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Variance Analysis and Handling of Clinical Pathway: An Overview of the State of Knowledge

GANG DU, LIYUAN HUANG, AND MENGWEI ZHOU
Faculty of Economics and Management, School of Business and Administration, East China Normal University, Shanghai 200062, China

Corresponding author: Gang Du (gdu@dbm.ecnu.edu.cn)

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ABSTRACT Clinical pathway is a multi-disciplinary treatment plan and work mode, which is favorable for improving healthcare service quality and reducing medical costs. Most of references demonstrate that variance analysis and handling is the key to clinical pathway management. Thus, the clinical pathway variance has become the focus of scholars. This paper uses the text mining technique to present a literature review of 496 academic articles in the field of clinical pathway variance analysis and handling, which published between 1994 and 2018. Moreover, this paper conducts a bibliometric analysis to visualize the clinical pathway variance research. In variance analysis and handling, there are a lot of imprecise knowledge and fuzzy relations to be reasoned with knowledge of different domains. In this study, methods of clinical pathway variance analysis and handling are illustrated. In addition, this paper points out the limitations of each method. Based on the results, the future prospects of clinical pathway variance analysis and handling research is proposed.

INDEX TERMS Clinical pathway, processing methods, text mining, variance.

I. INTRODUCTION

The rapid growth of medical costs has brought serious challenges to governments. How to minimize medical costs and save medical resources while ensuring medical quality is the focus of modern healthcare system reform. For specific clinical problems, procedures or medical events of specific population, a structured multidisciplinary care plan can be developed and promoted. This kind of progress plan with time-frames and standards can effectively improve service quality, reduce medical cost and prevent overtaxing of healthcare system [1], [2]. Such a valuable tool is called clinical pathway (CP) which was first introduced by Zander and Bower in 1980s. Clinical pathway includes detailed medical plans, diagnoses, treatment procedures, and follow-up programs. In addition, it contains the information needed to handle unexpected events during the execution of the clinical pathway. At the same time, it requires the flexibility to modify (or reconfigure) the treatment schemes quickly and appropriately to fit the patients' condition, so as to increase the flexibility of the treatment process. With the continuous development of medical treatment, clinical pathway has been widely used in the United States, Europe, and some developed countries and regions in Asia [3]. In order to promote the standardization of clinical pathway management in China, the National Health and Family Planning Commission (NHFPC) has issued 1212 clinical pathway guidelines covering more than 30 clinical specialties by 2017, and has carried out standardization management in 133 diseases by 2019.

Since 1994, the research and application of clinical pathway have been on the rise. Clinical pathway can significantly improve medical quality and early survival [4]. However, clinical pathway involves multi-disciplinary resources, such as education levels of staff, availability of medical equipment and other business management information. The formulation of clinical pathway requires a combination of multi-disciplinary knowledge, and consensus among multi-disciplinary team members of the hospital [5], [6]. However, due to the individual complexity and subjectivity of medical staffs and the unexpected nature of resource scheduling, the actual implementation of the treatment process may deviate from the original clinical pathway. The deviation of clinical pathway often leads to confusion in the later

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stage, which can not achieve the expected therapeutic effect and increase the costs of credit default. In severe cases, sudden changes may even endanger patients' lives. For this reason, the variance of clinical pathway gradually became an important issue and attracted the attention of many scholars [7]. The early establishment of clinical pathway was based on paper-based medical record. However, due to the subjectivity of manual record, the frequency of abnormal pathway was high, and the variance information was relatively lagging [8]. With the advent of computers, log records in semi-automation and automation were more authentic, effective, and timely. Computers also provided a basis for the scholars to deal with the clinical variance by semantic web technologies, process mining, data mining and ECA modeling.

This paper focuses on the field of analysis and handling of clinical pathway variance, and presents a literature review of 496 academic articles. This paper is organized as follows. Section 2 introduces the data sources and research methods. Section 3 explores the research distribution from the perspective of clinical pathway variance. Section 4 analyzes the research hotspots for clinical pathway variance analysis and handling, as well as the main factors and constraints that scholars considered in dealing with clinical pathway variance. Section 5 gives an analysis of the applications, advantages and disadvantages of the related methods. Section 6 concludes this study and proposes the prospects for future research.

II. RESEARCH METHODS

A. DATA SOURCES

The data in this paper are collected from the Web of Science, based on the theme of clinical pathway variance analysis and handling. This search covers a 25-year period from 1994 to 2018. In this paper, the above key topics and their references are searched. 496 qualified papers were obtained after excluding irrelevant research through the titles and abstracts. Irrelevant studies include those researches on CPS modeling directly, or studies only focusing on mutation risks, simulation process, etc.

B. RESEARCH METHODS

Bibliometric is a quantitative statistical analysis method, which uses mathematical and statistical methods to study the growth and distribution of scientific articles. Based on Price Law, Bradford's and Lotka's Law [9], this paper uses text mining, co-word analysis, visual analysis and other methods to study the relevant literature from 1994 to 2018 from the prospective of time and space, research strength and hotspots.

III. TEMPORAL, SPATIAL AND AUTHOR DISTRIBUTION OF CLINICAL VARIANCE RESEARCH

A. TEMPORAL DISTRIBUTION

The temporal distribution of the related literature can roughly reveal the law of scientific development. According to the growth and aging law of the literature, the temporal distribution of the research in a specific field is divided into four stages: germination, development, maturity and decline. The temporal distribution of clinical pathway variance studies (see figure 1) shows that research in this field currently has gone through two stages. From 1994 to 2010, the clinical pathway variance study was in its infancy. At this stage, scholars began to study the clinical pathway variance, but the amount of academic publications was limited. From 2011 to 2018, the clinical pathway variance research was in the development stage. A large number of scholars were committed to the study of clinical pathway variance analysis and handling. The number of publications has maintained steady growth, and the growth trend approximated the exponential function. The number of papers published increased from 14 in 2010 to 69 in 2018, and reached the first peak in 2015. Considering the prevalence of clinical pathway in the world, it is speculated that it will be the development stage of this research field in the next 5 to 10 years. The research on clinical pathway variance analysis and handling will still be a hot issue in the future, and the number of articles in this field will continue to grow.

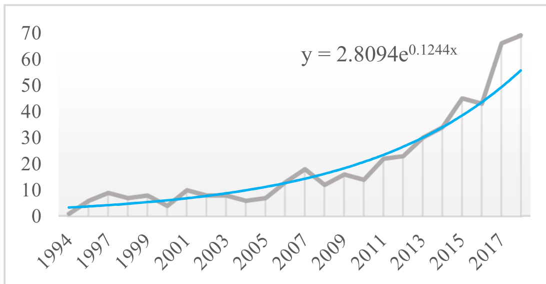

FIGURE 1. Temporal distribution of clinical pathway variance research.

