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Application of Large Electronic Medical Database for Detecting Undiagnosed Patients in the General Population

Tadashi Ishii,[1,2] Tetsuya Akaishi,[1,3] Kenji Fujimori,[4] Michiaki Abe,[1,3] Masato Ohara,[5] Mutsumi Shoji,[1] Shin Takayama,[1] Chiaki Sato,[2] Masaharu Nakayama,[6] Ichiro Tsuji,[7] Toru Nakano,[8] Noriaki Ohuchi[2] and Takashi Kamei[2]

[1]Department of Education and Support for Regional Medicine, Tohoku University Hospital, Sendai, Miyagi, Japan
[2]Department of Surgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
[3]Tohoku Medical Megabank Organization, Tohoku University, Sendai, Miyagi, Japan
[4]Department of Health Administration and Policy, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
[5]Department of Surgery, Ishinomaki Red Cross Hospital, Ishinomaki, Miyagi, Japan
[6]Department of Medical Informatics, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
[7]Department of Preventive Medicine and Epidemiology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
[8]Department of Gastroenterology and Hepatobiliary Pancreatic Surgery, Tohoku Medical and Pharmaceutical University, Sendai, Miyagi, Japan

Clinical application of accumulated medical big data is a hot topic in medical informatics. Not only for suggesting possible diagnoses in each individual, large medical database can be possibly used for detecting undiagnosed patients in the general population. In this study, we tried to develop a computerized system of detecting overlooked undiagnosed patients with rare chronic diseases in the community population by utilizing the uniformed national medical insurance record database. A cumulative total of 489,823 hospital visits at one tertiary medical center were collected for this project. As the target disease, we selected esophagogastric junction outflow obstruction (EGJOO), including achalasia, which is known to be easily overlooked without performing a barium swallow test. Patient selection software automatically picked out 17,814 individuals with the given suspected diagnoses that could be misdiagnosed in patients with the target disease, from which the software further picked out 526 individuals who underwent upper endoscopy but did not undergo barium swallow test. Of them, the hospital medical records suggested that 39 people still suffered from prolonged symptoms lasting for more than 6 months after the first hospital visit. Among them, 16 individuals agreed to undergo the barium swallow test. One of them was confirmed to suffer from EGJOO, possibly based on some undiagnosed connective tissue diseases. An automated computerized detection system with uniform big medical data would realize more efficient and less expensive screening system for undiagnosed chronic diseases in the general population based on symptoms and previously performed examinations in each individual.

Keywords: computerized detection; electronic medical record; medical big data; medical informatics; receipt diagnosis
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Introduction

Since the advent of computer technology, medical records and examinations data have been widely converted into an electronic format, making large datasets more accessible and easier to handle (Evans 2016; Kruse et al. 2018). With the advances in the field of artificial intelligence (AI), encompassing the field of machine learning (ML), even the process of diagnosis and therapeutic decisions are expected to be shared using the technology in the future (Jiang et al. 2017; Guo and Li 2018; Panch et al. 2018). However, at present, the exact methodology to efficiently utilize compiled large databases in an electronic format for the process of diagnosis and therapeutic decisions has not been established yet. Research on reliable utilization of computer technology in the diagnostic and therapeutic processes is

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Correspondence: Tadashi Ishii, Department of Education and Support for Regional Medicine, Tohoku University Hospital, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.
e-mail: t-ishi23@med.tohoku.ac.jp

still in the early stages (Challen et al. 2019).

As shown in Fig. 1A, one of the expected uses of computer technology in the diagnostic and therapeutic processes at the patient level is informative suggestion or prediction based on accumulated data about the symptoms and findings in previously performed examinations (Jiang et al. 2017; Guncar et al. 2018; Makino et al. 2019). This methodology has been vigorously attempted by many computer and electronic technology companies worldwide, but it has not prevailed and is not established in actual clinical practice at present. One of the difficult steps in establishing the AI-based diagnostic process is feedbacking the achieved precision of AI-based diagnosis to the initially built diagnostic algorithm. AI reinforced by ML techniques is expected to help us partly overcome this problem (Mesko et al. 2018). Such diagnostic technology will be developed and progressed through the collaboration of clinicians and information technology companies in the near future. Another problem to be addressed before applying AI-based diagnostic system to the actual clinical scenes is the lack of interpretability and explainability, which is termed as "black box" nature of AI technologies (Cath 2018; Chang et al. 2019; Montani and Striani 2019; Yang and Bang 2019). Such uncertainty regarding how the AI-based diagnosis has been reached would lead to another problem; namely, it is necessary to clarify who should be responsible when the AI tool makes harmful diagnoses and patients face harmful events based on the misdiagnosis (Petersen et al. 2019).

