RDmaster: a novel phenotype-oriented Q&A dialogue system assisting differential diagnosis of rare diseases

# Abstract

Differential diagnosis of rare diseases (RDs) is clinically urgent due to their complex and overlapping phenotypic features, yet few relevant studies. To address this gap, we propose RDmaster, a phenotype-oriented Q&A dialogue system that endeavors to collect additional phenotypes and aid clinicians in the differential diagnosis of RDs. Two Bayesian diagnostic approaches, PheLR and LIRICAL are integrated into RDmaster to improve clinical interpretability. To achieve an efficient dialogue strategy, we introduce a novel metric called Adaptive Information Gain and Gini Index (AIGGI) to evaluate the expected gain of interrogated phenotypes within real-time diagnostic states. An extensive simulation evaluation has validated the rationality of our dialogue strategy from multiple perspectives. A trial involving 238 published patients reveals that RDmaster outperforms most competing tools and can enhance diagnostic accuracy through Q&A. We also innovatively compare the performance of professional diagnostic tools and large language models in generating differential diagnosis lists for RDs. RDmaster has been implemented as an online web-based platform and offers clinicians exceptional visualization support for RD diagnosis.

# Introduction

Rare diseases (RDs), mostly genetic in nature, are defined by the World Health Organization (WHO) as conditions or disorders that affect a prevalence of less than 6.5-10 in 10,000 individuals [1]. Despite being referred to as “rare”, there are over 7,000 RDs that collectively affect tens of millions of people in the general population, creating a pressing clinical demand for RD diagnosis and treatment [2, 3]. RDs pose a great challenge for the clinical interview and further diagnosis due to their low individual frequency, complex genetic profiles, and the high heterogeneity and overlap of their phenotypic features [4, 5], which lead to many RD patients being misdiagnosed for years or remaining undiagnosed [6].

In clinical scenarios, the clinical interview is a vital step in the differential diagnosis (DDX) process, which plays a crucial role in decreasing diagnosis errors, enhancing diagnostic accuracy, and ultimately reducing healthcare costs [7, 8]. DDX involves conducting a systematic evaluation of the patient's symptoms and test results, comparing them to a list of potential diseases that can cause similar symptoms, and ultimately arriving at the correct diagnosis by narrowing down the possible options. The implementation of electronic differential diagnostic support (EDS) system for RDs is urgently needed for several reasons [9]. Firstly, unlike common diseases, clinicians often have limited experience in diagnosing RDs. Secondly, the wide variety and broad phenotypic overlap of RDs often present clinicians with multiple potential diagnoses. Lastly, realistic phenotype record often contains inaccurate descriptions and noise, and patients typically do not exhibit all symptoms of RDs they belong to, making clinical interviews challenging.

Currently, various knowledge bases (KBs) have been established to improve the management and treatment of RDs, such as OMIM [10], Orphanet [11], and Human Phenotype Ontology (HPO) [12, 13]. With the aid of these KBs, numerous diagnostic tools and algorithms have been developed to assist clinicians in accurately identifying the diseases and causative genes for RD patients [14-20]. Most of these tools utilize HPO to standardize patient signs and symptoms as input, sometimes supplemented by sequencing data in VCF format, and output a prioritized list (i.e., DDX list) of potential target diseases or disease-causing genes. The diagnostic pattern of these tools is to obtain a one-time diagnosis based on limited patient information, but it does not include subsequent differential diagnosis procedures in instances where multiple competing diagnoses exist, i.e., they are DDX generators (only generate a candidate list) rather than DDX executors [21].

Nowadays, artificial intelligence (AI) research is increasingly attracting attention in the field of medical diagnosis [22]. ChatGPT, which is a recently popular general chatbot based on the generative pre-trained transformer (GPT) architecture [23-25], has shown great potential in various domains, including assisting clinical diagnosis based on common chief complaints [26, 27]. However, these large language models (LLMs) cannot guarantee absolute correctness and lack authoritative credibility when conversing about specialized domain knowledge, and they have not been validated in the field of RD diagnosis. Many recent studies have explored reinforcement learning (RL) techniques for dialogue diagnosis, mainly the deep Q-network (DQN) algorithm [28], which simulate clinical interview in user-agent interaction to collect additional patient symptoms and thus improve diagnostic accuracy [29-31]. Specifically, the DQN algorithm calculates Q-values for candidate symptoms, which measure rewards for its agent asking for different symptoms. This approach represents an innovative way to assist DDX but has limitations when applied to RD diagnosis. One major limitation is the scarcity of conversation corpus for RDs. Additionally, most studies have only involved a few diseases and several dozens of symptoms, making it challenging to apply DQN to RDs due to the large scale of candidate diseases and phenotypic overlap. But the concepts of simulating clinical interviews and using agents to question symptoms based on calculated rewards have inspired us.