B. SPATIAL DISTRIBUTION

The Bradford's Law can be used to derive clinical pathway variance research from the core journals [10], which will help subsequent researchers to access theoretical data and conduct related research. The spatial distribution of clinical pathway variance is shown as figure 2. Through statistics, 496 journal articles related to clinical pathway variance analysis and handling are collected, which are distributed in 348 journals. According to Bradford's Law, there are 11 core journals in this field. *JOURNAL OF BIOMEDICAL INFORMATICS*, as the authoritative journal of medical informatics journals, published 13 related articles, ranking first. *BMC HEALTH SERVICES RESEARCH, BMJ OPEN, JOURNAL OF MEDICAL SYSTEMS* and *INTERNATIONAL JOURNAL OF MEDICAL INFORMATICS* are also well-known core journals in the field of medicine and medical informatics, which deserve great attention. In terms of content, *JOURNAL OF BIOMEDICAL INFORMATICS* focuses on process mining, data mining, semantic web and other technologies to deal with the clinical pathway variance. Moreover, *BMC HEALTH SERVICES RESEARCH* has recently published several articles that drew conclusions based on clinician interview records and clinical data consolidation.

TABLE 1. Authors distribution of clinical pathway variance.

Rank	Author	Quantity	Rank	Author	Quantity
1	Huilong Duan	12	6	Xiaodi Diao	6
2	Zhengxing Huang	11	7	Xudong Lu	5
3	Wei Dong	9	8	Gang Du	5
4	Kris Vanhaecht	6	9	Zhibin Jiang	5
5	Lei Ji	6	10	Massimiliano Panella	4

FIGURE 2. Spatial distribution of clinical pathway variance research.

C. AUTHOR DISTRIBUTION

Authors are the main body and backbone of the development of science. Price Law has pointed out that in the same subject [11], half of the papers were written by a group of high-capacity authors, the number of which is equal to the square root of the total number of authors. According to the regular counting method, 2224 authors of clinical pathway variance studies were obtained, and the core authors were calculated to publish more than three articles. Table 1 lists the core authors of clinical pathway variance analysis and handing studies. The top three publications are Huilong Duan, Zhengxing Huang, and Wei Dong. Only two people published more than 10 articles.

Table 2 is a one-dimensional cooperation matrix of some authors. The co-author data of clinical pathway variance research was imported into gephi, and figure 3 was obtained.

The nodes represent different authors, while the lines reflect the cooperative relationship between these authors. The thickness of the lines indicates the intensity of cooperation. The network of co-authorship is mainly divided into nine groups. The core authors such as Zhengxing Huang, Wei Dong, and Huilong Duan all have cooperative relationships, and form a fixed author cooperation group. There are also some independent or pairwise connected nodes.

The blue cluster is the most closely related group of authors, including Zhengxing Huang, Huilong Duan from Zhejiang University, and Wei Dong from the People's Liberation Army Hospital, etc. The research directions include exploring personalized treatment approaches through the detection of electronic medical records, the extraction of Web rules language, the establishment of probabilistic topic models (latent Dirichlet allocation, LDA), etc.

The cooperation of the authors of the dark green cluster is also frequent. The authors include Gang Du from East China Normal University/ Shanghai Jiaotong University, Zhibin Jiang from Shanghai Jiaotong University, Xiaodi Diao from Shanghai Putuo Central Hospital, and Yang Yao from the Sixth People's Hospital of Shanghai, etc. The authors of this cluster have more institutions and strong inter-institutional cooperation capabilities. The research directions include continuously optimizing modeling methods for clinical pathway variance through model-based establishment of Web-based rule language, improvement of algorithms based on Takagi-Sugeno (T-S), and fuzzy neural network (FNN), etc.

The light green cluster are Nordic authors that study clinical pathway variance, including Caron Filip, Vanhaecht Kris from Katholieke University Leuven, Baesens Bart from Southampton University, and Lodewijckx Cathy from the European Association, etc. The research directions include collecting data by event logs, interviews and so on, to extract valuable medical and organizational information from the care process.

The grey cluster are Australian authors who study clinical pathway variance, including Kinsman Leigh from Monash University, and James Erica from Newcastle University, etc. They mainly explore the development criteria for clinical pathways.

The authors of the coffee cluster include Chang PL, Huang ST, and Wang TM from Chang Gung University, etc. They mainly focus on the effect of clinical pathway on nursing quality.

The purple cluster have many related authors. There are a large number of countries and research institutions, including Yilong Wang, Chunjuan Wang from Capital Medical University, Haipeng Shen from Hong Kong University, Peterson Eric D from Duke University, and Schwamm Lee H from Massachusetts Gen Hospital of USA. Their research directions include the feasibility and effectiveness of targeted multifaceted intervention models.

The author groups in clinical pathway variance research field, as is illustrated above, are summarized in table 3.

IV. VARIANCE ANALYSIS AND HANDLING OF CLINICAL PATHWAY

A. RESEARCH HOTSPOTS FOR CLINICAL PATHWAY VARIANCE ANALYSIS AND HANDLING

The keywords can accurately reflect the research topic of the literature. According to the keywords of the clinical pathway variance analysis and handling research, the main issues in the research field can be mined. In this section, the keywords of the 496 papers collected are imported into Gephi, and

TABLE 2. One-dimensional cooperation matrix of SELECTED authors.

	Duan, Huilong	Huang, Zhengxing	Dong, Wei	Ji, Lei	Lu, Xudong	Jiang, Zhibin	Du, Gang	Diao, Xiaodi	Bachert, C.
Duan, Huilong	12	11	9	6	5	0	0	0	0
Huang, Zhengxing	11	11	9	5	4	0	0	0	0
Dong, Wei	9	9	9	5	2	0	0	0	0
Ji, Lei	6	5	5	6	2	0	0	0	0
Lu, Xudong	5	4	2	2	5	0	0	0	0
Jiang, Zhibin	0	0	0	0	0	5	5	5	0
Du, Gang	0	0	0	0	0	5	5	5	0
Diao, Xiaodi	0	0	0	0	0	5	5	5	0
Bachert, C.	0	0	0	0	0	0	0	0	4