In addition to supporting clinicians in reaching a correct diagnosis, another expected clinical application of computer technology is to suggest and advise clinicians on their possible oversight in cases of patients with undiagnosed diseases based on a compiled electronic format database that comprehensively contains the individual's background, symptoms, and findings from previously-performed diagnostic examinations (Fig. 1B). This second application is much more realistic, harmless, and an easier way of AI application than the first because computers are better at handling binary data or numerical data than language data or narrative data (Hashimoto et al. 2018). In this study, we attempted the above-mentioned second application, by using a large national medical record database to detect patients in a community population with a specific undiagnosed chronic disease.

Since the 1960s, every individual is covered by the national medical insurance in Japan (Ikegami et al. 2011; Sasaki et al. 2015). Comprehensive information of patient background, suspected diagnoses before examinations, definite diagnoses before therapeutic interventions, performed diagnostic examinations, and implemented treatments have been accumulated in a uniform format across the country, known as the national receipt database (Kimura et al. 2010; Ishikawa 2016). This information is used by clinics and hospitals to later claim official insurance coverage by governmental agencies, following which the agencies judge the validity of the claim. Although the specific finding of each performed diagnostic examination is not recorded, information regarding whether the targeted diagnostic examination has already been performed or not can be retrieved from the database.

As the specific chronic disease to be targeted in this study, esophageal motility disorders were selected based on the authors' specialties. In the field of gastroenterology, chest discomfort and nausea after meals are some of the most frequent complaints in daily clinical settings. Among patients with such complaints, there are some patients with motile abnormalities in the esophagus, resulting in the esophagogastric junction outflow obstruction (EGJOO).

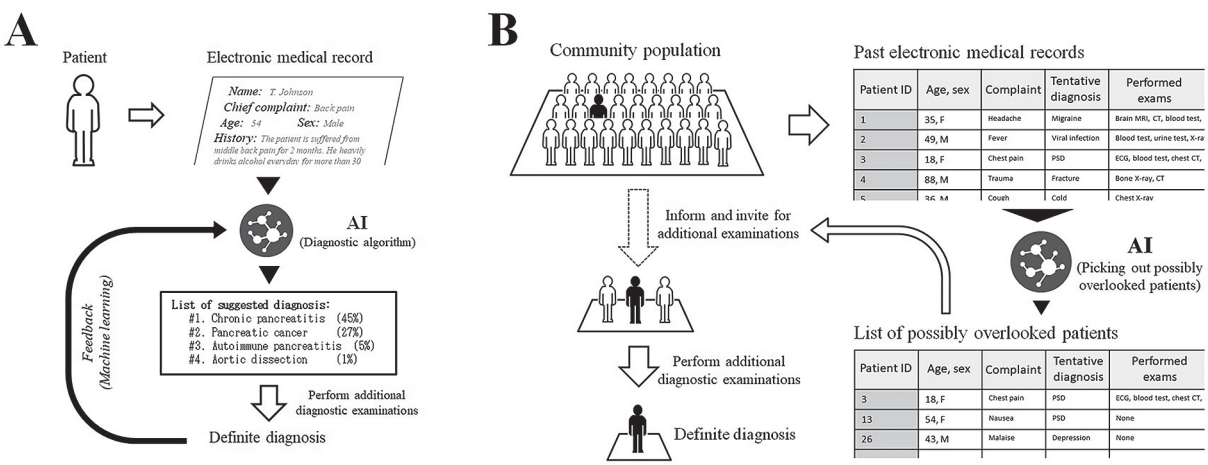

Fig. 1. Conceivable applications of artificial intelligence in clinical practice.
(A) Conventional concept of artificial intelligence (AI) application in clinical practice. The AI suggests several possible diagnoses for each patient, based on his or her complaints and the results of diagnostic tests. (B) Another conceivable application of AI in clinical practice, which is conceived and attempted in this study. The accumulated previous electronic medical records in a community population will be processed using AI resulting in a list of possibly overlooked patients with chronic diseases in the community. This efficient system may meet the demands of medical economics in the future.