In this study, we present a novel EDS system assisting the differential diagnosis of rare diseases, referred to as RDmaster, which enables the capture of additional crucial symptoms beyond the patient's initial medical record through phenotype-oriented question-and-answer (Q&A). Two clinically interpretable algorithms based on the likelihood ratio paradigm are integrated into our system to support the multi-omics diagnosis of RDs [32-34]. We also propose a novel indicator, AIGGI, by reference to two classic decision tree construction metrics (information gain and Gini index) [35, 36], to measure the expected gain of our agent questioning phenotypes in real-time diagnostic status. RDmaster is implemented as an online web tool and provides good visualization support (http://rdmaster.nbscn.org/). We conducted a simulation experiment to qualitatively analyze our dialogue strategy and confirmed its rationality. We further carried out a comprehensive diagnostic test (on both phenomic and genomic) on a cohort of 238 online published RD patients and validated that: (i) our dialogue strategy is effective in collecting diagnostically beneficial symptoms and improving the prioritization of target diseases and causative genes; (ii) LLMs, particularly GPT-3.5 and GPT-4, shows promising performance in RD diagnosis and have tremendous potential; (iii) compared to many KB-based diagnostic tools and the state-of-the-art LLM (GPT-4), our system demonstrates significant advantages in diagnostic accuracy and differential diagnosis for RDs.

# Results

## RDmaster overview: clinical scenarios and workflow

RDs are numerous and usually present complex, overlapping phenotypic features, making the need for assisting DDX of RDs clinically important. To address this, we proposed an EDS system called RDmaster, which aims to capture diagnostically beneficial phenotypes (signs and symptoms) in the form of human-computer interaction and make a better diagnosis based on sequencing data and enriched phenotypic information.

An overview of RDmaster's workflow is illustrated in Fig. 1. The procedure begins with an initial clinical report, in which users report the patient's phenotypic abnormalities (expressed in HPO terms) and variation data in Variant Call Format (VCF) [37]. RDmaster then engages in a multi-round Q&A dialogue with users to collect additional phenotypes beyond their initial report. Each turn of the dialogue starts with asking users if the patient has a specific phenotype, to which users can respond with “*Yes*”, “*No*”, or “*Not sure*”. Users are also allowed to proactively report phenotypes during the conversation. The user’s response is then fed-back to our agent to update the diagnostic status and take further actions, i.e., our agent will make a diagnosis according to enriched patient information and continue questioning in the next turn. These human-computer interactions are facilitated through RDmaster's user interface (UI) module. RDmaster's core functionalities consist of an interpretable multi-omics diagnostic method and an efficient dialogue strategy, both of which are designed based on authoritative KBs and tools.

The current implementation of RDmaster can diagnose 4,257 rare diseases (including 2,380 rare genetic diseases), which collectively have 8,161 different phenotypic abnormalities annotated (an average of 26 annotations per disease). A total of 16,226 phenotypic abnormalities of HPO constitute the controlled vocabulary to normalize signs and symptoms of patients, of which 9,087 RD-related phenotypes are candidate questioning terms during Q&A.

## Implementation of RDmaster: an online dialogue diagnostic platform for RDs

RDmaster is implemented as an online web-based tool (http://rdmaster.nbscn.org/) that comprises two main steps: clinical information collection and dialogue diagnosis, as depicted in Fig. 2. The UI for clinical information collection consists of several components (Fig. 2a), including fields for patient age and gender, a file uploader for variant data in VCF format, and a character-matching input box that prompts for matched HPO terms as a drop-down list. The SciGraph, developed by the Monarch Initiative as an HPO annotator [38], has been integrated to annotate user-provided free text with HPO concepts. To provide a comprehensive description of patient phenotypic features, entered HPO terms can be flexibly organized as “Present Phenotypes” or “Absent Phenotypes”. Only the “Present Phenotypes” field is mandatory while other fields are optional. If a VCF file is uploaded, a phenotype-genotype integrated diagnosis will be performed. If not, RDmaster will conduct a phenotype-driven diagnosis. Upon completion of the initial report, users can proceed to the dialogue diagnosis step. The RDmaster's dialogue diagnosis is supported by comprehensive and multi-dimensional data visualization (Fig. 2b). The UI of this phase is mainly divided into four modules:

* Dialogue Q&A module (Fig. 2b, part 1), which facilitates human-computer interaction through phenotype-oriented Q&A. Users need to judge the interrogated phenotype in each round based on the patient's phenotype features and can also proactively report symptoms in free words. A three-layer network, constructed based on HPO hierarchy, is designed to illustrate the semantic relationship between the current interrogated phenotypes and top-10 ranked diseases.
* Disease evaluation module (Fig. 2b, part 2), which provides detailed phenotypic and genotypic (if a VCF file is uploaded) analysis results for the top-10 ranked diseases. Specifically, the analysis results mainly include the prior probability (evaluated by its point prevalence) and posterior probability of tested disease, the disease-patient phenotypic match ratio, and likelihood ratio scores of collected phenotypes and disease-causing genes.
* Diagnostic state module (Fig. 2b, part 3), which indicates the real-time diagnostic status, mainly includes a four-dimensional (the posterior probability and phenotypic match ratio of the first-ranked disease, the entropy and Gini index calculated from posterior probability distribution of all tested diseases) radar chart, where a larger area represents a lower diagnostic uncertainty.
* Patient phenotypic state module (Fig. 2b, part 4), mainly a sunburst chart of patient phenotype features drawn based on the HPO structure and annotation propagation rule [39].

These modules are updated in real-time during Q&A, leveraging Spring context and Caffeine caching technologies in our back-end service to reduce request/response time, allowing our agent to ask a new question within a few seconds after receiving user feedback. Detailed introduction of RDmaster online platform is included in Supplementary Note 1.

## Analysis of RDmaster's dialogue strategy

RDmaster's phenotype-oriented Q&A dialogue strategy aims to reduce diagnostic uncertainty and narrow possible diseases by simulating clinical interviews. During each turn of the dialogue, the phenotype with the greatest expected gain (indicated by our proposed AIGGI, see details in the Methods section) will be asked by our agent. To evaluate the validity and plausibility of our dialogue strategy, we designed simulation experiments and tested tens of thousands of cases to investigate the association between candidate phenotypes for interrogation and candidate diseases in different diagnostic statuses (use the Gini index calculated from the posterior probability distribution of candidate diseases to indicate diagnostic uncertainty, see Formula 5).

### A questioning strategy consistent with the differential diagnosis

The association between the interrogated phenotype and top-5 ranked candidate diseases within different diagnostic statuses is illustrated in Fig. 3a. When diagnostic uncertainty is high ( greater than 0.9), the interrogated phenotype has similar association scores with all top-5 ranked diseases. In this case, our strategy focuses on information gain, which helps minimize diagnostic uncertainty by selecting the phenotype with the highest differentiation of candidate diseases. As diagnostic uncertainty decreases ( less than 0.9 and more than 0.5), the top-ranked diseases start showing advantages over others. In this stage, our strategy tends to select phenotypes related to diseases in their ranking order to validate the patient's potential phenotype and accentuate the target disease. When diagnostic uncertainty is low ( less than 0.5), the first-ranked disease typically has a significant diagnostic advantage over others. In this situation, our strategy focuses on asking for phenotypes related to the second and lower-ranked diseases, with the expectation that users will exclude these phenotypes. Excluding crucial phenotypes of non-first diseases (especially the second-ranked disease) may improve diagnostic purity better than verifying phenotypes of the first-ranked disease in this phase. Overall, as the diagnostic status changes, our dialogue strategy can adaptively adjust to follow DDX by maximizing the expected Q&A gain.

### Two intention-considered questioning strategies

The default dialogue strategy of RDmaster, as indicated by AIGGI, is completely agent-dominated and may sometimes seem inflexible. To increase the flexibility of Q&A, two intention-considered indicators, AIGGI-P and AIGGI-N, were proposed as supplements to AIGGI. These indicators were further analyzed to reveal their effect on our questioning strategy, as shown in Fig. 3a. When using AIGGI-P to validate phenotypes, the strategy increasingly prioritizes phenotypes of the first-ranked disease as diagnostic uncertainty decreases. This is reasonable because validating phenotypes of the first-ranked disease is more likely to reduce diagnostic uncertainty compared to other diseases. Meanwhile, for AIGGI-N, which is designed to exclude phenotypes, as diagnostic uncertainty decreases, the disease with the highest association score with the questioned phenotype changes in the diagnostic ranking, from 5th to 4th and finally to 2nd, while the association score for the first-ranked disease decreases. This trend is reasonable when users intend to exclude phenotypes. Combining AIGGI-P and AIGGI-N with AIGGI can provide users with comprehensive and logical questioning strategies.

### KB-based prioritization of candidate phenotypes

The importance of disease-related phenotypes varies depending on their annotation frequencies to a particular disease. Specifically, for several competing diagnoses, related phenotypes annotated as high frequency are more valuable to be validated, excluded, or queried than those annotated as low frequency, which is encompassed in our dialogue strategy. We counted the association scores of the top 100 candidate phenotypes for interrogation with the top 5 candidate diagnoses in each initial dialogue turn under our proposed three indicators and different diagnostic states, as shown in Fig. 3b. Our questioning strategy generally prioritizes more diagnostically beneficial phenotypes which have higher association scores with candidate diseases, regardless of user intention. Detailed statistics of RDmaster's dialogue strategies is provided in Supplementary Note 3.