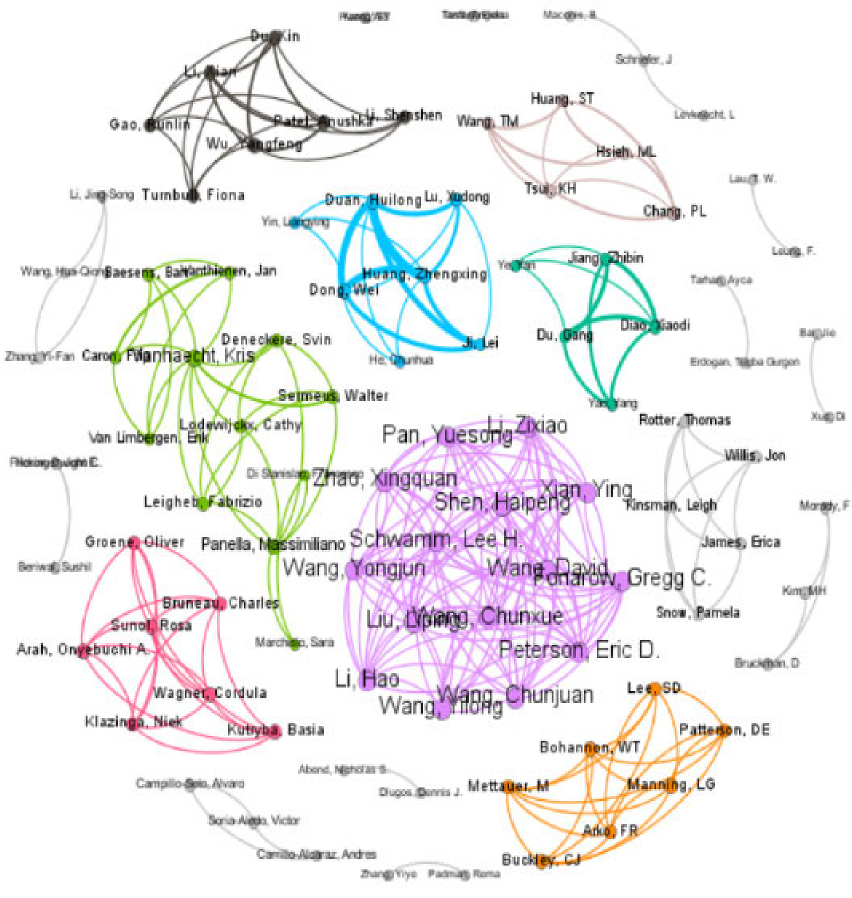

FIGURE 3. Authors collaborate distribution of clinical pathway variance research.

figure 4 is obtained. Figure 4 is a keyword distribution network diagram of clinical pathway variance articles. By analyzing the keywords in the black dotted bordered rectangle, the hotspots of clinical pathway variance can be derived into two aspects.

To show the part in the black dotted bordered rectangle more clearly, it is enlarged in figure 5.

1) THE STUDIES OF CLINICAL PATHWAY MONITORING AND PREDICTION

The monitoring and prediction of clinical pathway is to provide timely feedback if the practical process deviates from the standard clinical pathway. In recent years, the monitoring and prediction methods of clinical pathway variance have developed diversely. Wang *et al.* developed a probabilistic

FIGURE 4. Distribution of keywords in clinical pathway variance studies.

topic model that links patients' characteristics to treatment behavior, detects local anomalies from logs, and mines the mutations hidden in electronic medical records (EMR) [12]. Bezzini *et al.* used machine learning algorithms to learn data-driven and time-based clinical pathways for predicting future states with and without time information [13]. Erdogan *et al.* proposed an artificial neural network (ANNs) framework based on clinical pathway variance prediction [14]. An intelligent learning system consisting of offline analysis and online monitoring phases is proposed in [15], which can continuously monitor and predict CP using electronic medical records (EMR).

2) CLINICAL PATHWAY VARIANCE ANALYSIS AND HANDLING

Prerequisites for the discovery of clinical pathway variance rely on large-scale use of electronic medical records for disease records. By using data mining technology, process mining technology, data envelopment analysis method, semantic-based and semi-automatic text mining method and other techniques to extract the treatment program, the variance of clinical pathway can be found. Rolston *et al.* proposed to compare abnormalities with the original database by capturing clinical pathway variance data [16]. Lambert proposed a heterogeneous Markov model by mining sequential patterns [17].

The method of processing clinical pathway variance uses the artificial intelligence method of deep learning. Through the study of clinical pathway variance, the disease diagnosis problem can be found in time, the corresponding patient care can be provided, and the clinical pathway can be continuously improved and optimized. Di Lenarda *et al.* proposed a semi-automatic text mining process based on semantic methods to comprehensively review the pathway [18]. Garcia *et al.* developed a simple decision tree model to compare [19]. Rosen *et al.* proposed a TS-based fuzzy neural network, a new hybrid learning algorithm clinical pathway variance processing method. Jensen *et al.* proposed a modular petri net based on variable structure, and solved the mutation according to the combined mutation processing method of knowledge [20].

A comprehensive analysis of the techniques used in clinical process variance prediction and processing can dynamically monitor variance. Figure 6 shows the word frequency statistics of the pathway variance handling literature.

For the variance of clinical pathways, many scholars put forward some modeling and handling methods, including semantic web modeling (network ontology language), data mining or process mining methods, and rule-based modeling (ECA rules). This paper will describe and analyze the above methods as follows.

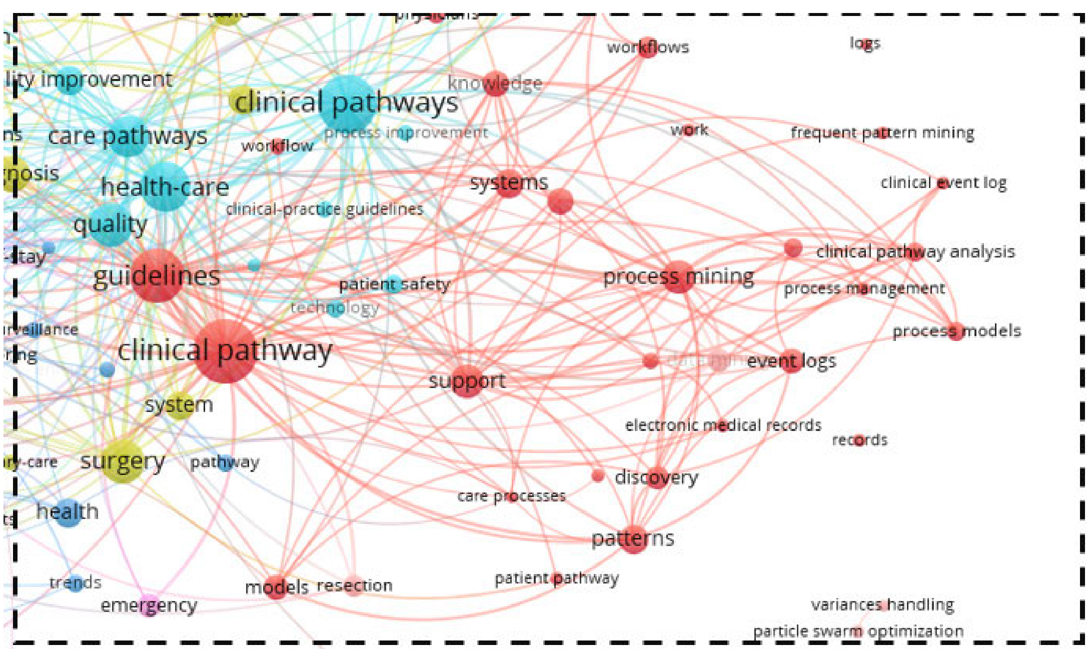

FIGURE 5. The keywords in the black dotted bordered rectangle.

TABLE 3. Author groups in clinical pathway variance research field.

