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Article

Digital Triage Tool Using Artificial Intelligence and Patient History for Detecting Selected Neurological Diseases and Sensing the Bottleneck between Symptoms, Diagnosis, and Therapy

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Abstract: During the COVID-19 pandemic, individuals with symptoms other than cough or fever have refrained from seeking medical advice. However, a delay in treatment might lead to serious consequences. At the same time, digital health initiatives have emerged to overcome this bottleneck of healthcare. Herein, we report the results of a multi-center initiative using a combination of patient history and artificial intelligence (AI) to identify individuals with rare neuromuscular diseases. First, a questionnaire with 46 items was developed by interviewing patients with muscular dystrophies, amyotrophic lateral sclerosis, Morbus Pompe, neuropathies, and myasthenia gravis. Second, patients with proven neurological diseases answered the questionnaire. Third, a combination of classifiers (artificial neural network, support vector, and random forest) was trained and, finally, the system was challenged with new questionnaires. Users with an abnormal questionnaire pattern received a unique code for data privacy and contact details for a neurologist for further advice. The neurologists confirmed or refuted the AI-based diagnosis. The questionnaire was accessed more than 3000 times. Only for a few patients the computer-based diagnoses and the confirmed final diagnoses were reported to us. However, for these few patients, the genetic testing and high CK levels finally ended their long-lasting diagnostic odyssey.

Keywords: artificial intelligence; data mining; diagnostic decision support; rare diseases; questionnaire anamnesis; neuromuscular diseases; high latencies

1. Introduction

A patient's medical diagnosis is made on the basis of information from their medical history and clinical findings, and, if necessary, with the help of laboratory chemistry, neurophysiological, and supplementary diagnostic procedures. Particularly in the case of the so-called orphan or rare diseases, long latencies can occur between the first symptom and the final diagnosis. This means considerable suffering for patients, and a possible delay in therapy or supportive and relieving measures. Those affected then frequently go from doctor to doctor and from examination to examination. During this search, many working hours and considerable costs are incurred on the medical side, distracting the concerned physicians from other tasks, such as the problems with the omnipresent pandemic.

Since 2007, an interdisciplinary team in Hannover (physicians, computer scientists, mathematicians, and nurses) has been developing various new approaches to shorten the path to diagnosis by applying artificial intelligence (AI) methods. Using the example of people with rare diseases and, in some cases, with long phases of diagnostic latency, we took on the challenge of querying the experiential knowledge of those affected and then modeling it mathematically. For this purpose, interviews with a focus on the time before diagnosis were conducted, analyzed, and used to create questionnaires for patients. In

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principle, this corresponds to a standardized questionnaire anamnesis with the possible answer levels of "no," "rather not," "rather yes," and "yes."

In contrast to a large number of business applications, the use of AI procedures in medicine is rather hesitant, yet AI procedures enable an extension of established diagnostic procedures. Of course, the application of these AI procedures, as well as the establishment of a final diagnosis, is fundamentally the responsibility of physicians.

In a series of publications [1–13], the authors presented the initial results and the basic principle of the procedures that they have developed over the last 10 years,. This publication describes the implementation and results of the continuing task of using the AI system in physicians' offices and at university centers for rare diseases as a diagnosis-supporting tool and testing it with the boundary conditions of medical institutions in the field. The field studies took place in a medical practice in Bonn, at the Center for Rare Diseases of the University Hospital Bonn, at the Pediatric Clinic of the Hannover Medical School, at the neuromuscular outpatient clinic of the Charité in Berlin, and at some other neurological medical practices.

2. Data Modeling

The response patterns of the completed questionnaires, together with the confirmed diagnoses of these patients, formed the database of the AI system. The "training" of these data sets, which is characteristic of every AI system, corresponds to an iterative solution of high-dimensional systems of equations and requires an enormous amount of computing effort. Afterward, in the so-called "recall phase," the evaluation of a completed questionnaire is carried out by simply inserting a new answer pattern into the solved equation systems stored on a server. The great practical advantage of AI systems is that the computation time for the "recall phase" is negligible. Therefore, immediately after answering the last question of the questionnaire, the diagnostic indications can be displayed to the physician or authorized medical personnel.