### A strategy implicating phenotypic hierarchical semantics: a case study

The application of the annotation propagation rule to our dialogue strategy makes it possible to imply phenotypic hierarchical semantic relationships beyond the disease-phenotype annotation file. We tested a published female patient (Patient No 8 in PMID:17056636) diagnosed with cardiofaciocutaneous syndrome [40], using all her phenotypic features as an initial report, without taking disease prevalence as the prior probability. In her DDX list, with is 0.50, the posterior probability of the first-ranked disease *Cardiofaciocutaneous syndrome* (ORPHA:1340) is 99% while the second-ranked disease *Autosomal recessive cutis laxa type 2, classic type* (ORPHA:357074) is 98%, which has an unreported phenotype *Delayed closure of the anterior fontanelle* (HP:0001476) annotated as always present, and the probabilities of other diseases are very low. Intuitively, excluding always-present phenotypes of the second-ranked disease would be most helpful in reducing diagnostic uncertainty in this situation, and our agent did rank it first. Meanwhile, in this turn, for the first-candidate phenotype, its two parent terms (*Abnormality of the anterior fontanelle* and *Delayed cranial suture closure*) are placed in the 2nd and 3rd positions, its two grandparent terms (*Abnormality of fontanelles* and *Abnormality of cranial sutures*) are 4th and 5th and its great-grandparent term (*Abnormality of the fontanelles or cranial sutures*) is 6th. When a phenotype is always present for a disease, its ancestor terms are also obligate. Therefore, our agent ranks *Delayed closure of the anterior fontanelle*'s ancestor terms at top positions in order of semantic distance, in case of users answer “*Not sure*” in this turn, then our agent will continue to ask its broader and more general ancestor terms.

## Diagnostic performance of RDmaster

A cohort of 238 online published rare disease patients was built to test the diagnostic performance of RDmaster, of which 225 cases had a rare genetic disease. A summary of collected cases is provided in Table 1. In the benchmarking performance of RDmaster, we introduced several competing approaches, including four phenotype-driven RD diagnosis tools (Phenomizer [14], BOQA [15], PhenoPro [20], and LIRICAL [34]), a previous state-of-the-art genomic analysis tool Exomiser [18, 41], and large language models GPT-3.5 and GPT-4.

### Dialogue diagnosis performance evaluation of RDmaster

We first tested the dialogue diagnostic performance (phenotype analysis only or combined with genotype analysis) of collecting additional patient phenotype information following our default dialogue strategy, i.e., calculating the expected gain of candidate interrogated phenotypes by our proposed AIGGI. For each patient, half of their phenotypic features were randomly chosen as an initial report (with or without variant data) with a phenotype-oriented multiple-turn Q&A dialogue performed without intention-considered. Ten experiments were performed for each case to consider the variance of the initial report in realistic clinical operations. During the Q&A dialogue, answer “*Yes*” to the patient's present phenotypes, “*No*” for excluded phenotypes, and answer “*Not sure*” if interrogated phenotype is not mentioned in the case report. In addition to analyzing the pre- and post-dialogue diagnostic performance of our approach, we also compared it with several competing tools in this benchmark.

For phenotype-only diagnosis, our approach significantly outperformed other competing phenotype-driven diagnostic tools in both pre-&post-dialogue, as shown in Fig. 4a and Fig. 4b. As turns of Q&A increases, the ranking distribution of the target disease becomes increasingly advanced. After 50 turns of Q&A, the cumulative number of target diseases ranked in the top 10 (56.9%, 1354 out of 2380 conversations) was markedly higher than pre-dialogue (52.7%, 1255 out of 2380 conversations). For disease-causing variant prioritization, the test result (shown in Fig. 4c) indicates that RDmaster has a remarkable advantage over Exomiser. After 50 turns of Q&A, the number of disease-causing variants placed in the first rank is the highest (67.9%, 1527 out of 2250 conversations), compared to 65.9% for pre-dialogue and 52.6% for Exomiser. In conclusion, RDmaster has excellent capabilities for RD diagnosis and disease-causing gene prioritization. This evaluation experiment demonstrates that our proposed phenotype-oriented Q&A dialogue diagnosis can assist clinicians in collecting additional phenotypic information that facilitates diagnosis and leads to better diagnosis.

### Comparison with LLMs for RD differential diagnosis

We also tested the performance of KB-based RD diagnostic tools (including our approach) and large language models (LLMs, mainly GPT-3.5 and GPT-4) in generating differential diagnosis (DDX) lists for RDs based on the phenotype information of patients. We utilized the ChatGPT online web tool (<https://chat.openai.com/chat>, 2023-3-14 Version) to test GPT-3.5 and GPT-4. The ChatGPT prompt was designed as “Please give a ranked list with 10 differential diagnoses (rare diseases only) based on the HPOs provided below”, followed by phenotypes standardized as HPO terms. In this benchmark, for each patient, all existing phenotypes were taken as input, and the rankings of the target disease in ranked DDX lists generated by different approaches were manually verified and counted. A summary of the DDX results of our cohort with 238 patients is in Table 2.