Representative institution	Representative authors	Representative articles	Research direction
Zhejiang University, People's Liberation Army Hospital	Zhengxing Huang, Huilong Duan, Wei Dong	Probabilistic modeling personalized treatment pathways using EHR	Web rule extraction/ Probabilistic topic model
East China Normal University, Shanghai Jiaotong University	Gang Du, Zhibin Jiang	Improvement of hybrid algorithm based on Takagi-Sugeno (T-S) and fuzzy neural network (FNN)	Optimal structure and parameters with RCDPSO and DPSO
Katholieke University, Leuven University Southampton	Kris Vanhaecht, Bart Baesens	A process mining-based investigation of adverse events in care processes	Use event logs to extract valuable medical and organizational information
Monash University, Newcastle University	Leigh Kinsman, Erica James	What is a clinical pathway? Development of a definition	Clinical pathway development criteria
Chang Gung University	Chang PL Huang ST	The implementation of clinical paths for six common urological procedures, and an analysis of variance	Improvement in the quality of care by the implementation of clinical pathways
Capital Medical University, Duke University	Yilong Wang, Eric D Peterson	Rationale and design of a cluster-randomized multifaceted intervention trial to improve stroke care quality in China	Significance of the clinical pathway

B. SEMANTIC WEB MODELING

Semantic Web modeling has become one of the main approaches to modeling pathway variance, which implements that the knowledge of healthcare systems as a central component of clinical pathway system. Semantic Web modeling is the combination of semantic network technology and electronic medical record, and the construction of clinical pathway knowledge base. In this knowledge system, scholars classify medical knowledge as ontology model according to medical index system and different standards. Then, they use

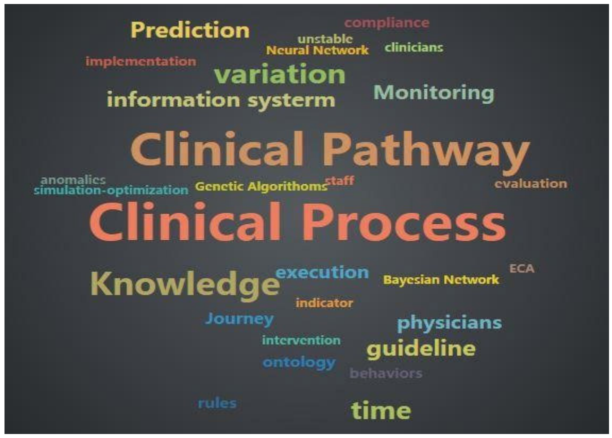

FIGURE 6. Word frequency of literature on pathway variance handling.

semantic reasoning techniques to simulate the occurrence of change and the implementation of simulation management measures [21].

At present, the Clinical Pathway Ontology (CPO) modeling method aims to provide the machine language to explain the medical clinical pathway knowledge and to represent the management environment of the business process. According to the modeling language, clinical pathway ontology (CPO) needs to capture a generic ontology as a structure representative and sort tasks. The CPO approach is to browse and analyze differences in intervention systems, trying to identify the underlying concepts and their resources, the organizational structure and interrelationships of knowledge [22].

In general, in ontology modeling, precise semantic relationship and description of domain knowledge can eliminate the communication constraints between people and heterogeneous applications by providing a shared common domain, so as to promote semantic interoperability, information sharing and knowledge reuse in the system [23]. Therefore, the method first provides a Clinical Pathway Ontology (CPO) as the general form of semantic modeling. Ontology can usually take into account that the system captures common concepts and relationships in an interactive and participating network environment, and provides explicit domains for clinical pathways and semantic web technology-based representations. Subsequently, Horrocks *et al.* proposed a hierarchical semantic modeling method (SWRL) based on Semantic Web Rule language [24]. Therefore, the research work in this area has focused on computerized clinical pathway system. In these studies, a large number of scholars paid attention to work flow research. Quaglini *et al.* built their work flow model by using an existing work flow standard, and then described their work flow models based on clinical pathways [25].

In this paper, we focus on the OWL modeling, that is, how to use network ontology language and rules to realize the dynamic adaptation of clinical pathway variance processing. The research of this paper is based on 8 publications of OWL modeling issue, and table 4 is the basic case of the literature dealing with clinical pathway variance based on network ontology language (OWL) modeling. Due to the different emphasis of each literature, the paper will analyze the main considerations and limitations of these studies.

TABLE 4. Basic literature statistics based on network ontology language (OWL) modeling of clinical pathway.

Literature	Year	Language based
Alexandrou et al. [26]	2008	SWRL Rule Bank (SEMPATH Prototype)
Alexandrou et al. [21]	2011	SWRl Rule base /JESS Expert System (SEMPATH Prototype)
Ye et al. [22]	2009	OWL Web Ontology language (OWL)/SWRL Rule
Yao et al. [28]	2013	SWRL Rule (CONFLEXFLOW)
Huang et al. [29]	2014	SWRL Rule
Wang et al.[12]	2015	Semantic Web Technology
Alexandrou et al. [30]	2009	SWRL Rule Bank (SEMPATH Prototype)
Yan et al.[31]	2017	Business process model and symbolic language（BPMN)

1) MAIN RESEARCH FACTORS

In order to further analyze the main factors considered in the study of the clinical pathway variance based on OWL modeling, this paper summarizes the main considerations of each literature, as is shown in table 5.

➢ Dynamic adaptability

Due to the changes of patients' clinical conditions and the internal conditions of medical institution, how to adapt to various needs and scenarios with a personalized clinical path has become an important issue in the development of modern medical care. Personalized treatment programs often mean real-time adapted treatment options.

Previous research trends often focused on abnormal adaptation in the case of static structures. Lenz *et al.* introduced that medical institutions needed WFMS (work flow management system) to deal with the internal organization process. Correspondingly, Lenz *et al.* proposed that the ADEPT system realized the dynamic changes of functions such as execution, monitoring and management in the medical process [32]. Colaert *et al.* pointed out that the adaptive clinical workflow was based on medical, practice, clinical and operation knowledge [33]. Abidi and Chen introduced the CarePlan system platform, which achieved the adaptability of clinical pathway based on Semantic framework [34]. Alexandrou *et al.* proposed that the purpose of SEMPATH prototype was to provide a real-time adaptive solution

TABLE 5. Main considerations in modeling based on OWL.

Literature	Compliance	Multiparty participants	Time constraints	Recessive paths	Isomerism	Adaptability	Ontology updating
Alexandrou et al. [26]		--	✓	--	--	✓	✓
Alexandrou et al. [21]	--	✓	--	--	--	✓	✓
Ye et al. [22]	--	--	✓	✓	--	✓	✓
Yao et al. [28]	--	--	✓	--	✓	✓	✓
Huang et al. [29]	✓	--	✓	--	--	✓	✓
Wang et al. [12]	✓	✓	✓	--	--	✓	✓
Alexandrou et al. [30]	✓	--	✓	--	--	✓	✓
Yan et al.[31]	✓	--	✓	✓	--	✓	✓

process for health-care services, and the prototype as a medical process execution engine that is assisted by an adaptive semantic framework. Its semantic framework was created by an ontology surrounded by the required knowledge based on the creation of semantic rule sets. The SEMPATH method was based on the continuous inference of the current knowledge to adapt to each step in the implementation of the clinical pathway [30]. Aalst *et al.* proposed an approach using flexibility as a service (FAAS). It was inspired by service-oriented architecture (SOA) and flexible classification [55]. Different services use different workflow languages to implement the corresponding activities. In this way, different models can be mixed and nested in any appropriate way.

Yao *et al.* proposed clinical background based on Flexible Workflow (CONFlexFlow), which was a new method of integrating clinical pathways into clinical decision support systems (CDSS) [28]. Flexible channel integration was the key to the success of credit default swaps. It allowed the body to undertake the correct rules for certain activities through the clinical background of the ontology, so as to realize the dynamic implementation of context specific medical pathways based on the specific needs of clinical pathways.