The developed AI system is a piece of software that is used as a diagnosis-supporting tool for physicians during field tests. After final actual diagnosis, the physician diagnosis is used to retrain the AI system and thus improve the algorithms. By incorporating these response patterns from patients with known diagnoses into subsequent training runs, a learning system is created that improves its performance with the response pattern of each diagnosed patient.

2.1. The Database

The database (Table 1) consists of a total of 289 response patterns related to 10 neuromuscular diseases.

Table 1. List of 289 confirmed disease groups.

	Disease	Amount(289)
1	Muscular dystrophy	50
2	Morbus Pompe disease	36
3	Spinal muscular atrophy	19
4	Amyotrophic lateral sclerosis	42
5	Polyneuropathy, HMSN	40
6	Other neuromuscular disease	20
7	Glycogenosis type V	21
8	Multifocal acquired demyelinating sensory chronic inflammatory demyelinating polyneuropathy multifocal acquired demyelinating sensory and motor	34

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9	Myasthenia gravis	15
10	Inclusion body myositis	12

An interesting visualization of the response patterns of the questionnaires is the profile graphs of typical response patterns (see Figure 1). For this purpose, the number of the questions is plotted at the top and the response level of a typical patient of a diagnostic group is plotted on the right. A typical patient is a virtual patient whose answers result from an averaging of all answer patterns in his diagnosis group. Since the response levels are discrete units, i.e., 1 for "no," 2 for "rather not," 3 for "rather yes," and 4 for "yes," the modal value is suitable as a statistical parameter. Figure 1 compares the modal response patterns for the two diseases "dystrophy" and "Morbus Pompe" in mirror symmetry. One can clearly see the differences in the response patterns and thus the mathematics of the AI is also able to distinguish between these diseases.

