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RESEARCH ARTICLE

Efficacy of intelligent diagnosis with a dynamic uncertain causality graph model for rare disorders of sex development

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Abstract **Disorders of sex development (DSD) are a group of rare complex clinical syndromes with multiple etiologies. Distinguishing the various causes of DSD is quite difficult in clinical practice, even for senior general physicians because of the similar and atypical clinical manifestations of these conditions. In addition, DSD are difficult to diagnose because most primary doctors receive insufficient training for DSD. Delayed diagnoses and misdiagnoses are common for patients with DSD and lead to poor treatment and prognoses. On the basis of the principles and algorithms of dynamic uncertain causality graph (DUCG), a diagnosis model for DSD was jointly constructed by experts on DSD and engineers of artificial intelligence. "Chaining" inference algorithm and weighted logic operation mechanism were applied to guarantee the accuracy and efficiency of diagnostic reasoning under incomplete situations and uncertain information. Verification was performed using 153 selected clinical cases involving nine common DSD-related diseases and three causes other than DSD as the differential diagnosis. The model had an accuracy of 94.1%, which was significantly higher than that of interns and third-year residents. In conclusion, the DUCG model has broad application prospects as a computer-aided diagnostic tool for DSD-related diseases.**

Keywords disorders of sex development (DSD); intelligent diagnosis; dynamic uncertain causality graph

Introduction

Disorders of sex development (DSD) are defined as a heterogeneous group of congenital conditions in which the development of chromosomal, gonadal, or anatomic sex is atypical [1,2]. DSD are classified into three major categories on the basis of a patient's karyotype: 46, XX DSD; 46, XY DSD; and sex chromosome DSD [1]. The incidence of DSDs is 1/1000 to $1/10^6$ in the general population [3–5]. DSDs have multiple intricate causes. Congenital adrenal hyperplasia (CAH) is the most common cause of DSDs [6], and the majority of CAH is caused by 21-alpha hydroxylase deficiency (21OHD) [7]. DSD diagnosis relies on family history, clinical symptoms, and specific signs, as well as on hormone profile analysis, chromosome karyotype analysis, and genetic testing results [8–10]. Distinguishing the exact etiology of DSDs is quite difficult, even for senior general physicians. However, diagnosing DSDs is an urgent issue because the decision-making concerning sex assignment is considered stressful and difficult for both family members and health care professionals [1,11]. Moreover, the risk of gonadal tumors may be as high as 40% in patients with dysgenetic gonads [8]. Therefore, an early and accurate diagnosis of DSDs is important for both patients and their families. However, in reality, the first step for most patients with DSDs is to consult with a primary care physician, which is typically composed of young doctors, such as residents and general physicians. Nevertheless, primary care doctors usually do not have intensive training in DSD diagnosis.

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Given that each patient has different manifestations and some patients have atypical symptoms, they may be misdiagnosed or receive a delayed diagnosis. In addition, clinical doctors, most of whom are endocrinologists, need long training cycles to obtain high proficiency in diagnosing DSDs. Thus, many patients with DSDs may have been misdiagnosed or have not received appropriate and early diagnoses. Missed or delayed diagnoses in turn lead to treatment delay and increase psychological, social, and familial burden. For example, DSDs in individuals with CAH due to 21OHD, which is the most common cause of DSDs, can lead to precocious puberty, premature epiphyseal fusion, short stature, and impaired adult height if undiagnosed and untreated at the early stage [12,13]. If the patient is diagnosed early, then the serious complications mentioned above could be reversed with glucocorticoid treatment.

In the past several decades, with the rapid development of the artificial intelligence (AI) technology, AI diagnostic tools have become popular and widely applied in the medical field of disease diagnosis. These tools have improved the sensitivity and specificity of diagnosing diseases. An AI diagnosis system greatly improves the general level of health care, reduces public health expenditure, and offers a distinctive value in less-developed areas of the world. As the technical aspects of AI developed, dynamic uncertain causality graph (DUCG) methods have been established to address the causal link between uncertain information and probability measurements through graphical expressions [14]. DUCG is a probabilistic graphical model that intuitively expresses a causal relationship among variables in an explicit pattern and uses a "chaining" inference algorithm to achieve efficient reasoning. In this study, we used DUCG theory to build an intelligent diagnosis system for rare DSDs caused by steroid hormone synthesis or disorders and tested the validity of the model with clinical cases.