➢ Generality and sharing

Reference [21] centralized the implementation of activity management by establishing a generic model, as well as providing different requirements for different types of user pathways. However, this approach was still limited to independent hospital systems. Reference [12] developed an independent clinical pathway design (ICP) system that can share different electronic medical records systems. An innovative knowledge base model stores global knowledge and local knowledge and real time situations in different name-spaces. Semantic web technology supports knowledge sharing and intelligent reasoning. The electronic CPS has the standard functionality without modifying the existing EMR system and the integration environment. Compared with embedded channel module, ICP system sharing is more intelligent. In order to support the sharing of ICP system, semantic web technology introduces a new knowledge base construction. A new model of knowledge base design is proposed to construct global knowledge, local knowledge and real time instances through Web ontology language (OWL) to construct together. By mapping rules between predefined global knowledge and local knowledge, ICP systems can share different electronic medical records systems.

➢ Real time compliance

Compliance inspection is to ensure that the medical institutions' treatment behavior is implemented according to the established CP norms. Once a non-compliant treatment behavior is detected, health care providers can update the CP specification to cover all cases, or may apply new mechanisms to implement the best clinical practice. One paper [29] proposed a semantic based CP compliance inspection system to provide clinicians with timely detection and improvement on violations of established CP specifications. A CP ontology model was constructed and a formal CP compliance check was provided. Using this CPO, local processing constraints were modeled through revenue Web semantic rules (SWRL). In addition, Little-JIL also became an important approach for online audit of essential / critical treatment behavior.

➢ Ontology updating

The core of the adaptive CPO and execution environment is to combine the implementation of clinical pathways with the need to generate the corresponding knowledge flow, and the results of the rule set execution may generate new ontologies inserted into the knowledge object. The rule base can create new knowledge and update ontology accordingly. Reference [26], [27] established the integration of knowledge reasoning infrastructure stored in the software architecture through the SWRL rule base and the JESS expert system. The continuous reasoning generates new knowledge ontology, provides feedback to the system, and then updates the ontology.

From the above summary, OWL-based modeling approaches are primarily used to provide machine-interpreted knowledge of clinical pathways and to represent business process management environments. It can quickly find the corresponding matching knowledge from the knowledge base in order to deal with the variance, so as to produce "relatively flexible" clinical pathway. In this process, the main research direction of scholars is how to adapt clinical pathways to meet the different needs dynamically. In order to better implement the adaptation, reference [28] also proposed a method that can dynamically implement the specific situation based on the clinical pathway of context related medical activities. In addition, the key advantage of OWL based modeling is that it can create new knowledge and update ontologies accordingly. Nevertheless, the real-time replenishment usually makes it only possible to consider predictable variance, and it is difficult to take the unknown variance into account. In addition, many studies also considered compliance issues, but only reference [29] considered providing a formal dynamic CP compliance check by constructing the CP Ontology (CPO) model. Most of the time constraints are considered in the literature, including time interval, time correlation, and difference time matrix, etc. Research and development of shared clinical pathway systems to expand knowledge and reduce costs is also an important consideration and important development direction of OWL modeling.

2) RESTRICTIVE FACTORS

Although OWL based modeling can handle the variance in the execution of many clinical pathways, due to the limitations of the present study, many factors have not been considered and become the constraints in the process. Table 4 and table 5 show that very few studies consider heterogeneous and implicit pathways, and most of the literature does not consider setting the weight model in the process of generating adaptive solutions based on the SEMPATH prototype. In compliance inspection, due to little research, its rules are not perfect, and the results are poor. For sharing research, although it can reduce the cost through non refactoring system, it also considers the special situation and the demand satisfaction is less.

According to the pathway generated by context activity, the requirement of specific situation can be dynamically realized. However, it does not consider the period of breach of contract and the error audit. The BPMN model can help to solve the above problems, but the use of this method is limited because of the false peaks or the unreliable results when deviations reach the peak. In addition, it is difficult to consider unexpected variance in OWL modeling. The restrictive factors are summarized in table 6.

C. DATA MINING AND PROCESSING

The design and implementation of clinical pathways often involve complex knowledge. Moreover, because of the subjectivity of human beings and the complexity of the actual activity relationship, many activities tend to deviate from the clinical pathway and cause unexpected variance in the actual implementation. The clinical pathway variance is usually complicated with fuzzy knowledge, heterogeneous situation, recessive pathway and so on. To solve the above problems, many scholars choose to solve clinical path variance problems through data mining.

This paper mainly analyzes 14 data mining publications. Table 7 is a summary of methods to deal with basic information of clinical pathway variance.

1) MAIN RESEARCH FACTORS

The data mining method is used to deal with the problem of clinical variance. The fuzzy knowledge, the unexpected variance and the time constraint are generally considered. The following will be explained and classified in detail in

TABLE 6. Restrictive factors based on the OWL modeling research.

Literature	Restrictive factors
Alexandrou et al. [26]	Medical ontology is not complete, user processing is poor, priority weight is not considered
Alexandrou et al. [21]	The pathway model diagram has poor applicability, no weight model and no adjoin service
Ye et al. [22]	Consider less demand for service objects
Yao et al. [28]	Breach of contract and lack of error auditing
Huang et al. [29]	Compliance rules show poor performance and less need for patient preferences
Wang et al.[12]	Priority weight is not considered
Alexandrou et al. [30]	Specialization is not considered
Yan et al.[31]	Loop, intermediate events and multi task parallelism are not supported, false deviations or deviations reach peak and unreliable results

TABLE 7. Clinical pathway variance data mining to process the basic information in the literature.

Literature	Year	Methods
Ye et al.[35]	2009	Fuzzy Petri Net
Huang et al.[36]	2012	Clustering method
Ye et al.[37]	2011	PK-TFPN
Huang et al.[15]	2014	Data-mining technology / Probability model
Helbig et al.[38]	2016	Data-mining technology /Clustering method
Du et al.[39]	2009	Reconfigurable modeling
Huang et al.[40]	2015	Data-mining technology / Probability model
Huang et al.[41]	2016	Data-mining technology / Probability model
Du et at al. [42]	2010	MCPN-CS
Huang et al. [43]	2013	Data-mining technology / Probability model
Qu et al. [44]	2014	Case-based Reasoning
Du et al.[45]	2008	Object oriented Petri Net
Du et al.[46]	2012	T-S model / Fuzzy neural networks
Du et al.[47]	2012	PSO/DPSO

this article. Table 8 summarizes considerations of the related literature.

➢ Uncertain events (fuzzy knowledge, relation)

Clinical pathway implementation often involves imprecise knowledge. Differential analysis and processing require the relevant knowledge in the medical field, such as management rules and medical knowledge. Knowledge usually includes linguistic aspects without explicit explanations, indicating the relationship between fuzzy concepts and fuzzy boundaries. More importantly, the knowledge mostly includes fuzzy relationships among patients, diseases, symptoms, physical signs, and examination and evaluation results.

TABLE 8. The main considerations of data mining methods.