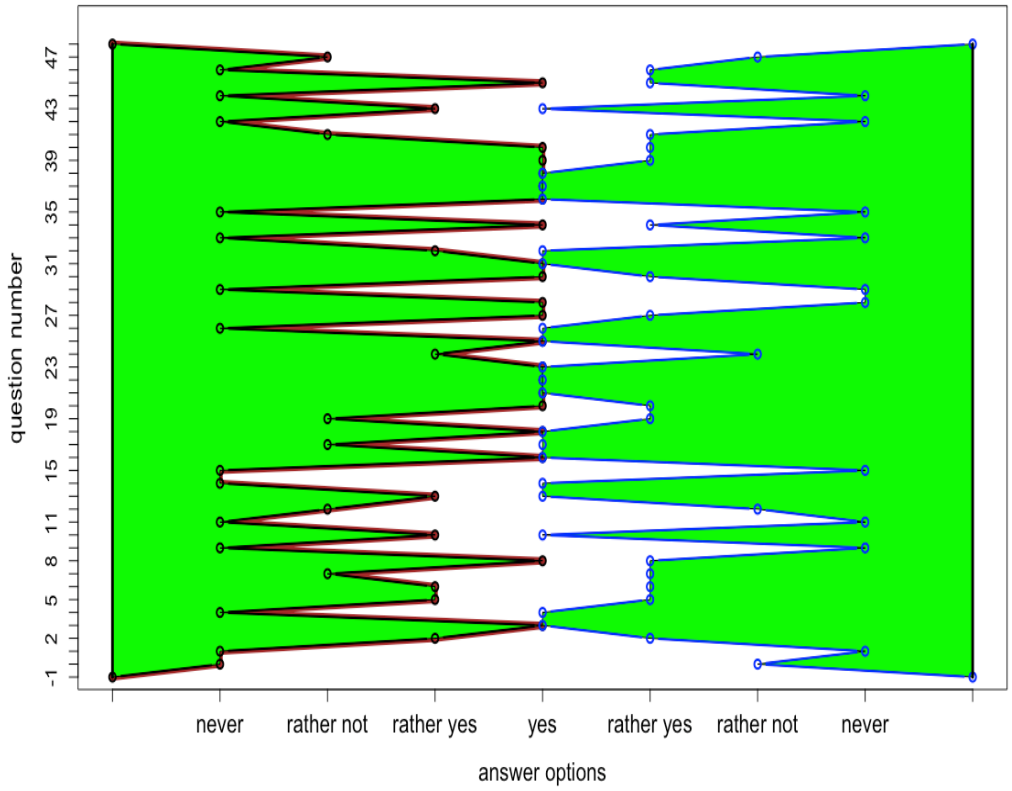

Figure 1. Modal profiles of the response patterns for the diseases "dystrophy" (**left**) and "Morbus Pompe" (**right**).

Modal virtual response patterns are particularly suitable for checking the results of the AI system. If, on the one hand, the AI system delivers a sufficiently high score for a certain diagnosis, but on the other hand, the response pattern of this patient deviates too much from the modal patient of this supposedly recognized diagnosis, then this contradiction indicates an incorrect value for the score and a diagnostic recommendation must not be issued.

Furthermore, a self-test of the AI system is based on evaluating all modal response patterns. For these cases, the scores take the relative maximum value of 100% and the scores for the other nine modal response patterns decrease to 0%. The averaged relative deviation from these theoretically correct results allows the determination of a relative value of the AI system integrity.

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2.2. The AI System

The core of the AI system consists of a perceptron deep learning artificial neural network. The number of input neurons was set equal to the number of input signals and thus contains 48 neurons (gender, 46 questions, age). The output layer contains 10 neurons and therefore matches the number of the 10 diseases (see Table 1). For example, if the maximum score occurs at the first output of the output layer, then the AI system has detected a suspected case of the disease "dystrophy."

Like the input layer, the hidden layers each comprise 48 neurons and consist of three individual layers. Figure 2 shows the basic principle of this neural network. For graphical reasons, five input channels, three intermediate layers with five neurons each, and an output layer with five neurons are shown here as an example. In fact, the neural network of the present AI system consists of 48 input arrows. Each single input arrow symbolizes 48 input signals, which are connected—in parallel—to all 48 neurons of the input layer, three intermediate layers with 48 neurons each, and an output layer with 10 neurons for the recognition of the 10 diseases according to Table 1.

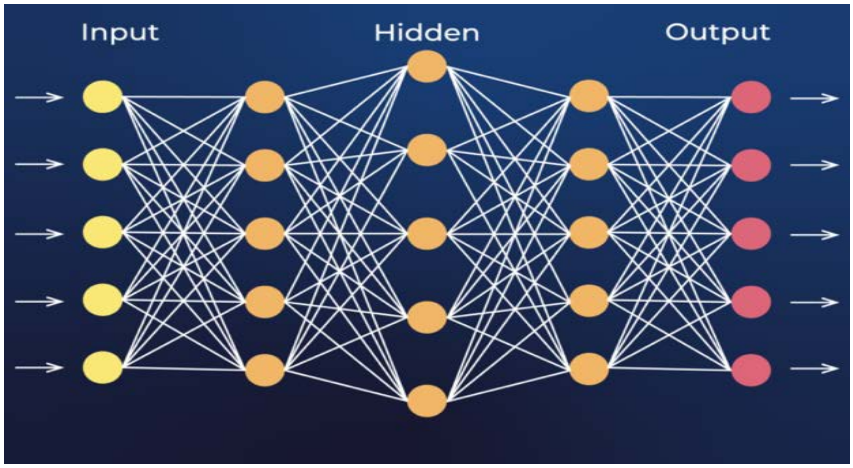

Figure 2. Simplified Structure of an artificial neural network.