Materials and methods

Establishment of a DSD knowledge base

First, a knowledge base for diagnosing DSDs was established. The knowledge base included demographic information, symptoms, physical signs, and laboratory test results, as well as imaging diagnostics, medical histories, and risk factors. The optimal diagnosis of DSDs depends on a patient's complete clinical data, including a prenatal and familial history, a detailed and comprehensive physical examination, pelvic imaging findings, hormone measurements, chromosome karyotype analysis, and gene detection [8]. The most common specific clinical signs of patients with DSDs include virilization in females, clitoromegaly, posterior labial fusion, formation of a urogenital sinus, early puberty, premature epiphyseal closure, and accelerated growth during childhood [15]. Other rare DSD-related diseases can manifest as delayed puberty, primary amenorrhea, bilateral undescended testes, microphallus, isolated perineal hypospadias, an inguinal/labial mass, breast development in males, and cyclic hematuria in males. The laboratory examination should include serum glucose, electrolytes, plasma renin activity, aldosterone, and optional stimulation tests, as well as hormone measurements of 17-hydroxyprogesterone, 11-deoxycorticosterone, 11-deoxycortisol, dehydroepiandrosterone, testosterone, pregnenolone, adrenocorticotropic hormone (ACTH), cortisol, gonadotropins, anti-Müllerian hormone, inhibin B, and urinary steroids [16]. Other evaluation methods, such as pelvic and adrenal imaging, chromosomal microarray, next-generation sequencing panel of DSD genes, and whole-exome sequencing in some special cases, can provide evidence to diagnose DSDs [9,10]. These methods provide a clear genetic diagnosis of these monogenic diseases. The process of diagnosing DSDs usually takes 1–2 weeks if well-arranged examinations are performed in comprehensive medical centers, but it can sometimes take months in primary care units. However, an intelligent possible diagnosis of DSDs only requires less than a minute. The accuracy and timeliness of a novel intelligent diagnostic model will guide general practitioners and primary care physicians toward a possible diagnosis and suggest the next investigational step.

The study protocol was approved by the Human Ethics Committee of Peking Union Medical College Hospital (PUMCH).

Methodology

The DUCG method for intelligent diagnosis of DSDs must address the following aspects: (1) how to represent the clinical knowledge of DSDs mentioned in the preceding paragraph, including causal relationships and uncertainties among different events, which serve as the basis for diagnosis; and (2) how to calculate the post-test probability for each disease by using the DUCG knowledge base.

The DUCG method provides a concise way of representing complex scenarios of clinical knowledge. Each disease can be represented by a subgraph in DUCG corresponding to a chief complaint, where the disease is the cause, and the pathological manifestations, such as symptoms, signs, and examination, are the results. An independent link event is used to quantify (in the form of a probability) the uncertain causal relationship between the cause and the result. The quantitative value can be set according to physician experience or machine learning, and this link event is a directed arc that points from the cause to the result. As shown in Figs. 1, 2, and 3, B_i (rectangle $\boxed{i}$) represents the root cause event variable, which is the hypothetical event variable (disease) in the

inference calculation. X_i (circle (i)) is the result event variable (pathological manifestation) and can also be used as the cause event of other events. BX_i (double circle ((i))) is the B variable that integrates the risk factors. D_i (pentagon ⟨i⟩) denotes the default root cause event of X_i, and each D_i corresponds to a unique X_i. SX_i (hexagon ⟨i⟩) is the gold standard variable; if SX_i is confirmed to be positive, then the corresponding disease is definitively diagnosed. C_i (dotted circle (i)) is a categorical variable that connects the upstream cause and the downstream result and represents a general term for a class of medical terms, such as symptoms, signs, and laboratory inspection results. The unconditional causal relationship between the cause and result variables is represented by $F_{n;i}$ (single line directed arc →). Similar to $F_{n;i}$, causal relationships with an observable validation condition event $Z_{n;i}$ are represented by conditional $Z_{n;i}$ (dashed directed arc ⇢). In $F_{n;i}$ and $Z_{n;i}$, "n" refers to the number of parent nodes, whereas "i" pertains to the number of child nodes; the states of both nodes form a matrix, and the matrix can be a sparse matrix. The causal uncertainties are encoded in the parameters of F variables (details can be found in Reference [17]).

For example, Figs. 1 and 2 show the subgraph of a single disease. Multiple subgraphs can be synthesized to form a complete knowledge database (such as that shown in Fig. 3) for inferential calculation by the DUCG cloud platform.