As shown in the comparison of the isolated methods in Table 2, GPT-4 showed promising performance in RD differential diagnosis, outperforming GPT-3.5 comprehensively. For the ability to put the target disease first, GPT-4 was better than Phenomizer, comparable to BOQA and PhenoPro, but weaker than LIRICAL and our system (which showed the best performance). When the size of the DDX list increased, KB-based methods showed a significant improvement in recall for the target disease and were generally superior to GPTs when the DDX list size reached 10. It is worth noting that GPT sometimes recommends broader concepts for the target disease, e.g., not considering disease subtypes or inheritance modes. If such recommendations are considered, the performance of GPT-4 in ranking the target disease as No.1 is only weaker than that of RDmaster.

In addition, it is worth noting that KB-based tools and GPTs sometimes exhibit discrepancies when dealing with different diseases. Specifically, in some cases, all introduced KB-based tools performed poorly while GPTs performed well, and there are also cases where KB-based tools performed well while GPTs fail to diagnose. We provide detailed testing results in the supplementary materials (Supplementary Note 5). To reflect this difference, we calculated the joint diagnostic performance of RDmaster and other methods and directly took the better diagnostic result of the two methods, as shown in the joint approaches in Table 2. Results showed that although the standalone diagnostic performance of GPT4 is mediocre, its combination with RDmaster yields significantly better results than the combination of other KB-based tools with RDmaster, suggesting a potential complementary diagnostic advantage between KB-based methods and GPTs.

# Discussion

A recent scoping review revealed that most clinical decision support systems (CDSS) for RDs do not involve the execution of DDX [42]. To address this gap, we developed RDmaster, a novel phenotype-oriented Q&A dialogue system to assist in the DDX of RDs. RDmaster engages in human-computer interaction to collect additional crucial symptoms beyond the initial clinician report, differentiate between potentially multiple competing diagnoses, and ultimately improve diagnostic accuracy. RDmaster has several core advantages: (i) an efficient and interpretable multi-omics diagnostic approach that represents the current state-of-the-art in RD diagnosis; (ii) a method for assessing the expected benefit of questioning phenotypes during real-time diagnosis; (iii) a well-designed online platform with rich visualization support; (iv) enriching patient phenotype information from the perspective of DDX and inspiring additional clinical testing.

Two Bayesian methods based on the likelihood ratio paradigm have been employed in RDmaster for RD diagnosis [32]. Our proposed method, PheLR, is a phenotype-driven analysis method that has demonstrated superior performance over most currently available phenotype-driven RD diagnostic tools and is robust to noise and imprecision in reported phenotypes [33]. Additionally, we integrated LIRICAL for genomic analysis in this study and demonstrated that these two methods can be perfectly coordinated to achieve excellent multi-omics diagnostic performance [34]. One important reason for adopting Bayesian analysis into RDmaster is its logical simplicity, diagnostic robustness, and clinical interpretability. Another is that the posterior probability and phenotypic frequency of diseases are both probabilities, making their combination more reasonable for our expected benefit calculation of candidate questioning phenotypes.

The decision tree (DT) is a typical classification method in machine learning that generates understandable rules and a binary-tree-formed decision process using an inductive algorithm. Two commonly used metric functions for DTs, information entropy and Gini index, measure the uncertainty or impurity for each split condition mathematically [35, 36]. Although both have similar accuracy for classification, they have different expressions and measurement focuses [43, 44]. We constructed two classification decision trees based on disease-phenotype associations from Orphanet, using information entropy and Gini index (see details in Supplementary Note 2). Results showed that information entropy performed better for messier data, while Gini index was more effective in rapidly purifying candidates. A previous study has shown that a linear fusion of these two metrics can achieve satisfactory classification performance [45]. To combine the strengths of both, we proposed an adaptive fusion metric, AIGGI, which focuses on reducing uncertainty when multiple competing diagnoses exists, primarily using information gain, and quickly obtaining a diagnosis when there are a few significant candidate diseases, mainly using Gini index.

Most DQN-based dialogue diagnosis systems and a limited number of human-computer interaction DDX applications for RDs aim to capture additional symptoms that exist in patients to improve diagnostic accuracy [29-31, 46, 47]. However, this approach may not always align perfectly with the process of DDX, as sometimes excluding phenotypes belonging to competing diagnoses that are not present in patients can better aid in narrowing down the possible diseases. RDmaster’s dialogue strategy can consider the overall benefit of users answering yes or no, as decision trees always have binary branches of yes or no, making our strategy more comprehensive and in line with DDX. Furthermore, two intention-considered questioning strategies were designed in case users explicitly want to verify or exclude phenotypes.