Looking at Figure 2, the number of all neurons, as well as all neuronal weights, for the present AI system can be determined as follows:

$$\text{Number of neurons} = 48 + 3 \times 48 + 10 = 4 \times 48 + 10 = 202$$

$$\text{Number of neuronal weights} = 48 \times 48 + 3 \times 48 \times 48 + 10 \times 48 = 9696$$

The challenging mathematical task is to iteratively determine these 9696 unknowns, which are initially set randomly and then using the backpropagation algorithm. All algorithms used are part of the R mathematical library "neuralnet" and are extensively described in the literature [14]. However, convergence problems may occur in practical applications, indicating an incomplete or weakly populated database. Successful control of modal response patterns for all 10 diseases confirms sufficient convergence in the computation of these 9696 neural weights. Figure 3 shows a typical course of a hit and error curve when computing the neuronal weights. Already after 300 training cycles, the backpropagation algorithm succeeds in increasing the hit rate of 0% to 95% and vice versa in reducing the error rate of newly offered answer patterns from 100% to approximately 5%.

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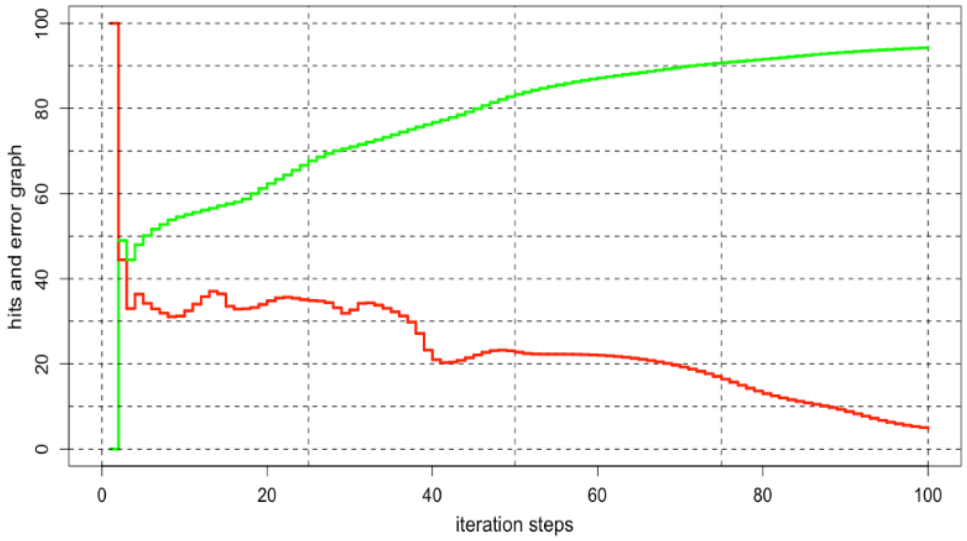

Figure 3. Deep learning with the backpropagation algorithm.

The enormous advantage of neural networks is primarily that after completion of the complex training, the evaluation of a new response pattern can take place without significant computing time, and new response patterns for which a final diagnosis is available can be quickly retrained.

Despite the high performance of neural networks, conflicting patient information or unusual manifestations of a neuromuscular disease may lead to erroneous results in the output layer of the network. Therefore, two more data mining classifiers (support vector and random forest) were used, whose results are suitable for testing the AI system and are extensively described in the literature [15,16]. In the end, a voting of the individual scores of all three classifiers, as well as plausibility tests by comparison with the modal response patterns, guarantee a reliable diagnostic indication. If contradictions occur in these tests, then no concrete diagnostic clue is issued.

3. Field Studies

Accompanying the standard diagnostic test, people with serious complaints were asked to answer the questionnaire in field studies and the results of the evaluation of the completed questionnaires were submitted to the physician for further diagnostics. After a final diagnosis, all results were used to improve the AI system. The field trial begins when a person with serious symptoms presents himself at a rare disease center, a general or neurological physician's office, or an outpatient clinic for neuromuscular diseases and, after informed consent, answers the questionnaire immediately on a tablet, his SmartPhone, or later at home via an Internet link. Information about his identity is generally not collected in the questionnaire. Regardless of the result of the evaluation of the completed electronic questionnaire, the patient is shown a unique code generated at random, the knowledge of which enables access to the anonymously stored results. With this procedure, the patient's data are protected and only the patient can allow access to his data by disclosing his unique code.