In terms of diagnostic reasoning, once a patient's clinical information (evidence E) is collected, the DUCG inference calculation begins; first, to simplify the DUCG according to E and form simplification rules 1–10 [18] and 16 [14], a beneficial simplification can be performed by deleting the part unrelated to the evidence and hypothesis, thereby narrowing the range of hypotheses to be determined and reducing the number of inference calculations. According to the simplified DUCG model, each X in evidence E can be expanded until only B or BX and F or Z exist, and these variables are all multiplied by X together by an "and" operation, as shown in Eq. (1).

$$E = \prod_i X_i \tag{1}$$

This calculation process completely follows the logic operation rules and Eq. (2) to calculate the probability of each disease B conditional on evidence E; then, the probabilities are sorted to obtain the desired result.

$$Pr\{B_i|E\} = \frac{Pr\{B_iE\}}{Pr\{E\}} \tag{2}$$

Statistical method

All study cases were verified by the DUCG diagnostic model, interns, and third-year residents. The diagnostic accuracy was then calculated. Moreover, the difference in diagnostic accuracy for each disease among the three groups was statistically analyzed by Pearson's χ^2 test using SPSS software (version 21.0).

Results

Diagnostic model for DSDs based on DUCG

The etiology of DSDs includes nearly 100 diseases that can be classified into those caused by 46, XX DSD; 46, XY DSD; and sex chromosome DSD [1,2]. A complete intelligent diagnosis model for DSD based on a DUCG would be large and complex. Hence, at this initial stage, the nine most common causes of DSDs were chosen to establish the diagnosis model (Fig. 3). In addition, a diagnostic model of three causes of non-DSD-related diseases with similar clinical manifestations was also established for differential diagnosis. These causes are listed in Table 1. For example, Figs. 1 and 2 demonstrate three subgraphs of Fig. 3 that represent several causal correlations between clinical features and diseases for patients with 21OHD and polycystic ovary syndrome (PCOS), respectively. All the included parameters and causalities were determined by the DSD multidisciplinary team, which included endocrinologists, geneticists, gynecologists, urologists, and psychologists, on the basis of domain knowledge, epidemiology statistics, and DSD research findings.

We constructed a diagnostic model for 21OHD with a DUCG (Fig. 1). The diagnostic flow chart of 21OHD is representative because it is the most common flow chart for DSDs. The collected medical evidence for diagnosing 21OHD currently includes demographic characteristics; family history; characteristic symptoms and signs, such as growth acceleration, female clitoromegaly, deepened voice in children, boys with precocious puberty, virilization in females, and short stature at the end of growth; imaging findings; laboratory examination results, such as elevated progesterone, testosterone, 17-hydroxyprogesterone, and ACTH; and CYP21A1 genetic assay and sex chromosome examination results.

Similarly, as depicted in Fig. 2, the diagnosis model graph for PCOS was constructed by a DUCG, and PCOS was considered as the control for DSDs in this study. The diagnostic factors for PCOS also included demographic characteristics; genetic history; typical clinical manifestations, such as weight gain, excessive body hair, and oligomenorrhea; laboratory examination results and imaging findings, such as mildly elevated testosterone and hyperinsulinemia; and pelvic ultrasound findings of polycystic changes in the ovary.