For example, esophageal achalasia is one disease characterized by the impaired relaxation of lower esophageal sphincter muscles, typically presenting difficulty in swallowing food, regurgitation of indigested food, and chest discomfort (Boeckxstaens et al. 2014). The prevalence of achalasia is thought to be around 1/100,000 per year (O'Neill et al. 2013). This rare chronic disease is known to be one of the diseases that is easily overlooked and is likely to be diagnosed late (Gockel et al. 2012; Ishii et al. 2019). Without proper therapeutic intervention, the disease is known to significantly impair the patient's quality of life. The sensitivity of upper endoscopy for achalasia is not very high, whereas some kind of abnormal findings can be observed with barium swallow fluoroscopy in almost all patients with achalasia (El-Takli et al. 2006; Ishii et al. 2019). Because upper endoscopy is a much more popular examination than barium swallow fluoroscopy in Japan, many patients with EGJOO in the community population remain undiagnosed. Based on these presumptions, we initiated a project attempting to detect undiagnosed cases in the community population by utilizing large medical records accumulated in the national database.

Material and Methods

General study design

In this study, we tried to automatically extract individuals with suspected undiagnosed EGJOO from the community population by utilizing the national receipt database. From the national receipt database, we extracted individuals with high probability of having undiagnosed EGJOO based on the information of suspected diagnosis before the examination, the types of diagnostic examinations performed, and age. More specifically, we extracted individuals (1) who were given the later-described suspected diagnoses that could be mistakenly given to EGJOO cases, (2) who were between 10 and 60 years old at the clinical onset, (3) who had already underwent upper endoscopy but had not undergone barium swallow fluoroscopy, and (4) whose digestive symptoms persisted for ≥ 6 months without complete remission. The onset age criterion was determined based on previous reports describing that most of the patients with EGJOO, including achalasia, had an age of onset below 60 years old (Gockel et al. 2012; Carlson et al. 2016).

Community population and study period

Ishinomaki City is located in the northern part of Japan with a population of about 150,000. Ishinomaki Red Cross Hospital is the only tertiary medical center in the city and has covered about 200,000 residents around the district after the Great East Japan Earthquake in 2011. In this study, all citizens who visited the hospital at least once between Sep. 2015 and Jun. 2017 were enrolled. In this study period, a cumulative total of 489,823 hospital visits were made.

Accumulated information in the national receipt database

For each of the cumulative total of 489,823 hospital visits, comprehensive information of name, age, sex, hospital ID, added suspected diagnoses, all laboratory and physiological examinations performed, and all medical treatments performed were accumulated from the national receipt database. All of these data are necessary for claiming insurance coverage by the governmental agency in charge. The notation of suspected diagnoses and examinations and treatments performed are standardized all across Japan, and are defined by the Japanese Ministry of Health, Labour and Welfare.

Targeted suspected diagnoses that could be mistakenly given to EGJOO cases

In advance of this study, the authors discussed how to select the possible suspected diagnoses that could be misdiagnosed in patients with EGJOO in reference to clinical experience and the previous published reports identified through a search of the PubMed database. As a result, the following diagnoses were selected as candidates of diseases misdiagnosed in EGJOO patients: anorexia/anorexia nervosa (Marshall and Russell 1993), pubertal emaciation, alcohol dependence/alcohol abuse, gastroesophageal reflux disease (GRED) (Jung and Park 2017), acute gastritis (Kwon et al. 2014), duodenal ulcer, schizophrenia, bipolar disorder, depression (Koyama et al. 2018), somatoform disorders, pharyngo-laryngeal paresthesia, congenial esophageal stenosis, psychosomatic disease (PSD), and anxiety neurosis.

Based on the comprehensive information in the national receipt database of the 489,823 hospital visits at Ishinomaki Red Cross Hospital, those with at least one of the above-described mistakenly given diagnoses were automatically extracted using an original extraction software based on a computing framework by Hadoop, which is a processing framework that can manage the processing and storage of large datasets across clusters of computers (Mohammed et al. 2014; Bao et al. 2018).