Literature	Time constraint	Fuzzy knowledge	Lsomerism	Self-adaption	Complication	Non correlation	Invisible path	Unexpected variance
Ye et al.[35]	✓	✓	--	✓	--	--	--	✓
Huang et al.[36]	✓	--	✓	✓	--	--	--	--
Ye et al.[37]	✓	✓	--	--	--	✓	✓	✓
Huang et al.[15]	--	--	--	--	✓	--	--	--
Helbig et al.[38]	✓	--	--	--	--	--	--	--
Du et al.[39]	✓	--	--	✓	--	--	--	✓
Huang et al.[40]	✓	--	--	✓	--	✓	--	--
Huang et al.[41]	✓	--	✓	✓	--	✓	✓	✓
Du et at al. [42]	✓	--	--	✓	--	✓	--	✓
Huang et al. [43]	✓	--	--	--	--	✓	✓	✓
Qu et al. [44]	--	✓	--	✓	--	--	--	--
Du et al.[45]	--	✓	--	✓	--	--	✓	✓
Du et al.[46]	--	✓	--	✓	--	✓	--	✓
Du et al.[47]	✓	✓	--	✓	--	✓	--	✓

Fuzzy models can describe vague sentences in natural language. Therefore, in order to solve the above problems, a knowledge extension process based on the type of fuzzy Petri nets (PK-TFPN) is proposed to deal with different types of CP differential decision support models and different processing decisions based on different types. In addition, the extended event action (ECA) rule method is proposed to deal with fuzzy knowledge effectively by CP differential modeling approach [39].

However, the above method relies on the fuzzy rules provided by experts, and these rules are usually difficult to obtain. In addition, fuzzy systems do not have much learning ability, and it is very difficult for human operators to adjust fuzzy rules and membership functions of training data. Artificial neural network (ANNs) has become an important tool for nonlinear data mapping. It can solve nonlinear problems effectively. Artificial neural networks allow complex data structures, multivariate data, and nonlinear computations to be well coordinated. However, artificial neural networks (ANNs) can not explicitly provide readable and understandable rules for medical professionals to make clinical decisions. Moreover, artificial neural networks (ANNs) are more difficult to operate. In this case, [49] proposed fuzzy neural network (FNNs) that combined fuzzy logic in dealing with uncertain information and neural networks with good learning ability, overcoming the weakness of ANNs. Fuzzy neural networks can also process imprecise information through language expressions.

With the continuous development, the network is becoming more and more concerned. The two typical models of network are Mamdani type and Takagi Sugeno (T-S) model [50]. According to the different characteristics of CPS, TS fuzzy neural network can be used to assist doctors in making CPS differential processing decisions.

Recently, a new evolutionary technique, particle swarm optimization (PSO), has become an important optimization technique [51]. Compared with genetic algorithm, particle swarm optimization has many attractive characteristics: fast convergence, easy to implement and less parameters. Although many studies have shown that PSO algorithm has good global search ability, because it can quickly find and explore useful areas in search space, they are relatively efficient local search and easy to lead to premature convergence. To solve this problem, many studies have made many modifications. In order to improve the accuracy and efficiency of different Takagi Sugeno processing (T-S), fuzzy neural network (FNNs), and treatment method of clinical pathway, a new variance (CPS) is proposed. The optimal structure and parameters can be achieved simultaneously by the integrated stochastic cooperative decomposition particle swarm optimization (RCDPSO) algorithm and the discrete binary PSO algorithm (DPSO) [46].

➢ A nonlinear correlation

The abnormal changes of parameters and patients can lead to different types of CP variance, so it is very important to establish the relationship model between them. By mining the useful information from the relevant historical database, it is possible to predict the trend of clinical pathways with the change of related parameters to realize the pre-diagnosis of CP variance. However, these issues are inherently highly non-linear, which makes it difficult to establish a comprehensive mathematical model. In the early study, statistics were the most commonly used methods for constructing related models.

Since the classification problem of the real world is complex and highly nonlinear. Recently, a few nonlinear and complex machine learning methods have been proposed by researchers. For example, there are artificial neural network, decision tree, support vector machine (SVM), combination support vector and neural network, combined with fuzzy set theory and rough set theory. Artificial neural network (ANNs) has excellent ability of nonlinear pattern classification, powerful self-organization, self-learning and parallel information processing. However, it is difficult to be highly accepted. In order to improve its understanding, Shavlik proposed the artificial neural network of MOFN rules knowledge, though this method is still very complex and requires much time.

In recent years, many scholars have tried to apply evolutionary algorithm (EA) to solve the problems in data mining, knowledge extraction, classification and prediction [52]–[54]. At the same time, particle swarm optimization (PSO) with optimized parameters and feature subset is also a new branch of evolutionary algorithm. Although PSO algorithm has been developed rapidly, there are some problems such as premature and low precision. Therefore, some improved methods are also proposed. To some extent, these methods improve the global processing ability of particle swarm optimization, but it is still difficult to achieve a good compromise between global convergence and its efficiency. In addition, many researchers have adopted the mutation mechanism existing in random perturbation. A two-layer multi swarm cooperative particle swarm optimization algorithm is proposed to solve the local search problem [47].

2) RESTRICTIVE FACTORS

It can be seen from table 8 that although many studies have taken the fuzzy knowledge into account, the researches in this area are still relatively scarce, and it is the direction to be further developed. Furthermore, the implicit pathway and heterogeneity are still not paid much attention to. In addition, a new research direction in the pathway mining is the study of comorbidity. However, there is few studies on this aspect.

D. PROCESS MINING

Most patients, because of their specific needs, do not necessarily follow the pathway described by activities. This fact will lead to modifications of the clinical pathway instances for each specific patient. If these modifications are stored and further analyzed, it will be possible to create new pathways, including these exceptions, or to correct errors in previous design iterations. This technique is usually impossible to execute manually, but it can be approached by using process mining (also workflow mining) techniques. The idea of process mining is to learn the workflow automatically based on business process reasoning [55]. Process mining algorithms use execution samples to infer workflows describing real processes. The action of nursing protocols using this technique is applicable to each patient's log, which can be used to learn the workflow that formally represents these clinical pathways. This helps the clinical pathway design modify the previous iteration process according to the real new exception and correct error design. This study will classify the main factors that affect the study of variance through process mining.

At present, process mining methods have been successfully used to identify changes and differences in the treatment process, and to provide guidelines or clinical best practice [56]. In addition, they have been used to discover special situations and automatically identify dishonest patients, etc. [57] This paper will further classify the main considerations of the literature in this area.

➢ The time constraint

Clinical pathways usually include various clinical interventions/activities along a predetermined schedule, the logical and timing relationships among these activities, and the criteria for expected outcomes at different intervals.

Time is an important constraint in the treatment of clinical pathway variance. Scholars have conducted a lot of research in the consideration of this constraint. Huang *et al.* developed a new method based on dynamic programming algorithm to divide the observed time segments into continuous and overlapping intervals. In the given event log file, a frequent medical behavior pattern can be found at each particular time interval. In addition, Huang *et al.* developed another method based on unsupervised probabilistic clustering technique (called latent Dirichlet allocation). The model consists of a set of therapeutic activities based on the basic features of CP. It is found that the temporal structure of the CP model can be successfully extracted with consideration of the time stamp of the treatment. However, because they lack relevant information, such as the time or precedence constraints between CP scheduling steps, these methods find the CP cannot be used in the treatment of service variability under patient scheduling. In addition, data processing in heterogeneous patient situations or from highly variable processes is also challenging in process mining [58].

