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ORIGINAL

Development and validation of a new artificial intelligence tool (GeneClin) for the clinical diagnosis of genetic diseases

Desarrollo y validación de una nueva herramienta de inteligencia artificial (GeneClin) para el diagnóstico clínico de enfermedades genéticas

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ABSTRACT

Introduction: advances in the field of Artificial Intelligence (AI) and Machine Learning (ML) have considerable potential to improve the diagnosis and management of rare genetic diseases, due to the human inability to memorize information on a multitude of these diseases, which AI tools could store, analyze and integrate.
Objective: to develop and validate a new AI tool for the clinical diagnosis of genetic diseases.
Method: a prospective, cross-sectional, analytical, observational study was conducted at the application level, with a qualitative-quantitative approach and contributing to a technological development project. It was characterized by four stages: selection of the AI tool, selection of the knowledge base, development of the virtual assistant, validation process and implementation in the clinic.
Results: a total of 246 patients with genetic diseases and congenital defects were evaluated. The most predominant genetic category was monogenic genetic syndromes with 223 patients who attended the consultation (90,7 %). A success rate of 84,1 % was obtained and a success/no success ratio of 4,34. The highest percentage of successes was achieved in monogenic or Mendelian syndromes. There were no significant differences between successes and failures in both chromosomal aberrations and congenital defects of environmental etiology.

Conclusions: through this research, an AI virtual assistant has been validated for the clinical diagnosis of genetic diseases with a high percentage of effectiveness of 84 %, which confirms its usefulness to support the clinical diagnosis of cases with genetic diseases.

Keywords: Artificial Intelligence; Virtual Assistant; Rare Diseases; Genetic Diseases; Diagnosis.

RESUMEN

Introducción: los avances en el campo de la Inteligencia Artificial (IA) y el Aprendizaje Automático (AA) tienen un potencial considerable para mejorar el diagnóstico y la gestión de enfermedades genéticas raras, debido a la incapacidad humana de memorizar información de la multitud de estas, que las herramientas de IA podrían almacenar, analizar e integrar.
Objetivo: desarrollar y validar una nueva herramienta de IA para el diagnóstico clínico de enfermedades genéticas.
Método: se realizó una investigación observacional analítica transversal y prospectiva, del nivel aplicativo, con un enfoque cuali-cuantitativo y que tributó a un proyecto de desarrollo tecnológico. Se caracterizó por cuatro etapas: selección de la herramienta de IA, selección de la base del conocimiento, desarrollo del asistente virtual, proceso de validación e implementación en la clínica.
Resultados: se evaluaron un total de 246 pacientes con enfermedades genéticas y defectos congénitos. La categoría genética que más predominó fueron los síndromes genéticos monogénicos con 223 pacientes que asistieron a consulta (90,7 %). Se obtuvo un 84,1 % de aciertos y un índice de aciertos/no aciertos de 4,34. El mayor porcentaje de aciertos se alcanzó en los síndromes monogénicos o mendelianos. No existieron diferencias significativas entre los aciertos y no aciertos tanto en las aberraciones cromosómicas como en los defectos congénitos de etiología ambiental.
Conclusiones: a través de la presente investigación se ha validado un asistente virtual de IA para el diagnóstico clínico de enfermedades genéticas con un porcentaje elevado de efectividad de un 84 %, lo que confirma su utilidad para apoyar el diagnóstico clínico de casos con enfermedades genéticas.

Palabras clave: Inteligencia Artificial; Asistente Virtual; Enfermedades Raras; Enfermedades Genéticas; Diagnóstico.

INTRODUCTION

Medical care has advanced with rapidly developing technologies known as artificial intelligence (AI) and machine learning (ML). AI is the ability of machines to perform operations that usually require human intelligence, such as learning, problem-solving, and decision-making. At the same time, ML, as a subset of AI, is the ability of machines to learn from experience and improve their performance without being explicitly programmed. Both tools can help doctors optimize and speed up the time for disease diagnosis, treatment, and management.[1]

In recent years, these systems have been helpful for the early, rapid, and efficient diagnosis, management, and treatment of rare genetic diseases (RGD) by compiling information networks and registries to diagnose new cases.[1,2]