DSD diagnostic model verification

The data of 153 patients diagnosed with DSD

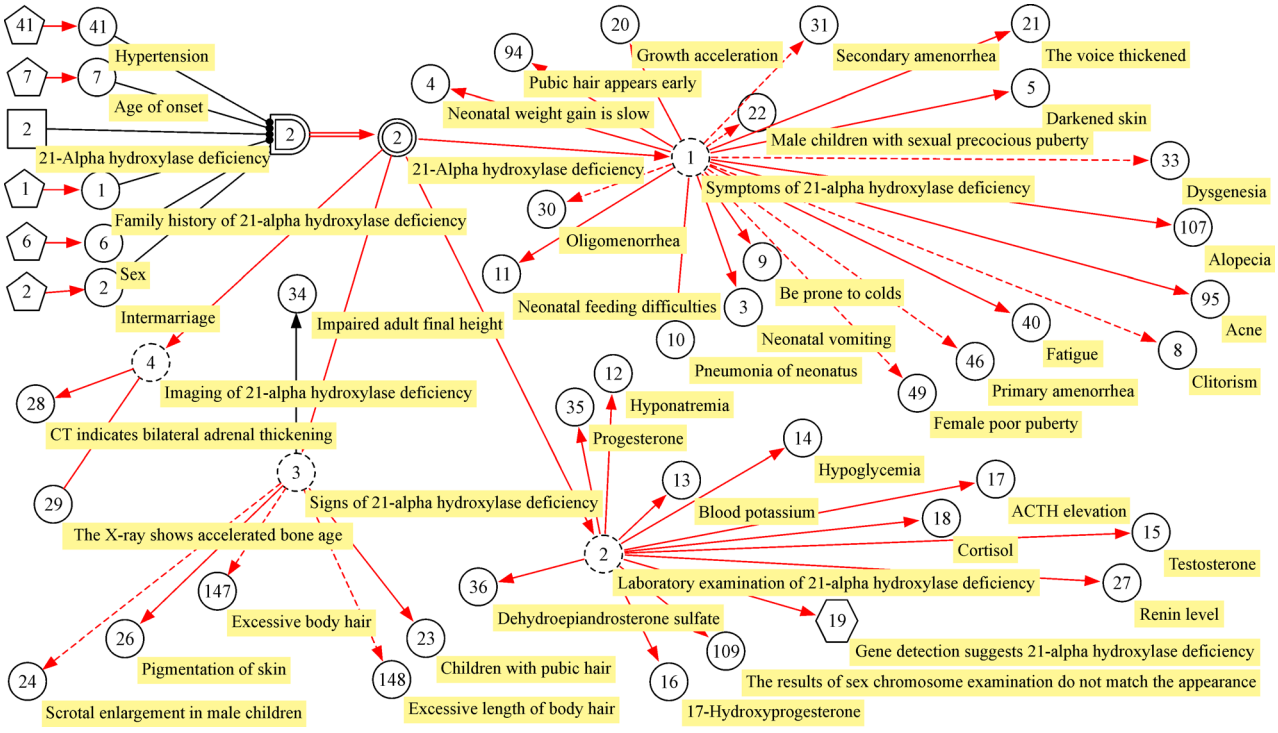

Fig. 1 Subgraph of the 21OHD model in the DUCG. Rectangle represents the root cause event variable, which is the hypothetical event variable (disease) in the inference calculation. Circle is the result event variable (pathological manifestation) and can also be used as the cause event of other events. Double circle is the variable that integrates the risk factors. Pentagon denotes the default root cause event. Hexagon is the gold standard variable. Dotted circle is a categorical variable that connects the upstream cause and the downstream result and represents a general term for a class of medical terms, such as symptoms, signs, and laboratory examination results. Dotted line indicates a conditional connection. Solid line expresses an unconditional connection.