LLMs, such as GPT-3, have been studied extensively for diagnosing common diseases [26, 27], and have been found to outperform a well-known DDX generator Isabel Pro [48, 49]. But their effectiveness for diagnosing RDs has not been thoroughly investigated. In this study, we compared the performance of KB-based RD diagnostic tools with LLMs (specifically GPT-3.5 and GPT4) in generating DDX lists for RDs and demonstrated the enormous potential of LLMs for RD diagnosis. However, the clinical application of LLMs for RD diagnosis needs to be cautious. Even the most advanced GPT-4 still has some limitations: (i) instability, meaning that the DDX list may vary even when using the same prompt; (ii) inability to analyze sequencing data, while RDs are mostly genetic diseases; (iii) cannot recommend RDs well that have not been trained or have limited training data; (iv) bias of professional knowledge, e.g., confusing the ORPHA codes of RDs.

Nonetheless, there are several limitations to this work. Firstly, the diagnostic accuracy of RDmaster cannot be completely assured, as patients usually do not present all phenotypes of the target disease and often exhibit symptoms that are not related to the target disease. If the initial report does not provide enough evidence to support a viable diagnosis, the target disease may be placed lower in the DDX list, in which case RDmaster usually does not perform well. Secondly, the diagnostic methods and Q&A strategies used by RDmaster are designed based on KBs. However, even in the most authoritative KB Orphanet, many rare diseases lack phenotypic and/or genetic evidence. As of February 2022, Orphanet only recorded 4257 RDs with phenotypic information and 3884 RDs with associated genes. With the advent of next-generation sequencing technology, hundreds of new disease-gene associations are revealed every year [50]. As more research is conducted and more RDs are identified, the relevant KBs will become increasingly comprehensive.

# Methods

## Data sources

RDmaster follows evidence-based medicine and all evidence data used in RDmaster is derived from authoritative KBs. The Human Phenotype Ontology (HPO) is used to standardize clinical symptoms and signs (collectively referred to as phenotypes) and serves as the entity for Q&A. The hp.obo file (version 2022-02-14), which models the HPO, and the phenotype.hpoa file (version 2022-02-14), which provides HPO frequency annotations for 4257 ORPHA diseases, can be obtained from the HPO website (<https://hpo.jax.org/app/>). Additionally, we downloaded a series of RD-related files from Orphadata (<https://www.orphadata.com/>), including the en\_product6.xml (version 2022-02-01), which provides ORPHA-gene relationships, en\_product9\_prev.xml (version 2022-02-01), which offers epidemiology data of ORPHAs, and en\_product9\_ages.xml (version 2022-02-01), which has onset and death ages and inheritance types of ORPHAs. These files give multivariate information to facilitate RD diagnosis. For genomic analysis, Exomiser is integrated to annotate, filter, and score potentially causative variants. Supporting data for Exomiser, the Jannovar-derived exome functional annotation files (2102\_hg19 and 2102\_hg38) [51], can be downloaded from <https://data.monarchinitiative.org/exomiser/data/index.html>.

## Diagnostic method of RDmaster

To perform multi-omics diagnosis, RDmaster integrates two interpretable diagnostic approaches with the likelihood ratio paradigm, PheLR for phenotypic analysis, and LIRICAL for genotypic analysis. The likelihood ratio (LR) is the percentage of people with a specific test result divided by the percentage of healthy people with the same result. Theoretically, people with a specific disease should present more typical phenotypes and variants than people with other diseases or healthy people, resulting in a relatively high LR. According to Bayesian principles, the prior odds of disease multiplied by the LR of patient test results gives the posterior odds, which can be converted to posterior probability by simple arithmetic [32].

PheLR [33], a phenotype-driven LR analysis method developed in one of our previous studies, is integrated into RDmaster for phenotype-based diagnosis. It utilizes epidemiological data from Orphanet to estimate the prior probabilities of RDs. Multiple computational models of LR for both present and absent phenotypes are designed in PheLR based on the annotation propagation rule [39], which quantifies the contribution of individual phenotypes to tested diseases.

LIRICAL [34], a recently developed method for interpretable clinical genomics, is integrated into RDmaster for genomic analysis only. It models the expected counts of pathogenic variants in disease-causing genes as a Poisson distribution based on different modes of inheritance. The LR of a genotype is the probability of observing the number of pathogenic variants within a Poisson distribution of this genotype in a sequenced individual compared to the situation in which its variants originate from the population background. The pathogenicity of variants in LIRICAL is determined according to Clinvar database or pathogenicity scores calculated from Exomiser [52].