More than 7 000 rare diseases have been described, with a prevalence ranging from less than 1 in a million to more than 1 in 10 000.[3]

In total, it is estimated that between 263 and 446 million people suffer from rare diseases all over the planet, affecting an estimated 8 to 10 % of the world's population, and all of them face numerous challenges such as late or erroneous diagnosis, no response to therapies, worsening symptoms and the appearance of complications. About diagnosis, the overlapping of clinical characteristics and the lack of molecular data further complicate this process.[3,4]

Despite these obstacles, impressive technological developments, such as advanced sequencing techniques, next-generation sequencing, and "omics" technologies, have substantially improved diagnostic capacity. However, this has been accompanied by a significant increase in the volume of data (big data), which is impossible for humans to handle and requires selection, analysis, and integration processes. Suppose we add to this evidence the increase in genetic syndromes, which are impossible to memorize. In that case, it becomes clear how AI, particularly ML, emerges as a powerful tool to address these challenges.[3,4,5]

ChatGPT and the GPT Projects, based on AI, are presented as innovative solutions with the potential to revolutionize the practice of clinical genetics worldwide. These tools, which take advantage of natural language processing and ML, offer doctors the ability to analyze genetic syndromes and other clinical alterations more efficiently, generate clear and accessible summaries of complex information, and obtain support in interpreting genetic variants, among other applications.[6,7]

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Current uses of AI in medical and clinical genetics include the clinical and molecular diagnosis of genetic syndromes, in this case, identifying phenotypes associated with rare genetic syndromes using facial recognition algorithms and clinical analysis. In interpreting genomic variants, classification algorithms are used to determine the clinical relevance of genetic variants through complementary databases such as ClinVar and Human Gene Mutation Database (HGMD). In the prediction of genetic risks, polygenic risk models for diabetes, cancer, and cardiovascular diseases have been created. In the identification of structural variants through the detection of deletions, duplications, and inversions in genomic sequencing, among other applications.[8,9]

Even though medical thinking and ethical-professional responsibility are considered fundamental elements in diagnosing genetic diseases and congenital disabilities, they must be accompanied by AI for time optimization and self-learning. Although tools exist to make this process viable, they are still insufficient. They must be adjusted to the specific objectives pursued in each country's clinical diagnosis of genetic diseases. The scientific problem is: how can an AI tool be developed for the clinical diagnosis of genetic diseases?

This article aims to develop and validate a new AI tool for the clinical diagnosis of genetic diseases.

METHOD

Type of study

A cross-sectional, prospective, observational and analytical study was carried out at the application level, with a qualitative-quantitative approach, which contributed to a technological development project.

Stages of the investigation

Figure 1 shows the stages of the research process. First, the AI platforms for developing the virtual assistant were selected. In the second stage, 55 clinical geneticists were selected to choose the key scientific literature based on the functionality of the virtual assistant and that they were experts in the validation process. In the third stage, the virtual assistant was developed. In the fourth stage, the assistant was validated. Finally, it was implemented in clinical practice to support clinical diagnosis.

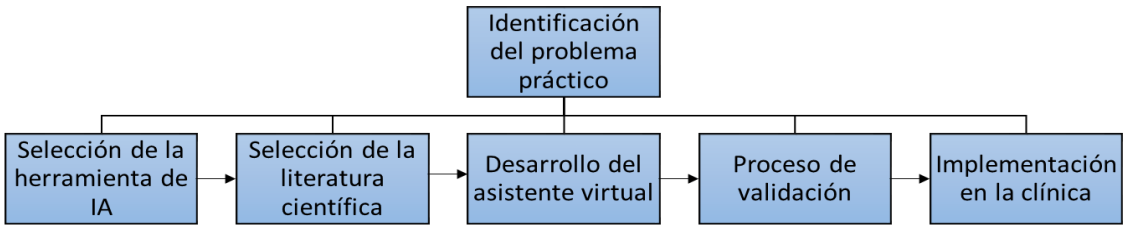

Figure 1. Flowchart of the research

Stage 1: Selection of the AI tool

The virtual assistant was developed using the Taskade platform, an AI-based tool with GPT-4 technology, which enables project management, task integration, note-taking, and real-time communication. Its intuitive interface facilitated the coordination of multidisciplinary teams, the automation of workflows, and the optimization of collaboration, enabling the efficient integration of bibliographic resources and clinical data.[10,11]

Stage 2: Selection of the scientific literature

To strengthen the assistant's capacity for interpreting genetic variants and recognizing rare syndromes, specialized databases such as OMIM[12], ClinVar[13] and GeneReviews[14] were integrated, thus guaranteeing access to updated and validated information.