In order to find homogeneous conditions, clustering technology is generally a more effective method [59]. Unfortunately, clustering algorithms are likely to confuse heterogeneous patients, which means that this approach cannot be used for realistic scheduling and reduce the transparency of the hospital process. To bridge this gap, the two main challenges of mining technology need to be solved. First, the strong heterogeneity of patients in the treatment process of large variability. Second, the IT system has different structures and contents [38], [60], [61].

➢ The anomaly detection

The accuracy and reliability of clinical pathway output is very important, because they directly affect the performance of clinical processes. However, previous studies focused only on the analysis of clinical abnormalities rather than detecting them. In recent years, anomaly detection has gradually attracted the scholars' attention. Process mining, as a general method of business process analysis, is gaining more and more attention. The idea of process mining is to analyze potential business processes from event logs that record event execution information. For compliance checking, there are three kinds of process mining techniques, namely process discovery, consistency checking, and logic based property verification. The discovery process is (RE) building the process model from the event log analysis. Consistency checking is the consistency check between the specified process model and the corresponding actual process instance. Attribute verification based on logic is a specific process that attribute to analyze a single process instance, such as activity precondition, activity sequencing, etc. For example, Aalst proposed an anomaly detection method based on process mining [59]. How to implement the anomaly detection of business process management in the event log, and discuss the anomaly of the perceptual detection system in four process logs is proposed in [61]. Although most of the process mining algorithm in a structured way to detect the abnormal traces in the process, the actual complexity of CPS in the treatment of behavior and diversity is much higher than the general business process. Previous methods cannot achieve dynamic monitoring. To this end, a computational model for local CP anomaly detection was proposed in [15]. The probabilistic topic model is used to describe the general features of patient traces from the clinical event logs generated by the hospital information system. Local anomalies can be detected by fitting the normal treatment behavior described in the model. Traces shared by most patients can be used as a compliance measure. In the broader field of business process management, a variety of process mining techniques have been proposed to measure the consistency between logs and prescribed process models. For example, complex constraints with UML activity diagram model that can be used to check process compliance.

E. RULE-BASED MODELING

In clinical pathway modeling, the clinical pathways between different individuals are different, which means that when a computer program intends to simulate a pathway in reality, it must decide if the input data set is an accident and what should be done later. If the variability data set is specific, the rules can handle these exceptions. However, if the pathway is difficult to describe, there are many factors that are difficult to describe. In the actual clinical process, there are many statements and conditions that cannot be easily qualified or classified. Therefore, how to use these rules correctly becomes a realistic problem. Contrary to an event, an uncertain event is not easily restricted, so it is not easy to determine whether it is happening or not. An extended knowledge model based on mixed exception handling, namely generalized fuzzy event - condition - action (GFECA) rule and fuzzy Petri net knowledge extension process (PK-TFPN) was proposed in [37]. This method implements the integration representation and reasoning of fuzzy/non fuzzy knowledge, as well as specific application domain knowledge and workflow process knowledge. A fuzzy number theory with fuzzy numbers to represent uncertain time was given in [62]. These ambiguous sentences or events in clinical pathway can be regarded as a normal condition and involved in operations.

These existing verification ontology systems, the semantic inference rules in the database, can be well compatible with the model, in order to solve the abnormal situation of knowledge (especially fuzzy knowledge).

V. ADVANTAGES AND DISADVANTAGES OF CLINICAL PATHWAY ANALYSIS AND HANDLING METHODS

As mentioned above, the clinical pathway analysis and handling have involved many methods, such as semantic web modeling, data mining, process mining and rule-based modeling. Limited by the technical characteristics and the research level, each method has its advantages and disadvantages.

A. SEMANTIC NETWORK MODELING

Semantic Web modeling is the combination of semantic network technology, electronic medical records, and the construction of clinical pathway knowledge base. In this knowledge system, scholars classify medical knowledge as ontology model according to medical index system and different standards. After that, they use semantic reasoning techniques to simulate the occurrence of changes and the implementation of simulation management measures. The model based on Semantic Web semantics/rules will be responsible for executing and observing the application status of clinical pathways, providing automatic recognition of abnormal events and decision support services to handle exceptions. Therefore, Semantic Web Modeling mainly studies how to identify the variance and propose corresponding modifications (or reconstruction), and can dynamically adapt the pathway under the continuous inference of the current knowledge. Usually, semantic web modeling can absorb new knowledge and update ontology constantly, so as to realize self-updating and self-maintenance of knowledge. In order to implement the adaptation, a new method was proposed to implement the specific situation based on the clinical pathway of context related medical activities dynamically [28]. In addition, many studies have also used semantic web modeling methods for compliance testing.

Although semantic network modeling can deal with many difficulties in clinical pathway variability, it also has many shortcomings. There are very few studies on heterogeneous and implicit pathways in current research, and most of the literature does not consider setting the weight model in the process of generating adaptive solutions based on the SEMPATH prototype. In compliance inspection, due to less research, its rules are not perfect, and the results are poor. For sharing research, although it can reduce the cost through non refactoring system, it considers the special situation and the demand satisfaction is less. According to the pathway generated by contextual activities, it can dynamically achieve the specific needs of the situation. However, it considers the default period and error audit deficiencies. The BPMN model can help only solve limited problems of default because of the false bias or the peak deviation. In addition, semantic network modeling usually considers the adaptive problem of the modified real-time discovery and processing, which takes less unexpected variance into account.

B. DATA MINING PROCESS

From the results perspective, the clinical process abnormality is defined as reliability (the standard deviation of some output parameters) and accuracy (as time goes by, relative to the average value of certain targets). Accuracy and reliability of output are important because they directly affect the performance of the clinical process. With such challenges, how to automatically detect abnormal, timely identification of changes in the hospital care journey is very important. Semantic web modeling or rule-based methods mostly rely on human subjective awareness. How to automatically and objectively detect the anomaly through a priori knowledge of the clinical process model is a major research direction of data mining.

Besides the accuracy problem, the data mining method is suitable for dealing with uncertain events. Variance analysis and handling require the use of relevant knowledge in the medical field, such as management rules and medical knowledge. Knowledge usually includes linguistic aspects without explicit explanations, indicating the relationship between fuzzy concepts and boundaries. In order to solve the above problems, a knowledge extension process based on type fuzzy Petri nets (PK-TFPN) was proposed to deal with different types of CP differential decision support models and handling decisions based on variance. In addition, the extended event action (ECA) rule method was proposed to deal with fuzzy knowledge effectively in CP differential modeling.

However, the above methods rely on the fuzzy rules provided by experts, and these rules are usually difficult to obtain. In addition, fuzzy systems do not have much learning ability, and it is very difficult for human operators to adjust fuzzy rules and membership functions of training data. Artificial neural network (ANNs) has become an important tool for nonlinear data mapping. Artificial neural networks allow complex data structures, multivariate data, and nonlinear computations to be well coordinated. However, artificial neural networks (ANNs) cannot explicitly provide readable and understandable rules for health care professionals to make clinical decisions. In overcoming the weakness of ANNs, fuzzy neural networks can also process imprecise information by means of language expressions [63]. Recently, a new evolutionary technique, particle swarm optimization (PSO), has become an important optimization technique. Compared with genetic algorithm, particle swarm optimization has many attractive characteristics: fast convergence speed, easy to implement and less adjustment parameters. Although many studies show that PSO algorithm has good global search ability because it can quickly discover and explore useful regions in search space [64], [67]. However, they are relatively efficient local search and easily lead to premature convergence. Current research is also constantly considering the optimization of particle swarm optimization algorithm. Due to the high fuzzy knowledge and uncertain relationship/target, the method of data mining usually takes the unexpected variance into account.