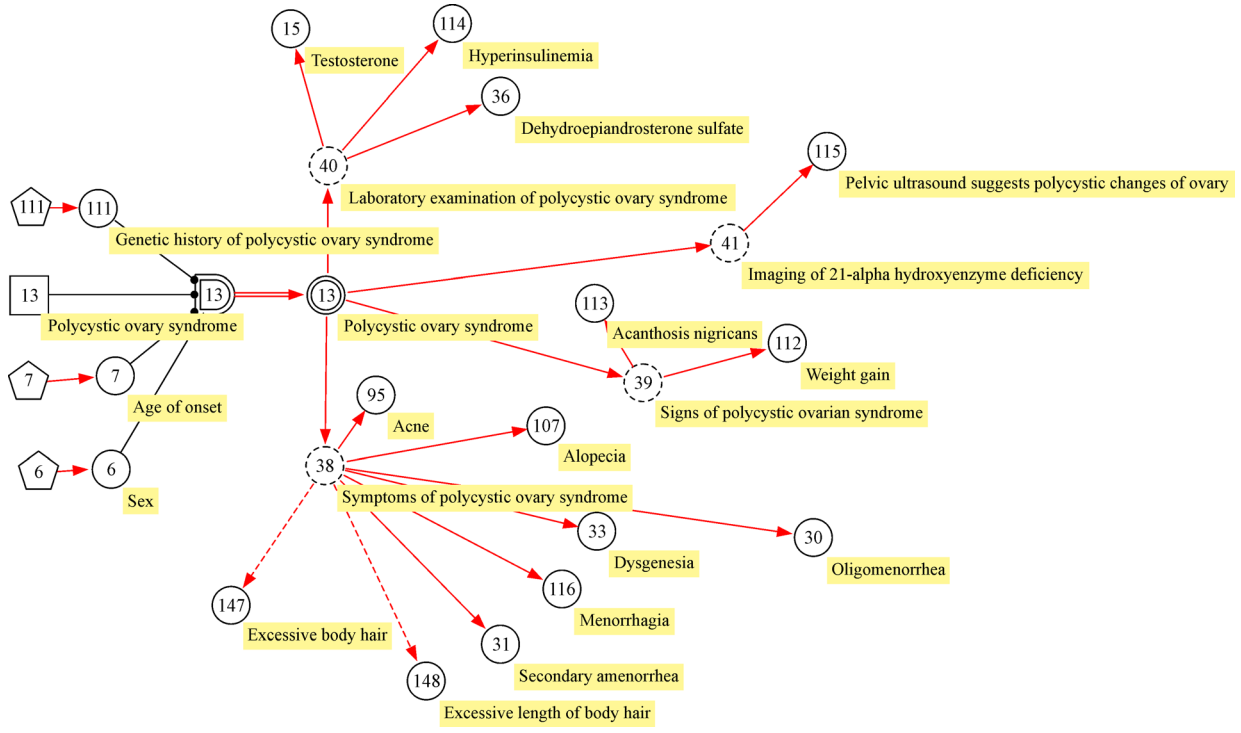

Fig. 2 Subgraph of the PCOS model in the DUCG. The sequence numbers represent only one sort or index or code. The number of repeated variables is only 111, 7, or 6. DUCG requires that *X* (circle) must have a reason, whereas 111, 7, and 6 have no reasons but are objective facts, all of which are represented by the same number of pentagons. A dotted line indicates a conditional connection, whereas a solid line represents an unconditional connection. For example, 147 and 148 are only found among women, and women are the conditional limitation.

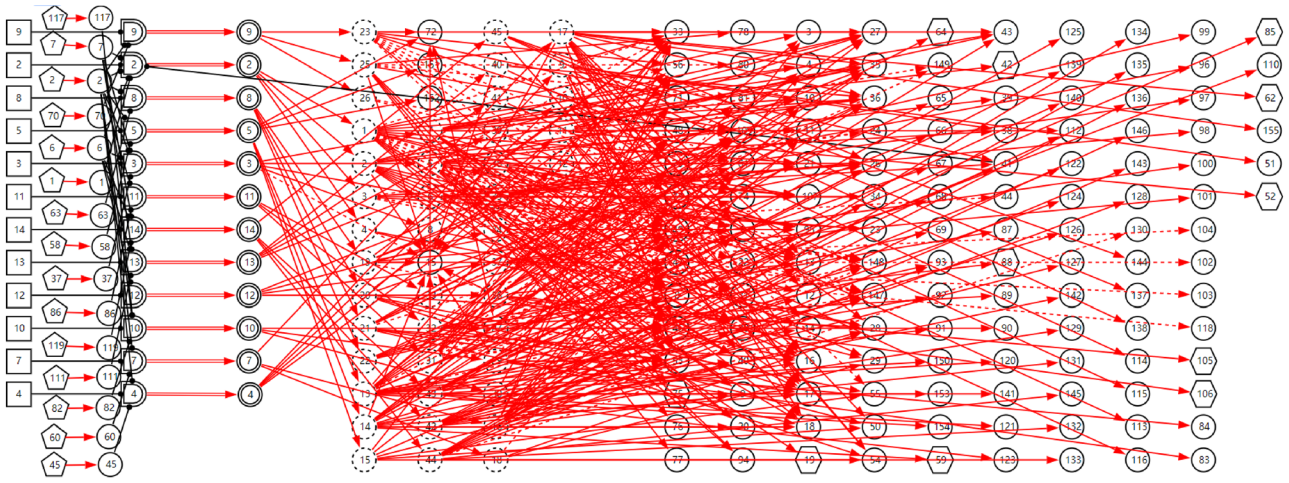

Fig. 3 DUCG with DSDs as the chief complaint combined with 12 subgraphs, two of which are illustrated in Figs. 1 and 2.