The resources that make up the assistant's knowledge base are listed below.

- The Bedside Dysmorphologist: classic clinical signs in Human Malformation Syndromes and Their Diagnostic Significance.
- The Encyclopedia of Genetic Disorders and Birth Defects. James Wynbrandt y Mark D. Ludman.
- Smith's Recognizable Patterns of Human Malformation
- Inborn Metabolic Diseases: diagnosis and treatment.
- Inherited Metabolic Diseases: a clinical approach.
- Inborn Errors of Metabolism: from neonatal screening to treatment.
- Gale Encyclopedia of Genetic Disorders.
- Atlas of Genetic Diagnosis and Counseling.
- Genética Pediátrica (Scanned Resource)
- Gale Encyclopedia of Genetic Disorders.
- Atlas of Genetic Diagnosis and Counseling.
- GeneReviews.
- Genetics Home Reference (MedlinePlus Genetics).

- PubMed.
- HGNC (HUGO Gene Nomenclature Committee).
- ClinVar.
- Orphanet.
- GARD (Genetic and Rare Diseases Information Center).
- Decipher.
- Human Phenotype Ontology (HPO). +

Stage 3: Development of the virtual assistant

To evaluate the accuracy of the assistant, its responses were compared with clinical descriptions documented in the Atlas of Genetic Diagnosis and Counseling[15] and the Gale Encyclopedia of Genetic Disorders.[16] The relevance algorithms were adjusted based on epidemiological criteria and expert consensus. In addition, to guarantee an ethical and humanized approach to emotional counseling, protocols from Genetics Home Reference[17] and the World Health Organization (WHO) guidelines were implemented.[18]

In the implementation phase, advanced Natural Language Processing (NLP) tools were incorporated to interpret complex queries, supported by algorithms from specialized databases such as Decipher[19] and Orphanet.[20]

Stage 4: Validation process

For the validation process of the assistant, a quantitative and a qualitative component were considered. Both involved 55 international geneticists who identified essential needs in genetic counseling through focus groups and expert panels. Among the key aspects, the standardization of phenotypic terms using the Human Phenotype Ontology (HPO)[21] stood out, as well as the correlation of genetic data with clinical manifestations described in prestigious references such as The Bedside Dysmorphologist[22] and Smith's Recognizable Patterns of Human Malformation.[23]

The application was used in postnatal clinical genetics consultations, prenatal genetics consultations, and the educational teaching process with doctors studying the specialty.

The classification of genetic diseases took into account three categories: monogenic syndromes, chromosomal aberrations, and multifactorial disorders. Additionally, congenital disabilities induced by teratogenic factors of an environmental nature were included.

In the validation process, it was allowed to have a retrospective and a prospective sense. In the retrospective sense, the medical records of patients seen were reviewed, with or without a diagnosis, and in the prospective sense, the new cases that attended the consultation were reviewed, with or without a diagnostic impression.

For quantitative validation, each specialist was given a form to fill in with the data provided and follow the instructions for completion.

For qualitative validation, each evaluator was asked for their opinion on functionality, ease of use, speed, accuracy, and collaboration.

Operationalization and definition of variables

A total success was considered to be when the assistant reported the diagnosis among the first five answers.

A partial success was considered to be when the syndromic diagnosis was found from the sixth option onwards.

A failure was considered to be when the assistant did not offer the correct diagnosis from any of the options offered.

For qualitative validation, the following variable definitions were taken into account:

- Functionality: capacity to perform tasks related to genetic testing.
- Ease of use: intuition and learning curve.
- Speed: time needed to complete tasks.
- Accuracy: level of detail and reliability of results.
- Collaboration: possibility of sharing results with other users.