3.1. Evaluation of the Field Study

The evaluation uses two feedback questionnaires. The high level of agreement, which is visible in the compilation of the feedback, was also noticeable in the discussions with the patients concerned. At the same time, we received many valuable suggestions for improving the question texts, which were incorporated into the update of the questionnaire and the AI system after completion of the field study. Figure 4 graphically

 doi:10.20944/preprints202203.0178.v1

represents the averaged response levels to these questions. Overall, the patients rated the software positively or as good or very good and were comfortable with its use. During the free-text entries, we received further information that contributed to the improvement of the AI system.

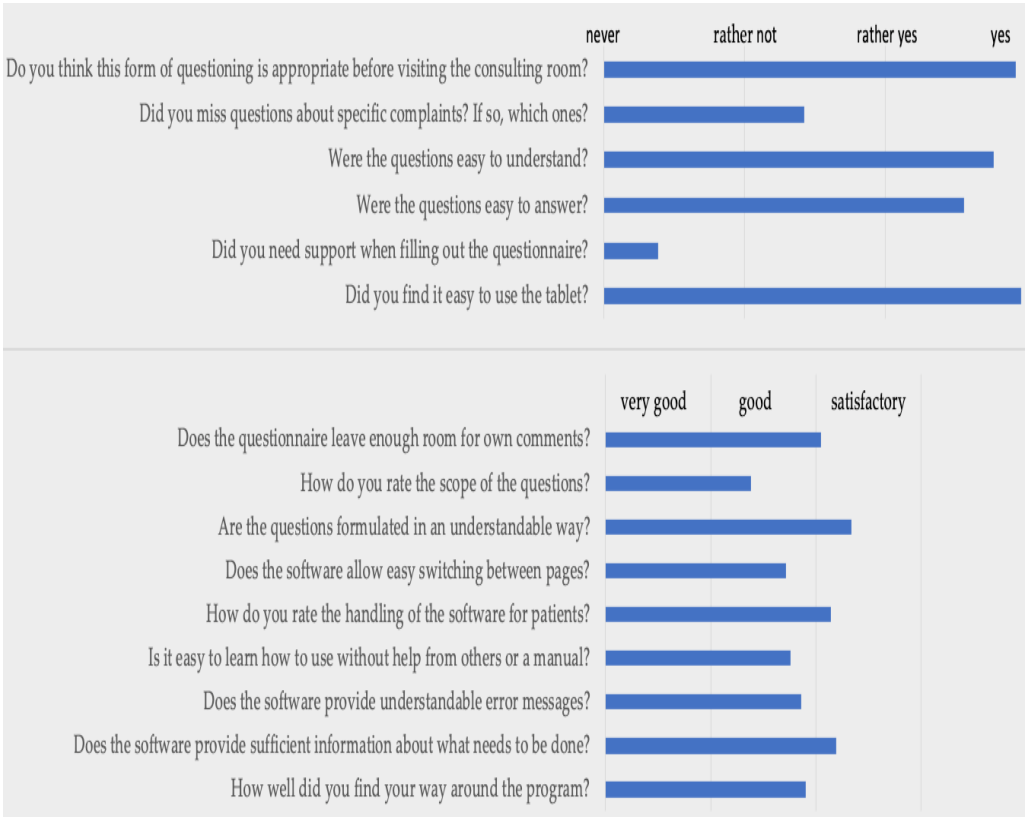

Figure 4. User evaluation results.

3.2. Setting Optimal Limits for the Output of the Results

Of great importance for the number of "true positive(TP)" or "false positive(FP)" results is the score from which the diagnostic indication is announced. This threshold value is based on the ROC curves, AUC values, and confidence intervals. A typical ROC graph is shown in Figure 5 for the "Morbus Pompe" disease. It can be seen that the optimum limit was calculated by 52%. In total, such representations are available for each of the 10 diagnoses. After setting all threshold values, a maximum number of TP and a minimum number of FP results are gained. If, because of the medical consequences, the number of FP outputs should be particularly low, then a higher limit value can be set. In the later field studies, the limit was set at 70% instead of the optimal 52% for the disease "Morbus Pompe", i.e., an indication of this disease requires a dry blood test for further diagnostics.