Extraction of individuals with suspected EGJOO

From the database of the cumulative total of 489,823 hospital visits, those who were given at least one of the above-described possibly-mistaken diagnoses were automatically selected using software developed by NISSAY Information Technology Co., Ltd. (Tokyo, Japan). For the extracted individuals, the compiled information in the national receipt database was extracted; the patient's name and hospital ID were encrypted using an anonymization tool. Then, from this anonymized data, we compiled a structured query language (SQL) database with the support of Nissay Information Technology Co., Ltd. Lastly, this anonymized SQL database was converted into a Microsoft Office Access® database file (Microsoft, Washington, USA).

With this Access® database, we designed a query to extract individuals between 10 and 60 years old who had already undergone upper endoscopy but had never undergone barium swallow fluoroscopy. For these extracted primary candidates of undiagnosed cases of EGJOO, we further selected patients with persisted digestive symptoms lasting more than 6 months with repeated hospital visits without complete remission by checking their respective electronic medical records. Furthermore, we excluded individuals who were found to have other definite diagnoses such as esophageal cancer. The process of above-described initial extraction from big data is shown in Fig. 2.

Notification of extracted individuals to undergo barium swallow fluoroscopy

We sent letters to the individuals extracted by the above-described computerized algorithm to notify them that they possibly had undiagnosed EGJOO and to inform them that undergoing the barium swallow fluoroscopy would be desirable to rule out the disease. We also notified them that the fee for barium swallow fluoroscopy would be fully covered by the research fund, and the expected inva-

siveness of fluoroscopy would be minimal with a low level of radiation exposure. For those individuals who responded to our notification letter and agreed to undergo barium swallow fluoroscopy, we performed the examination at Ishinomaki Red Cross Hospital between Sep. 2018 and Feb. 2019. These data purification and diagnostic process are illustrated in the lower half of Fig. 2.

Institutional review board

This study was approved by the institutional review boards of the Tohoku University Graduate School of Medicine (IRB No. 2018-1-848) and Ishinomaki Red Cross Hospital (IRB No. 16-44). All of the processes in this study were performed in accordance with the Declaration of Helsinki (World-Medical-Association 2013).

Results

Initial extraction process with big data by applying the Hadoop framework

By using software developed by NISSAY Information Technology Co., Ltd., a total of 17,814 individuals in the community were initially extracted for having at least one of the suspected diagnoses that could not be denied in patients with EGJOO. For these individuals, the necessary information was compiled as a SQL database and converted into a Microsoft Office Access® database file after encrypting patient names and hospital IDs.

With this Access® database containing the comprehensive information of 17,814 individuals, the information of 6,293 individuals with an onset age of between 10 and 60 were further extracted. Among the 6,293 individuals, the number of individuals with previously given suspected diagnoses that could be mistakenly given in EGJOO cases are shown in Table 1. The cumulative total number of these suspected diagnoses surpassed 6,293 because some of the extracted individuals were given more than two of the suspected diagnoses.

From these extracted 6,293 individuals with the above-listed easily-mistaken diagnoses between 10 and 60 years