Information processing techniques

Once the specialists had sent their tables, a database was created in Excel and exported to version 29 of the Statistical Package for the Social Sciences (SPSS) in order to create the corresponding tables related to the validation process.

Statistical methods

Descriptive statistics (absolute frequency and percentage) were applied to ordinal qualitative variables (such as the level of accuracy) and nominal variables (such as the classification of genetic disease, the name of the disease, and the expert).

The index of correct/incorrect answers was obtained, considering partial accuracy in the first category. A series of hypotheses of difference of proportions for mutually exclusive samples from a group was carried out to demonstrate significant differences in the percentage of correct answers for each category of genetic disease, as well as a Fisher's exact test to determine a possible relationship between the category of genetic disease and the percentage of correct or incorrect answers. For this, a level of statistical significance of α=0,05 was taken into account. The Odds Ratio (OR) was estimated as a measure of the magnitude of the association, as well as its 95 % confidence interval (95 % CI).

Information presentation techniques

Frequency distribution tables, tetrachoric tables to relate variables and grouped bar charts were used.

Ethical considerations

The development of the assistant was carried out in strict compliance with international privacy regulations, such as the General Data Protection Regulation (GDPR), in addition to considering specific ethical principles in genetics.[24] The ethical challenges of artificial intelligence in the medical field were also analyzed, following the recommendations of Genetic Editing and Artificial Intelligence: ethical challenges.[25]

The ethical principles of autonomy were taken into account in the case of the experts' participation, who offered their informed consent to participate in the research.

Beneficence and non-maleficence verify in incident and prevalent cases without a diagnosis that the genetic diagnosis offered by the assistant is accompanied by an exhaustive professional evaluation using the clinical method as the gold standard for issuing the diagnosis.

In the case of prevalent cases with diagnoses issued, the only purpose is to verify the assistant's level of accuracy. Their attending physician handled the patients' data, whose identities were not revealed.

The model was trained using anonymous case reports and bibliographic records of genetic syndromes, which allowed phenotypes to be correlated with diagnoses.

RESULTS

Of the 55 experts selected to validate the instrument, 12 geneticists (21,81 %) submitted their validation reports, evaluating a total of 246 patients with genetic diseases and congenital defects. The most predominant genetic category was monogenic genetic syndromes, with 223 patients attending consultations (90,7 %) (table 1).

Table 1. Diseases validated in the assistant according to their classification

Classification of genetic disease		Frequency	Percentage	Valid percentage	Cumulative percentage
Valid	Chromosomal aberration	17	6,9	6,9	6,9
	Congenital defect of environmental etiology	6	2,4	2,4	9,3
	Monogenic disease	223	90,7	90,7	100,0
	Total	246	100,0	100,0	

Of the genetic diseases analyzed, those that predominated in frequency with 7 (23,8 %) and 4 (1,6 %) cases were Sotos syndrome, Turner syndrome, Ehlers Danlos syndrome, Duchenne Muscular Dystrophy and Tuberous Sclerosis Complex respectively. The rest of the syndromes were frequently found to be below four.

An 84,1 % accuracy rate and an accuracy/inaccuracy rate of 4,34 were obtained; that is to say that for every four correct diagnoses the assistant missed one genetic diagnosis (table 2).

Table 2. Overall success rate of the AI virtual assistant for the diagnosis of genetic diseases

		Frequency	Percentage	Valid percentage	Cumulative percentage
Valid	I can't get it right	39	15,9	15,9	15,9
	Partial success	7	2,8	2,8	18,7
	Total Success	200	81,3	81,3	100,0
	Total	246	100,0	100,0	

If we take into account the percentage distribution of correct answers according to the expert, it is clear that in all cases the percentage was high (figure 2).