As a data mining method, although many studies have considered the fuzzy knowledge, there are few studies on this method. The implicit pathway and heterogeneity are still not paid much attention to. A new research direction in the pathway mining is the study of comorbidity. In addition, a clinical pathway based on the adaptive Bayesian network model (ABN) method was designed [65], which effectively improves the accuracy and flexibility of the pathway. However, this method has not been introduced into the research of variance handling.

C. PROCESS OF MINING

The idea of process mining is to automatically learn the workflow [66], [68]–[70] based on business process reasoning. Process mining algorithms use execution samples to infer workflows describing real processes. The use of this technique in the care protocol action for each patient's log can be used to learn the workflow that formally represents these clinical pathways. This helps the clinical pathway design modify the previous iteration process and correct the error design according to the real implantation. Now, process mining methods have been successfully used to identify changes and variance in the treatment process, and can give guidelines or clinical best practice. In addition, they are also used to discover special situations and identify dishonest patients automatically. Process mining is also used for traffic scheduling and other issues.

Process mining has the ability of self-learning, maintenance and updating. Considering the accuracy of exception handling, it can be used for real-time anomaly detection. However, it has weak ability to deal with test compliance, and fails to consider implicit pathway and fuzzy knowledge (relation).

D. A RULE-BASED MODELING

In clinical pathway modeling, the clinical pathways between different individuals are different, which means that when a computer program intends to simulate the pathway, it must decide if the input data set is abnormal and what should be done later. If the variability data set is specific, the rules can handle these variance. The uncertain events are not easy to be restricted. Therefore, it is hard to determine the occurrence or nonoccurrence. Fuzzy event - condition - action (GFECA) rules can deal with this problem. A hybrid anomaly extension knowledge model of science based on the generalized fuzzy based on event - condition - action (GFECA) rules and fuzzy Petri net knowledge propagation process (PK-TFPN) is proposed. This method implements the integration representation and reasoning of fuzzy/non fuzzy knowledge, as well as specific application domain knowledge and workflow process knowledge.

As can be seen from the above summary, the method based on semantic network modeling mainly considers the extraction of the mutation processing method from the knowledge base, the dynamic adaptation after the mutation processing, and the self-maintenance by constantly updating the ontology. The processing of unexpected variance are not taken into account. Data mining and rule-based modeling approach mainly deal with the relationship between fuzzy knowledge and event dependencies (such as time dependence) in the process of mutation, and can handle unexpected variance [71], [72]. Process mining mainly considers scheduling, dynamic monitoring and mutation design through self-learning. In addition, based on Semantic Web Modeling, data mining and process mining methods, the variability accuracy problem is considered, and dynamic monitoring variability can be realized.

VI. CONCLUSION AND PROSPECTS

Clinical pathway has gradually become the most widely used medical management mode in standardized medical management. However, in the actual medical activities, the deviation between the actual care and the standardized clinical pathway may occur at any time [73], [40]. If the clinical pathway variance is not handled timely and scientifically, the actual utility of the clinical pathway will be affected. Analyzing and handling various variance phenomena, revealing the causes of variance and providing continuous and timely positive feedback for the clinical pathway are the key points to smoothly implement and continuously improve the clinical pathway [31], [74], [75].

This paper is a literature review of the previous research in the field of clinical pathway variance analysis and handling. To the best of our knowledge, there is no review of this specific field. We mainly introduce the temporal, spatial and author distribution of clinical variance research based on the 496 academic articles of Web of Science. Furthermore, we introduce different methods, including semantic web modeling, data mining and processing, process mining, and a rule-based modeling. Finally, we compare the advantages and disadvantages of these methods.

There are some core journals publishing clinical pathway variance research which may deserve attention, such as *JOURNAL OF BIOMEDICAL INFORMATICS, BMC HEALTH SERVICES RESEARCH*, etc. As for the contributing authors, Huilong Duan, Zhengxing Huang, and Wei Dong are the core authors to promote the study of clinical pathway variance.

Results based on the text mining method indicate that the existing research of clinical pathway variance include the monitoring and prediction of clinical pathway variance based on electronic medical records, and the handling of clinical pathway variance through process analysis. Compared with the clinical pathway designed by experts, data-driven execution clinical pathway is more objective, convenient to design, implement and detect variation of clinical pathway [76], [77]. Several studies analyzed and managed clinical pathway variance based on semantic web technologies, process mining, data mining and ECA modeling. However, current research on predicting clinical pathway variance is still insufficient, and is limited to a few diseases and with low prediction accuracy [78].

The monitoring and prediction of clinical pathway variance are the important research directions in the future. Firstly, for monitoring variance, in addition to discovering variance through semantic-based text mining techniques, text association analysis and text clustering can also be used to extract variance and establish rules. Secondly, for the optimization of prediction model, artificial intelligence algorithm can be used to improve the prediction accuracy. For example, the artificial intelligence algorithm is used to optimize the fuzzy neural network, so as to carry out variance analysis and processing. Moreover, we can also use the knowledge discovery algorithm based on the data mining to extract reasonable and effective rules from massive data, which can be used as the existing expert knowledge. Finally, multi algorithm fusion is an important development trend in the future. The ensemble algorithm will solve the problem of the narrow scope of a single method application, and the problem of low accuracy in special cases. For instance, the construction of knowledge-based artificial neural network can provide technical support for the classification, monitoring and prediction of clinical pathway variation.

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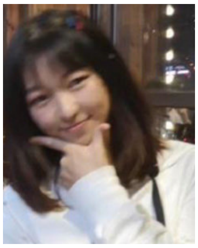
GANG DU was a Research Fellow with the National University of Singapore from 2011 to 2013. He is currently a Professor with the Faculty of Economics and Management, East China Normal University. His work has been published in leading economic and *Management Journal*. His research interests include the variance analysis and handling of clinical pathway, and artificial intelligence algorithm.

He is a member of POMS, INFORMS, and Operations Research Society of China, and serves on the peer Reviewer of the *International Journal of Production Economics*, *Computers & Industrial Engineering*, the *European Journal of Operational Research*, and *Production Planning and Control*.

LIYUAN HUANG received the B.S. degree in business administration from East China Normal University, in 2020, where she is currently pursuing the M.S. degree.

From 2016 to 2019, she has participated in the research of medical operation management. Her research interests include the development of clinical pathway variance analysis and handling, and the prediction of disease risk using artificial intelligence algorithm.



MENGWEI ZHOU received the B.S. degree in business administration from East China Normal University, in 2020, where she is currently pursuing the M.S. degree.

From 2016 to 2019, she has participated in the research of medical operation management. Her research interests include clinical pathway variance modeling and business analysis.