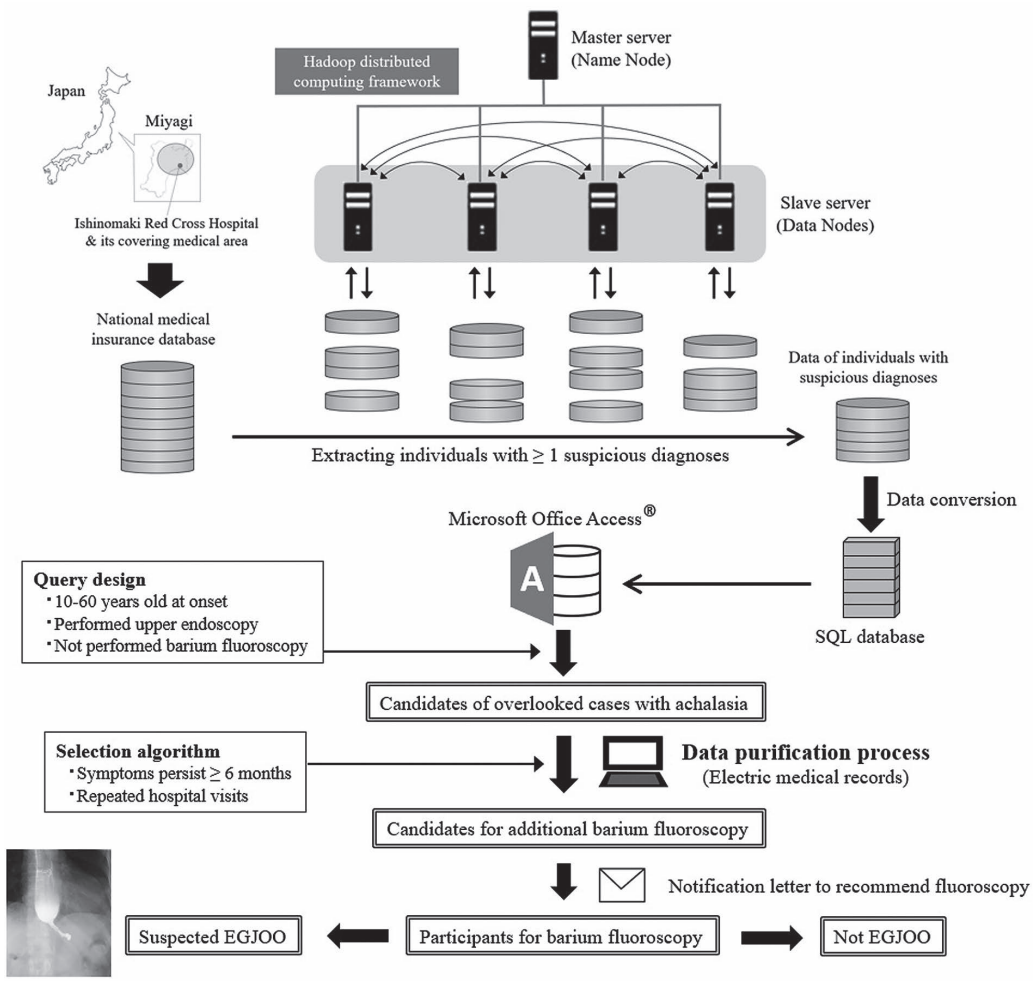

Fig. 2. Extraction process to detect overlooked patients with EGJOO from the community population.
In this study, the step of data purification process based on the persistence of initial symptoms was manually performed because of the absence of information regarding the duration of the symptoms in the database. Ideally, by adding this information to the database in the future, all of the process will be automatically performed by utilizing the artificial intelligence with machine learning techniques.
EGJOO, esophagogastric junction outflow obstruction.

old at onset, 526 individuals who had undergone upper endoscopy but had never undergone barium swallow fluoroscopy were further extracted by designing appropriate queries.

Table 1. List of the doubtful suspected diagnoses in EGJOO cases and the number of cases with each suspected diagnosis among 10-60 years old patients.

Suspected diagnosis	n
Anorexia/anorexia nervosa	110
Pubertal emaciation	0
Alcohol dependence/alcohol abuse	57
GERD	2,340
Acute gastritis	3,111
Duodenal ulcer	202
Schizophrenia	314
Bipolar disorder	29
Depression	274
Somatoform disorders	9
Pharyngo-laryngeal paresthesia	50
PSD	99
Anxiety neurosis	486

The listed diseases are suspected diagnoses that could be mistakenly given to patients with EGJOO. The shown numbers are the actual numbers of each suspected diagnosis within the 6,293 individuals with at least one of these suspected diagnoses, with age between 10-60 years. The summation of the numbers exceeds 6,293 because some of them were given more than one of these diagnoses.
GERD, gastroesophageal reflux disease; PSD, psychosomatic disease.

Data purification process based on the information in medical records

For the 526 individuals who were selected based on the computerized extraction algorithm, their medical records from Ishinomaki Red Cross Hospital were checked for the persistence of digestive symptoms lasting ≥ 6 months and for repeated hospital visits for persisting symptoms without definite diagnoses. As a result, 39 individuals were extracted for having suffered from persistent digestive symptoms without remission, irrelevant of the therapeutic interventions.