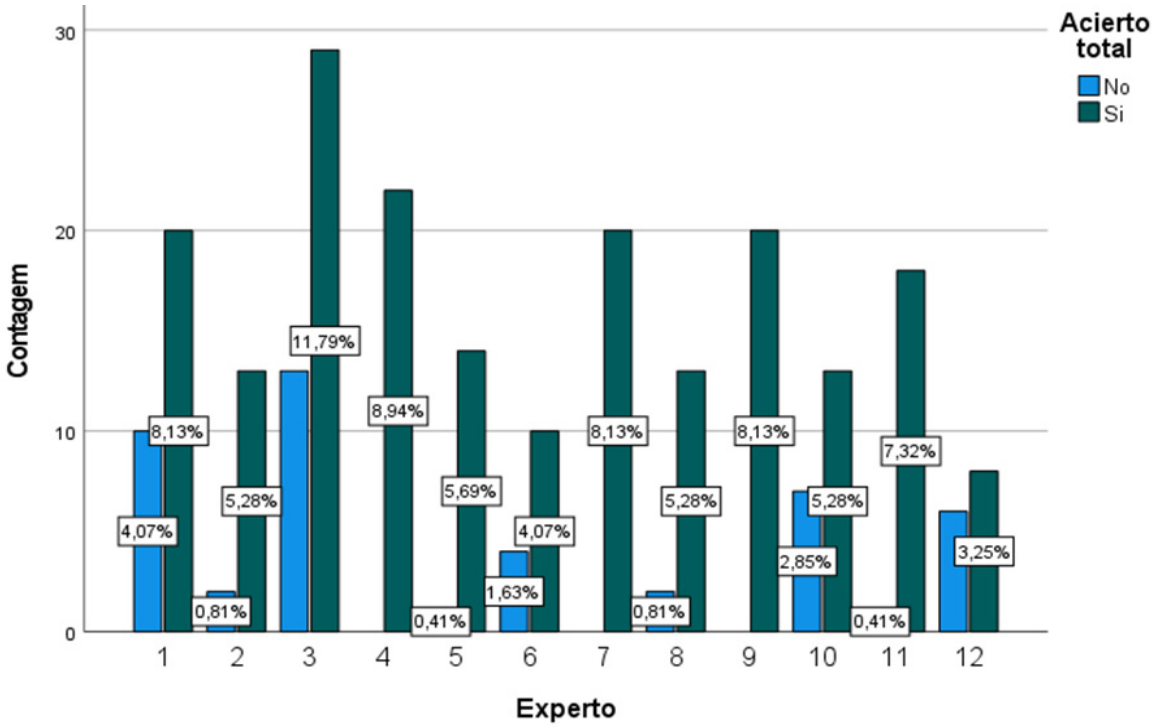

Figure 2. Percentage distribution of correct and incorrect answers according to the expert

If the diagnostic effectiveness of the assistant is taken into account, according to the category of genetic disease, it was evident that the highest percentage of correct diagnoses was achieved in monogenic or Mendelian syndromes, and chromosomal aberrations and congenital disabilities achieved the lowest percentages. Of the inborn errors of metabolism tested with the assistant, the majority did not reach a correct diagnosis. (Table 3)

There were no significant differences between the correct and incorrect diagnoses for either chromosomal aberrations or congenital disabilities of environmental etiology; however, there were significant differences for monogenic syndromes and overall, which shows the effectiveness of the assistant in supporting the diagnosis of monogenic diseases.

To demonstrate whether the number of correct answers was related to the category of monogenic syndromes, table 4 shows a significant p-value from Fisher's exact test, which means that if the patient presents a monogenic syndrome, the assistant is five times more likely to diagnose it when compared to a chromosomal aberration or congenital disability of environmental etiology.

Table 3. Effectiveness of the assistant according to the type of genetic disease

Classification of genetic disease			Total success		P* value	Total
			No	Yes		
	Chromosomal aberration	Absolute frequency	8	9	0,40	17
		% in total accuracy	17,4 %	4,5 %		6,9 %
	Congenital defect of environmental etiology	Absolute frequency	3	3	0,13	6
		% in total accuracy	6,5 %	1,5 %		2,4 %
	Absolute frequency	Absolute frequency	35	188	<0,001	223
		% in total accuracy	76,1 %	94,0 %		90,7 %
Total		Absolute frequency	46	200	<0,001	246
		% in total accuracy	100,0 %	100,0 %		100,0 %

Note: *Hypothesis Test of difference of two mutually exclusive proportions of a group

In relation to qualitative validation, in terms of functionality, the experts considered it to be an excellent tool for the planning and monitoring of healthcare and teaching activities, real-time collaboration, moderate speed, high precision in terms of clinical analysis, and, finally, very intuitive for organizational tasks.