In RDmaster, candidate diseases and causative genes are prioritized based on calculated posterior probabilities. Phenotypic and genotypic analysis can be performed separately or simultaneously, but separate single genome analysis is not recommended.

## Dialogue strategy of RDmaster

During a phenotype-oriented Q&A dialogue, the selection of interrogated phenotypes is a crucial task. To evaluate the expected gain of candidate phenotypes within real-time diagnostic states, we propose a novel metric called Adaptive Information Gain and Gini Index (AIGGI). The AIGGI metric is inspired by metric functions of two decision tree algorithms (ID3 and CART). As with the binary-tree decision process, our dialogue strategy allows users to answer “*Yes*” or “*No*” to interrogated phenotypes, corresponding to the positive or negative branches of decision tree nodes, respectively. Rather than a dichotomous distribution (whether a phenotype is associated with a disease or not), we use a numerical probability , which represents the degree to which phenotype is related to disease , to measure the weights of two branches. We take the median value (refer to as ) of the frequency range (e.g., 0.9 for “Very frequent (99-80%)”) in the HPO annotation file as the numerical probability, and apply the annotation propagation rule on HPO to exploit implied phenotypic features of diseases. can be calculated as:

where is ’s annotated phenotypes and represents ancestor terms of phenotype . Real-time diagnostic states can be indicated as the uncertainty or purity of the diagnostic result, which is measured using the information entropy () and Gini index () calculated from the posterior probability distribution of all candidate diseases:

and

where is a set of numerical weight and is the sum of the elements in . represents all candidate RDs and is the posterior probability of disease . For a candidate phenotype , its conditional entropy and information gain can be calculated as:

and ’s conditional Gini index and Gini gain can be calculated as:

In Equation 6 and 8, the first term corresponds to the positive branch and the second term to the negative branch. equal 1 minus . is the weight of positive branch and is calculated as the sum of divided by the sum of . Ultimately, AIGGI can be calculated as:

where is an indicator reflecting the uncertainty or clutter of current posterior probability distribution, which can be taken directly as .

To account for user intention, we further proposed two intention-considered AIGGI-based indicators. The first indicator, AIGGI-P, is used when users expect to validate phenotypes (answer “*Yes*”). In this case, we minimize the gain from answering “*No*” by setting the conditional entropy and Gini index of the negative branch in Equations 6 and 8 to a constant value of 1. Another indicator, AIGGI-N, is used when users expect to exclude phenotypes (answer “*No*’). In this case, we minimize the gain of answering “*Yes*” by setting the conditional entropy and Gini index of the positive branch to 1.

In each turn of Q&A, our agent will select a phenotype with the highest expected gain to interrogate users. A response of “Yes” or “No” will prompt a re-diagnosis and update the diagnostic status. If users respond with “Not sure”, the diagnostic status remains unchanged and our agent will interrogate the next-ranked phenotype. To enhance the efficiency of our dialogue strategy, previously reported and interrogated phenotypes will not be re-asked. Additionally, following the annotation propagation rule [43], ancestors of known existing phenotypes and descendants of excluded phenotypes will not be considered by our agent in future turns.

## Implementation of RDmaster

RDmaster is implemented as an online web tool (http://rdmaster.nbscn.org/), which includes a RESTful back-end server developed using the Spring (<https://spring.io/>) framework, a front-end server developed using the React (<https://reactjs.org/>) framework and a web-based UI that enables human-computer interaction. The back-end server provides data access, Q&A dialogue, and RD diagnosis services. To reduce response time, we used the Spring context to store preloaded and pre-calculated data and the Caffeine plugin (<https://github.com/ben-manes/caffeine>) to cache genetic diagnosis results on our back-end server. Two open-source JavaScript visualization libraries, D3 (<https://d3js.org/>) and ECharts (<https://echarts.apache.org/>) provide essential visualized decision-support information on UI [53, 54].

## Evaluation

To evaluate our dialogue strategy, we simulated tens of thousands of patients according to HPO frequency annotations from phenotype.hpoa file and randomly assigned inaccurate phenotypes (ancestor terms of annotated phenotypes) and noise to each simulated case. The phenotype information of each simulated patient was reported to RDmaster to compute a ranked candidate questioning phenotype list, and then we analyzed and quantified the relationship between candidate phenotypes and top-ranked diseases within different diagnostic states.

We further evaluated the diagnostic performance of RDmaster using real-diagnosed patients published online. A total of 238 case reports involving 92 RDs were collected, of which 225 cases involving 86 RDs had causative genes in KB and were eligible for genetic diagnosis. For each published case, we endeavored to capture all recorded phenotypic features (present or absent) and ultimately generated standardized patient information within the Phenopacket schema [55]. Detailed information on the 238 published cases is provided in Supplementary Table 1. Like many previous studies [56-58], we simulated exomes for the 86 RDs with causative genes by randomly adding known pathogenic variants from the Clinvar database (homozygous for recessive diseases, heterozygotes for dominant) to our internally randomly selected 86 exomes (see Supplementary Table 2). In this evaluation, several influential KB-based RD diagnostic tools (Phenomizer, BOQA, PhenoPro, and LIRICAL for phenotype-driven diagnosis; Exomiser for disease-causing genes prioritization) were introduced to compare diagnostic performance with RDmaster. In addition, we also explored the effectiveness of large language models, specifically GPT-3.5 and GPT-4, in RD differential diagnosis.