We sent written letters to these 39 individuals that notified them of the possibility of overlooked EGJOO and asked them to visit the hospital again to undergo barium swallow fluoroscopy. As the result, 16 individuals responded and agreed to undergo barium swallow fluoroscopy. As a result of the fluoroscopy, a 56-year-old female with the suspected diagnoses of GERD and anxiety neurosis was confirmed to show characteristic findings of EGJOO with retained intra-esophageal fluids. She later underwent esophageal manometry, which revealed that achalasia was deniable for this case. An overview of the above-described results with the actual number of extracted individuals at each step is shown in Fig. 3A, together with the acquired image of barium swallow fluoroscopy from the 56-year-old patient (Fig. 3B). Written informed consent was acquired from the patient to publish her age and fluoroscopic image.

Discussion

In this study, we successfully detected one patient with EGJOO from the massive community population by utilizing a uniform national receipt database. Judging from the low prevalence of EGJOO in the healthy population, the computerized extraction algorithm developed in this study can be highly efficient and powerful for detecting overlooked patients in the community population.

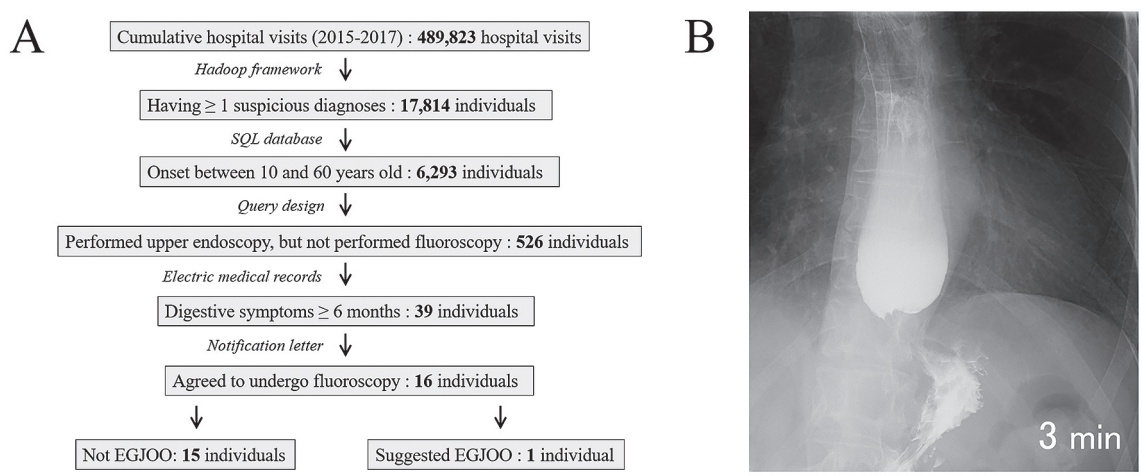

Fig. 3. Number of individuals at each extraction step and the fluoroscopy image of a 56-year-old female with EGJOO.
(A) The number of cumulative hospital visits at the first step and the number of individuals extracted at each step are shown. (B) The barium-contrasted liquid retained in the esophagus 3 minutes after ingestion. The retained liquid finally drained into the stomach about 7 minutes after ingestion. EGJOO, esophagogastric junction outflow obstruction.

We selected EGJOO as the target disease in this study, but the utilized computerized extraction algorithm along with comprehensive individual information (*i.e.*, background, suspected diagnoses, performed examinations) can be generalized into other rare chronic diseases that can be easily overlooked without proper diagnostic examinations with high sensitivities. The generalized scheme utilized in this study is shown in Fig. 4. The essential point of this algorithm is that there is a diagnostic examination with very high sensitivity that is frequently forgotten to be performed in the diagnostic process of the targeted disease (*i.e.*, barium swallow fluoroscopy in EGJOO (Ishii et al. 2019)). To maximize the power and efficiency of such a detection system, the sharing of past uniform medical information between different hospitals in the nation or community is essential. Official authorities should prompt building such a standardized medical database covering wide community areas.

Though the Japanese national receipt database does not contain information about the symptomatic duration for each suspected diagnosis, such additional information would be highly effective for more efficiently implementing the detection system. In this study, as shown in Fig. 2, the only process that clinicians manually checked the medical information of each individual was the step to check the symptomatic duration among the extracted 526 individuals who had undergone upper endoscopy but had not undergone barium swallow fluoroscopy. Though this step requires less than three man-days of effort, if it could be computerized by including the information about symptomatic duration in the database, the entire process of the detection system could be computerized and fully automated without any manual operations that require additional labor.

