. Yang MC, Chang MH, Chiu SN, Peng SF, Wu JF, Ni YH, et al. Implication of early-onset biliary atresia and extrahepatic congenital anomalies. Pediatr Int 2010;52:569-72.
7. Kasai M, Suzuki M. A new operation for non-correctable biliary atresia: hepatic portoenterostomy [Japanese]. Shujutsu 1959;13:733-9.
8. Nio M, Sano N, Ishii T, Sasaki H, Hayashi Y, Ohi R. Long-term outcome in type I biliary atresia. J Pediatr Surg 2006;41:1973-5.
9. Superina R, Magee JC, Brandt ML, Healey PJ, Tiao G, Ryckman F, et al. The anatomic pattern of biliary atresia identified at time of Kasai hepatoportoenterostomy and early postoperative clearance of jaundice are significant predictors of transplant-free survival. Ann Surg 2011;254: 577-85.
10. Serinet MO, Wildhaber BE, Broué P, Lachaux A, Sarles J, Jacquemin E, et al. Impact of age at Kasai operation on its results in late childhood and adolescence: a rational basis for biliary atresia screening. Pediatrics 2009; 123:1280-6.
11. Nio M, Sasaki H, Wada M, Kazama T, Nishi K, Tanaka H. Impact of age at Kasai operation on short- and long-term outcomes of type III biliary atresia at a single institution. J Pediatr Surg 2010;45:2361-3.
12. Kasahara M, Umeshita K, Inomata Y, Uemoto S , Japanese Liver Transplantation Society. Long-term outcomes of pediatric living donor liver transplantation in Japan: an analysis of more than 2200 cases listed in the registry of the Japanese Liver Transplantation Society. Am J Transplant 2013;13:1830-9.
13. Matsui A, Dodoriki M. Screening for biliary atresia. Lancet 1995;345: 1181.
14. Hsiao CH, Chang MH, Chen HL, Lee HC, Wu TC, Lin CC, et al. Universal screening for biliary atresia using an infant stool color card in Taiwan. Hepatology 2008;47:1233-40.
15. Kasai M. Treatment of biliary atresia with special reference to hepatic porto-enterostomy and its modifications. Prog Pediatr Surg 1974;6:5-52.
16. Gu YH, Kato T, Harada S, Sato Y, Kakee N. Medical aid program for chronic pediatric diseases of specified categories in Japan: current status and future prospects. Pediatr Int 2008;50:376-87.
17. Ibrahim M, Miyano T, Ohi R, Saeki M, Shiraki K, Tanaka K, et al. Japanese biliary atresia registry, 1989 to 1994. Tohoku J Exp Med 1997;181: 85-95.
18. Matsui A, Ishikawa T. Identification of infants with biliary atresia in Japan. Lancet 1994;343:925.
19. Shinkai M, Ohhama Y, Take H, Kitagawa N, Kudo H, Mochizuki K, et al. Long-term outcome of children with biliary atresia who were not transplanted after the Kasai operation: >20-year experience at a children's hospital. J Pediatr Gastroenterol Nutr 2009;48:443-50.
20. Howard ER, MacLean G, Nio M, Donaldson N, Singer J, Ohi R. Survival patterns in biliary atresia and comparison of quality of life of long-term survivors in Japan and England. J Pediatr Surg 2001;36:892-7.
21. Altman RP, Lilly JR, Greenfeld J, Weinberg A, van Leeuwen K, Flanigan L. A multivariable risk factor analysis of the portoenterostomy (Kasai) procedure for biliary atresia: twenty-five years of experience from two centers. Ann Surg 1997;226:348-53.
22. Davenport M, Ong E, Sharif K, Alizai N, McClean P, Hadzic N, ét al. Biliary atresia in England and Wales: results of centralization and new benchmark. J Pediatr Surg 2011;46:1689-94.
23. Chardot C, Buet C, Serinet MO, Golmard JL, Lachaux A, Roquelaure B, et al. Improving outcomes of biliary atresia: French national series 1986-2009. J Hepatol 2013;58:1209-17.