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# Figure Legends

**Fig. 1: Workflow overview and system architecture of RDmaster.**

**Fig. 2: Web-based user interface screenshots of RDmaster.** **a** User interface for clinical information collection. **b** User interface for dialogue diagnosis.

**Fig. 3: Brief statistics on RDmaster’s dialogue strategy.** Our proposed three dialogue strategies are marked in the top right corner of each legend. All these graphs are averages of test results from tens of thousands of simulated cases. **a** Average association scores of top-5 ranked diseases with the interrogated phenotype under different diagnostic states. The horizontal axis from 1 to 0 represents a decrease in diagnostic uncertainty, i.e., the Gini index of the diagnostic status tends to 1 when there are multiple competing candidate diagnoses, and tends to 0 when there is only one obvious candidate diagnosis. **b** Average association scores of top-100 ranked candidate phenotypes with top-5 ranked diseases.

**Fig. 4: Diagnostic performance of RDmaster.** DS\_T0 represents the diagnostic effect of RDmaster before the dialogue, DS\_T10 represents after 10 turns of dialogue, DS\_T20 is after 20 turns, and so on. **a** Ranking distribution of target diseases in phenotype-driven diagnosis. Note that there are two vertical coordinates, the left-hand one corresponding to the blue box plot and the right-hand one to the grey. **b** Cumulative number of target diseases ranked in the top 10 in phenotype-driven diagnosis. **c** Distribution of disease-causing gene rankings in phenotype-genotype diagnosis.

# Tables

**Table 1** **Summary of collected published cases for evaluation.**

|  |  |
| --- | --- |
| Total published case reports | 238 |
| **Patient** | |
| Male | 113 |
| Female | 119 |
| Unrecorded gender | 6 |
| **Rare diseases** | |
| Total disease number | 92 |
| Mean-median-maximum # cases per disease | 2.6-1-18 |
| Total cases | 238 |
| **Rare genetic diseases** | |
| Total disease number | 86 |
| Autosomal-dominant diseases | 34 |
| Autosomal-recessive diseases | 42 |
| X-linked dominant diseases | 1 |
| X-linked recessive diseases | 3 |
| Disease-causing genes | 86 |
| Mean-median-maximum # cases per disease | 2.6-1-18 |
| Total cases | 225 |
| **HPO terms** | |
| Total recorded HPO terms over all cases | 811 |
| Mean # HPO terms per case | 9.1 |
| Mean # excluded HPO terms per case | 1.0 |

**Table 2 Statistic results of target disease rankings of collected patients in differential diagnosis lists generated by KB-based tools and LLMs.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Methods | Target disease in | | | |
| Top 1 | Top 3 | Top 5 | Top 10 |
| Isolated Approaches: | | | | |
| GPT-4 | 33.61% | 41.60% | 44.54% | 46.22% |
| GPT-3.5 | 24.79% | 31.09% | 35.29% | 41.18% |
| RDmaster | **41.60%** | **51.26%** | **58.40%** | **68.49%** |
| LIRICAL | 37.39% | 51.26% | 57.56% | 66.81% |
| PhenoPro | 34.45% | 44.96% | 53.78% | 65.55% |
| BOQA | 32.35% | 44.96% | 50.42% | 58.82% |
| Phenomizer | 26.05% | 36.97% | 43.70% | 55.04% |
| Joint Approaches (min\_target\_disease\_rank (A, B)): | | | | |
| RDmaster & GPT-4 | **57.56%** | **67.23%** | **72.69%** | **77.31%** |
| RDmaster & GPT-3.5 | 51.68% | 60.92% | 68.49% | 76.47% |
| RDmaster & LIRICAL | 43.70% | 56.30% | 63.03% | 72.27% |
| RDmaster & PhenoPro | 44.54% | 54.20% | 61.34% | 72.69% |
| RDmaster & BOQA | 45.80% | 56.72% | 61.76% | 72.69% |
| RDmaster & Phenomizer | 44.96% | 54.20% | 61.76% | 72.27% |
| LLMs, considered the potentially correct recommendation, which is a broader concept of the target disease | | | | |
| GPT-4 | 38.66% | 48.32% | 53.78% | 56.30% |
| GPT-3.5 | 29.41% | 36.97% | 43.70% | 50.42% |