Table 5 shows the effectiveness in the percentage of the application validated in the present investigation with others reported in the literature, where differences are evident between them.

Table 4. Distribution of the sample according to disease classification and total accuracy. Results of Fisher's Exact Test

Classification of genetic disease		Total success		Total
		No	Yes	
Non-monogenic diseases	Absolute frequency	11	12	23
	% in total accuracy	23,9 %	6,0 %	9,3 %
Monogenic disease	Absolute frequency	35	188	223
	% in total accuracy	76,1 %	94,0 %	90,7 %
Total	Absolute frequency	46	200	246
	% in total accuracy	100,0 %	100,0 %	100,0 %

Note: P value of Fisher's Exact Test: p=0,0008. OR=4,92- 95 % CI (2,01-12,04))

Table 5. Comparison of the effectiveness of the GeneClin virtual assistant for the diagnosis of rare diseases with other AI tools described in the literature

Tool	Effectiveness (%)	Comments
GeneClin	84,1	Useful for relatively frequent monogenic syndromes that are not heredometabolic diseases, with room for improvement and analysis of genomic molecular results.
DeepVariant	95-97	Very precise in the detection of variants, but depends on the quality of the data.
Face2Gene	91-96	Effective for syndromes with distinctive phenotypes.
Phenomizer	85-90	Useful for prioritizing candidate genes, but less effective in atypical cases.
CADD	90-92	Good for classifying variants, but less accurate in VUS.
REVEL	93-95	High precision in rare variants and Mendelian diseases.
Raremark	80-85	It reduces diagnosis time, but depends on the availability of data.
UDN	35-50	Effective in complex cases, but still has room for improvement.

DISCUSSION

The overall effectiveness obtained was due to the fact that the system failed to accurately diagnose some inborn metabolic errors, chromosomal aberrations, congenital defects of environmental etiology, and rare monogenic diseases. Therefore, it is open to improvement in the sense of incorporating specialized scientific literature in these categories.

However, it is assumed that because it is indexed to the OMIM, even if the syndrome is novel, it should be on the list of genetic syndromes offered by the assistant, as it is a constantly updated database, hence the fact that specialists are trained in the definition of mandatory signs or the standardized vocabulary of phenotypic anomalies found on the Human Phenotype Ontology site (https://hpo.jax.org/).[21]

This database contains more than 18 000 terms and more than 156 000 annotations on hereditary diseases. The HPO, as part of the Monarch Initiative, is a central component of one of the 13 projects driving the strategic roadmap of the Global Alliance for Genomics and Health. This database is embedded in the virtual assistant.

In the case of inborn errors of metabolism, it has been shown that AI can analyze metabolic profiles to diagnose diseases such as glutaric aciduria type I, a rare condition that affects amino acid metabolism. Still, the assistant developed in the present research does not have that algorithm, nor is it its objective.

In this sense, a thorough analysis of the vocabulary used in the different books on hereditary metabolic diseases should be carried out to offer a prompt that aims to refine the diagnosis and incorporate reference books on inborn errors of metabolism.

When comparing the effectiveness of the GeneClin tool with others described in the literature, the following characteristics are described:

DeepVariant is a tool based on deep neural networks that detect genetic variants from sequencing data. In terms of its effectiveness, it has demonstrated an accuracy of 99,7 % in the detection of single nucleotide variants (SNVs) and 98,3 % in the detection of insertions and deletions (indels) in whole genome sequencing (WGS) data. Its effectiveness in identifying pathogenic mutations is around 95-97 % for rare diseases, depending on the case's complexity.[26]

Face2Gene (FDNA) is a platform that uses AI and facial recognition to identify rare genetic diseases based on phenotypic characteristics. It showed 91 % accuracy in identifying rare genetic syndromes based on facial features. For specific syndromes, such as Cornelia de Lange syndrome, accuracy can reach up to 96 %.[27]

Phenomizer is a tool that uses AI to analyze clinical phenotypes and suggest genetic diagnoses. It has an 85-90 % accuracy in prioritizing candidate genes for rare diseases. Its effectiveness can decrease to 70-75 % in complex cases, especially when phenotypes are atypical.[28]