There are some limitations to this study. First, a great deal of effort will be needed to construct such a uniform national or local medical record database covering large community areas. Although such a database will surely enable clinicians to detect overlooked individuals in the community population and offer benefits to citizens, as realized in this study, financial and operational support from public organizations is needed to run such a large-scale computerized detection system. Another limitation is that there is an ethical problem of utilizing previous medical records for future use in such a detection system without acquiring the written informed consent from all residents in the community or the nation. In this study, institutional review boards of the hospitals involved approved this study because of the high expectancy of social well-being and the advantage to the participants. However, if such a massive uniform medical record database is to be newly constructed in the future, consensus should be achieved in advance whether written informed consent for utilizing individual medical records in a computerized detection system should be obtained from all residents in the community or not.

In conclusion, we successfully extracted one patient with EGJOO from the community population by utilizing a computerized extraction algorithm based on a national receipt database. Such a uniform medical record database with standardized information such as the individuals' background, suspected diagnoses, symptoms and their dura-

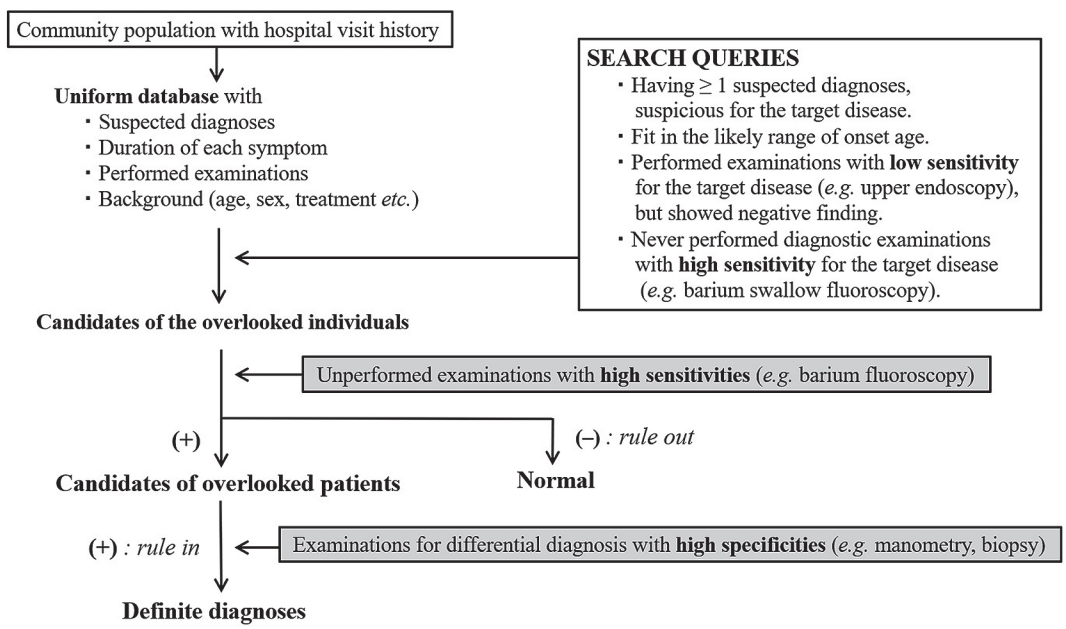

Fig. 4. Schema of generalized algorithm for the computerized detection of overlooked patients from the community population.
The initial establishment of searching algorithm with proper selection of clinical history and diagnostic examinations should be performed by expert clinicians. As a future perspective, by applying an artificial intelligence with supervised learning processes, we will be able to increase the accuracy and efficiency of selecting candidate patients from the general population.

tions, diagnostic examinations performed, eventual definite diagnoses, and implemented treatments would surely create an effective system to detect overlooked patients with rare chronic diseases in the community population, which would realize a more efficient and less expensive screening system based on symptom-based reasoning.

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Author Contributions

T.I. originally conceptualized the study, supervised the process of the study, and analyzed data. T.A. collected data, analyzed data, and drafted the initial manuscript. K.F., M.O., M.N., I.T. invented the software, and analyzed data. M.A., M.S., S.T., C.S., T.N. collected the data. N.O. T.K. helped to conceptualize the study, and supervised the study process. All authors critically revised the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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