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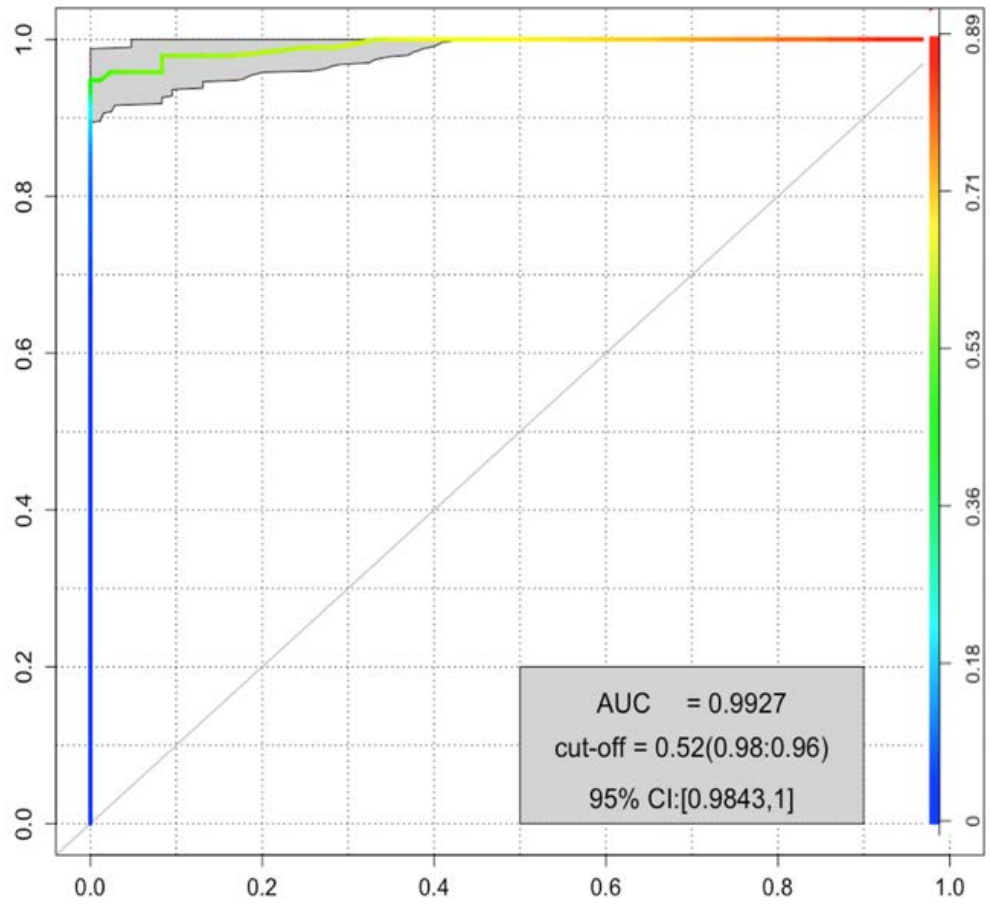

Figure 5. ROC graph for the disease "Morbus Pompe."

3.3. Field Study at the Neuromuscular Outpatient Clinic of the Charité in Berlin

The University Outpatient Clinic for Muscular Diseases of the Charité in Berlin-Buch offers specialized help in the diagnosis and long-term care of patients with muscular diseases and has a large patient pool with confirmed neuromuscular diseases. Among them are numerous rare diseases, such as patients with "limb-girdle muscular dystrophy" (LGMD) or Morbus Pompe disease. The head of the university outpatient clinic, Prof. Dr. Simone Spuler, MD, selected seven patients without initially specifying the disease to us (blind field study condition). Because of the limitations of the COVID-19 pandemic, we called these patients in turn by phone and read the questions to them. We then entered the responses online into the electronic questionnaire. After evaluating all seven response patterns, we compiled the results in a table (Table 2) and discussed them the next day. As it turned out, the AI system had correctly assigned all four Morbus Pompe disease patients. For the remaining three patients with LGMD disease, the AI system provided incorrect results, however with strikingly high scores of 62%, 61%, and 60% (see right column in Table 2) for the correct LGMD disease. A review of the training data set revealed that in the diagnosis group "dystrophy," the present disease type of LGMD was not present in sufficient numbers. Therefore, the training set was expanded to include these three response patterns. This was followed by further training of the AI system. After that, the AI system correctly recognizes the diagnoses of all seven patients.