Table 1 Accuracy of the DUCG diagnostic model for patients with DSDs and non-DSD-related diseases

Recruited DSD patients	Number of cases	Diagnostic accuracy of the DUCG model	Diagnostic accuracy of interns	Diagnostic accuracy of third-year residents	*P* value
21-Alpha hydroxylase deficiency (21OHD)	23	100%	82.6%	86.9%	0.127
11β-Hydroxylase deficiency (11βOHD)	10	90%	70%	70%	0.475
17-Hydroxylase deficiency (17OHD)	20	90%	75%	85%	0.432
Steroidogenic acute regulatory (StAR) protein mutations	11	100%	72.7%	81.8%	0.192
3β-Hydroxysteroid dehydrogenase deficiency (3βHSD)	9	88.9%	55.6%	55.6%	0.223
P450 oxidoreductase deficiency (PORD)	3	100%	0%	66.7%	NA
Androgen insensitivity syndrome (AIS)	13	84.6%	53.8%	76.9%	0.293
5α-Reductase deficiency	10	90%	40%	70%	0.080
17β-Hydroxysteroid dehydrogenase deficiency (17βHSD)*	13	100%	53.8%	61.5%	0.019
Androgen-producing tumor	19	89.4%	68.4%	73.7%	0.376
Polycystic ovary syndrome (PCOS)*	12	100%	58.3%	83.3%	0.046
Hypercortisolism	10	100%	70%	90%	0.286
Total* (all the above DSD cases)	153	94.1%	64.7%	77.1%	<0.001

* indicates $P<0.05$; NA indicates that no result was calculated in PORD due to the limited number of cases.

manifestations in the endocrinology department of PUMCH were searched from the hospital information system, covering 2012 to 2019. They were set as the verification samples. Nine of the most common DSD-related diseases were included (Table 1) [6]. Ninety-nine patients were diagnosed with CAH: 23 patients with 21OHD, 10 patients with 11β-hydroxylase deficiency, 20 patients with 17-hydroxylase deficiency, 11 patients with steroidogenic acute regulatory protein mutations, 9 patients with 3β-hydroxysteroid dehydrogenase deficiency (3βHSD), 10 patients with 5α-reductase deficiency, 13 patients with 17β-hydroxysteroid dehydrogenase deficiency (17βHSD), 3 patients with P450 oxidoreductase deficiency (PORD), and 13 patients with androgen-insensitivity syndrome (AIS). For each disease, 10 cases were randomly selected for testing. When fewer than 10 cases existed for a disease, all available cases were tested. Moreover, patients with androgen-producing tumors (n = 19), PCOS (n = 12), and hypercortisolism (n = 10) were selected as the control group for the differential diagnosis of DSDs.

Diagnostic performance

A total of 153 patients with possible DSD manifestations were tested to verify the efficacy of the DUCG diagnostic

system. Although all cases of monogenic diseases were confirmed by genetic diagnosis, we did not provide genetic data in the process of verifying the efficacy of the DUCG diagnostic system. The total diagnostic accuracy of the DUCG system was 94.1%, and the diagnostic process took 1–3 s. For some extremely rare cases of DSDs, such as AIS and 3βHSD, the diagnostic accuracy of the DUCG model was relatively low (84.6% and 88.9%, respectively). In comparison, the total diagnostic accuracy of interns and third-year residents in the endocrinology department was 64.7% and 77.1%, respectively, which were substantially lower than that of the DUCG diagnostic system. For the extremely rare cases, the diagnostic accuracy of interns and residents was also considerably lower than that of the DUCG diagnostic system. Moreover, the diagnostic process took an average of 29 s for interns and 20 s for third-year residents. Significant differences in diagnostic accuracy were observed for cases of 17βHSD ($P = 0.019$), PCOS ($P = 0.046$), and all cases as a total ($P < 0.001$) among the three methods.

Discussion

As a newly developed AI diagnostic system, the DUCG model has been increasingly and widely applied in the field of clinical medicine. In 60 cases of 18 different vertigo-related diseases, Dong *et al*. found that the diagnostic accuracy of the DUCG model was 88.3% and 81.7% with complete and incomplete medical information, respectively, which were considerably higher than those of junior and senior physicians [14]. Furthermore, in 203 cases covering 27 jaundice-related diseases, Hao *et al*. reported that the accuracy of the DUCG diagnostic system was 99.01% and 84.73% with or without laboratory tests, respectively, and the system increased the diagnostic efficacy and accuracy [19]. Recently, Bao *et al*. stated that the average diagnostic accuracy of the DUCG model was 94% for 139 clinical cases of 17 sellar diseases [20]. The results of these studies indicate that the DUCG technology can be feasibly used in diagnosing clinical diseases.