CADD (Combined Annotation Dependent Depletion) uses AA to predict the functional impact of genetic variants. CADD has an accuracy of 90-92 % in classifying pathogenic versus benign variants. For variants of uncertain significance (VUS), its effectiveness is 80-85 %.[29]

REVEL (Rare Exome Variant Ensemble Learner) is an AA algorithm that combines multiple tools to predict the pathogenicity of rare variants. It is 93-95 % accurate in identifying pathogenic variants in rare diseases. It is particularly effective in classifying variants in genes associated with Mendelian diseases.[30]

Raremark is a platform that uses AI to connect patients with rare diseases and facilitate diagnosis. It has helped reduce diagnosis time by 30-40 % for patients with ultra-rare diseases. Its accuracy in identifying candidate genes is 80-85 %.[31]

UDN, which stands for Undiagnosed Diseases Network Project, is an initiative in the United States that uses AI to analyze genomic and clinical data from patients with undiagnosed diseases. AI has identified mutations responsible for rare diseases in several cases, enabling accurate diagnoses. The UDN has diagnosed 35-40 % of previously unresolved cases. In some disease subgroups, such as metabolic diseases, the diagnosis rate can reach 50 %.[32]

When comparing the tool's overall effectiveness with others in the literature, it is similar to Phenomizer and Raremark, the only two with similar purposes (table 6).

The rest of the applications have higher percentages than GeneClin, such as Face2Gene, CADD and REVEL; and higher than UDN, whose purpose is to work with genomic data.

When evaluating the effectiveness of the assistant according to the category of genetic disease, it turned out to be higher in monogenic and Mendelian diseases. This is probably due to the fact that the largest percentage of the scientific literature that forms part of the assistant's knowledge base is specialized for this category of genetic diseases, with OMIM standing out as a site indexed to the assistant.

Among its advantages, this assistant issues a greater number of diagnostic suggestions than other AIs and integrates multiple projects and users. However, it does not allow the generation of clinical data, requires manual configurations to structure complex tasks, and depends heavily on the details of the clinical signs entered to generate results.

With the tool used in the present research, GeneClin, it has been possible to consult variants of uncertain significance in an exome by Next-Generation Sequencing of clinical cases. The assistant carried out the relevant analysis, obtaining diagnostic possibilities, which is an advantage for the geneticist.

Finally, ethical dilemmas are highlighted in the management of AI for the purpose of diagnosing genetic diseases. Firstly, the accessibility and payment of these diagnostic tools; secondly, the neglect of the clinical method and the failure to achieve a critical analysis of what the assistant reports about the patient in terms of clinical diagnosis and therapeutic conduct. Last, the inability to consider the molecular results of "omic" technologies could clarify the diagnosis in many diseases with variable phenotype expressivity.

Challenges remain to be developed, such as inserting the database of genetic variants and their relationship with different diseases to consult molecular results. However, it is issued to prepare educational information sheets according to the diagnosis, among other aspects.

It is worth emphasizing that the assistant can never replace the ethical and professional responsibility, clinical thinking, and expertise of the specialist in case management. However, the assistant can be considered a tool that could assist the work of the clinical geneticist in healthcare, teaching, and academic activities.

It is recommended that the virtual assistant be implemented in teaching and care activities and that books dealing with chromosomal aberrations and inborn errors of metabolism be incorporated. The validation process should be continued until 3000 cases viewed with the assistant have been completed.

A bright present and future is in the application of AI tools in genetics. Development in this sense is incipient and will require drawing up ethical regulations on its use to diagnose genetic diseases.

Research limitations

It is important to consider that most of the experts presented problems of access to the virtual assistant, and of connectivity, which interfered with the sending of validation results in 100 % of them.

CONCLUSIONS

Through the present research, a virtual AI assistant has been developed and validated for the clinical diagnosis of genetic diseases. It is highly effective, which confirms its usefulness in supporting the clinical diagnosis of cases with genetic diseases.

Effectiveness is increased in Mendelian diseases and not in the rest of the classifications due to the link established with the OMIM site and that most of the books inserted correspond to monogenic syndromes.

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CONFLICT OF INTEREST

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