24. Nio M, Ohi R, Miyano T, Saeki M, Shiraki K, Tanaka K, Japanese Biliary Atresia Registry. Five- and 10-year survival rates after surgery for biliary atresia: a report from the Japanese Biliary Atresia Registry. J Pediatr Surg 2003;38:997-1000.
25. Ramonet M. Stool Color Cards for Screening for Biliary Atresia. BA Single Topic Conference. Bethesda (MD): National Institutes of Health; September 12–13, 2006.
26. Wildhaber BE. Screening for biliary atresia: Swiss stool color card. Hepatology 2011;54:367-8. author reply 369.
27. Lien TH, Chang MH, Wu JF, Chen HL, Lee HC, Chen AC , et al., Taiwan Infant Stool Color Card Study Group. Effects of the infant stool color card screening program on 5-year outcome of biliary atresia in Taiwan. Hepatology 2011;53:202-8.
28. Takakura M, Yoshinaga M, Hanai J, Takahashi H, Sasaki Y, Okada T. Screening of biliary atresia during 2001-2011 in Sapporo City [in Japanese]. Annual Report of Sapporo City Institute of Public Health 2012; 39:41-7.
29. Gu YH, Matsui A. Screening of biliary atresia [in Japanese]. Pediatr Japan 2014;55:1191-7.

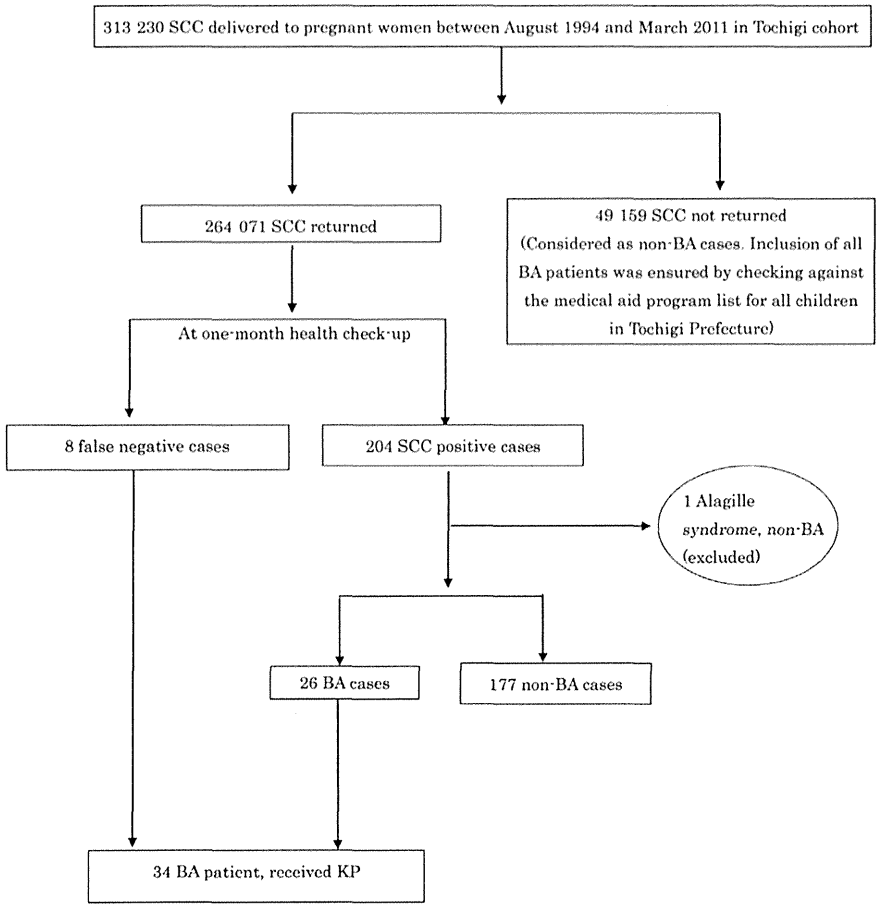

Figure 1. *The flowchart for stool color chart screening. The numbers of participants, positive cases, false-negative cases, patients with biliary atresia in the Tochigi cohort from August 1994 to March 2011. BA, biliary atresia; KP, Kasai procedure; SCC, stool color card.*