At present, AI has been increasingly used for disease diagnosis and treatment, but the application of AI in the diagnosis of rare diseases mainly involves facial recognition [21]. However, DSDs are difficult to diagnose via facial recognition and require diagnosis by using complete symptomatic, physical, and laboratory data. Furthermore, more than 5 to 10 years of training may be required for an experienced physician to have the ability to manage DSDs. As demonstrated by the present study, the DUCG technology can also be applied to diagnose rare DSDs.

In this study, the diagnostic accuracy of the DUCG model was 94.1% for 153 cases of nine DSD-related diseases and three non-DSD-related diseases, whereas the accuracy of interns and third-year residents in the endocrinology department were 64.7% and 77.1%, respectively. Thus, even if the data were given to residents or interns, the test results may not be perfectly judged to diagnose the disease accurately. Therefore, a considerable number of patients may have been delayed, missed, or incorrectly diagnosed, and they need help from experts on DSDs to obtain a correct diagnosis. DUCG can be a feasible approach to address the lack of experts on DSDs. A remarkable difference in diagnostic accuracy was found among the three diagnostic groups. The DUCG model was based on the knowledge and experience of experts on DSDs. Hence, when given multiple symptoms and signs, the DUCG model will provide 3–5 possible diagnoses ranked according to probabilities. The advantages of more accurate diagnoses provided by the DUCG model are evident. In addition, the DUCG model has a great advantage in terms of the time required to achieve a diagnosis. The diagnostic process took only 1–3 s with the DUCG model, but it took 29 s and 20 s for interns and third-year residents, respectively. The DUCG model greatly improved the accuracy of the diagnosis, shortened the time and process to obtain a diagnosis, and reduced the cost of medical management for patients. In most cases of DSDs, an early and accurate diagnosis and early treatment can substantially improve patient prognosis, including both physical and psychological prognoses.

DSDs cover a variety of diseases. However, our study does not include all of these diseases, especially considering that some DSDs are extremely rare and that sex chromosome DSDs can be easily identified by chromosome detection in certain cases. Therefore, sex chromosome DSDs were not included in this diagnostic model. The DUCG system must be further improved for diagnosing certain very rare DSD diseases. Moreover, a few DSD diseases cannot be accurately diagnosed because the causes of these DSD diseases have clinical symptoms that resemble other conditions and because laboratory examinations lack specificity. Thus, comprehensive diagnostic assessments and advanced technologies, including genetic detection, are needed to accomplish a correct diagnosis. Nevertheless, before obtaining the final diagnosis, further examinations that are needed can be derived from the knowledge base of the DUCG model. The DUCG system can present possible diagnoses and also recommend further corresponding examinations to physicians. We will discuss these aspects in another paper. The advantages of the DUCG model are notable. The DUCG model is an excellent computer-aided diagnostic tool to assist physicians in primary care hospitals. This model can improve their ability to recognize DSD-related diseases early, thus providing patients with an appropriate referral to experts on DSDs for better management.

However, the DUCG model also has several deficiencies. DSDs cover various diseases, and we included only

nine relatively common diseases that are the most frequently observed by experts on DSDs in clinics. Certain rare or unknown diseases may not be diagnosed from the inference engine of the DUCG model, the knowledge base of which still needs to be expanded in the future.

Conclusions

The DUCG model has the characteristics of low-parameter dependence and graphical representation, which are beneficial for the application of this model for medical diagnostics in primary care settings. At present, DUCG diagnostic models are seldom used to diagnose rare diseases. However, this diagnostic system for rare DSD diseases has higher accuracy and efficacy than interns and third-year residents who lack special training. Additionally, the model can provide a recommendation for the next investigatory step. In summary, the DUCG diagnostic model is a promising tool for diagnosing rare diseases, and its application is worth promoting. However, more cases need to be verified, and the DUCG system, including its knowledge base, must be improved. We believe that the application of the DUCG model would further improve patient prognosis and reduce the burden on public health care resources.

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Compliance with ethics guidelines

Dongping Ning, Zhan Zhang, Kun Qiu, Lin Lu, Qin Zhang, Yan Zhu, and Renzhi Wang declare that they have no potential conflicts of interest associated with this manuscript. All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000 (5). Informed consent was obtained from all patients included in the study.

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