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Table 2. List of patients, Charité, Berlin-Buch.

Patient	Age in Years	Latency	Confirmed Diagnosis	Recognition	Relative Score
1	45	5 years	Morbus Pompe	True positive	75%
2	38	2 weeks	Morbus. Pompe	True positive	68%
3	50	10 years	Morbus. Pompe	True positive	58%
4	70	11 years	Morbus. Pompe	True positive	65%
5	66	1 year	LGMD	False negative	62%
6	40	10 years	LGMD	False negative	61%
7	50	1 week	LGMD	False negative	60%

The short latency periods in patients 2 and 7 are striking. In patient 2, a physician in the family gave the corresponding indication, and in patient 7, there was a hereditary strain that had already triggered the same disease in the older brother. However, it should be emphasized that patients 1, 3 and 4 had a long latency period of 5, 10 and 11 years. This could have been avoided according to the current state, because the filling out of the questionnaire took approximately 15 min and after a few seconds of evaluation time, the AI system gave the correct indication of the present rare disease "Morbus Pompe."

3.4. Field Study in a General Practice in Bonn, Germany

This field study took place in the Bonn medical practice of Dr. Martin Mücke, MD, who is an expert for rare diseases. Most of his patients have been suffering from complaints for years without knowing their diagnosis. At the end of the consultation, the patients filled out the questionnaire online in our presence. The many hints and useful comments we received in the process were incorporated into the improvement of the AI system. In the months following this field study up until present, Dr. Mücke has repeatedly asked selected patients to complete the questionnaire online and at home via browser access. For this purpose, the AI system generates a PDF file with an overview of all of the results and automatically sends this file as an e-mail attachment to the practice. There, an assistant moves the PDF file into the patient's file by a mouse click. The protection of the patient's data is ensured by an anonymous unique code, which is issued to the patients by the practice and thus establishes the link to the personal patient file in the practice. Neither patient names nor addresses are required for the evaluation of the response pattern on the server.

Although the answer patterns were very helpful and increased the robustness in the practical operation of the AI system in the case of erroneous entries and in the case of occurring Internet disturbances, we had wished for spectacular results. However, the AI system could not detect any of the mathematically modeled neuromuscular diseases and corresponding diseases are not confirmed by further medical diagnostics. Looking at it the other way round, it is pleasing that in patients without neuromuscular diseases, no FP results were generated by the AI system.

3.5. Rare Diseases Center, University Bonn

Further field studies took place at the Center for Rare Diseases at the Hospital University Bonn. Here, as well, patients filled in the questionnaire, whereby the results of the evaluation of the response pattern were immediately available to the attending physician and any further diagnostic measures could be taken immediately. In total, 80 questionnaires were received from patients with mostly unknown diagnoses, whose response pattern rarely led to a diagnostic indication due to too low scores. The few cases were useful, because in the case of patients with a known diagnosis, these response patterns again served to expand the database of training data.

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Whenever patients had an unusual manifestation of their symptoms, "false negative" results occurred. Mathematically, in such a case, the patient's response pattern deviated greatly from the modal response pattern of the suspected disease. Therefore, we used this relative deviation of the response pattern as a criterion for issuing a diagnostic recommendation. In the case of deviations above a threshold value, no results are then available after evaluation of the response pattern. Specifically, in the field studies, this limit was set to 17%, i.e., of the 46 responses, no more than eight responses were allowed to have opposite answers, based on the modal response pattern.

3.6. ARTIS Project

The ARTIS[1] project serves to offer the AI system in the field of neuromuscular diseases to a broad public for use. Via the PatientConcept app of the company NeuroSys GmbH[2] or directly via the website www.patientconcept.de/artis/, the user is presented with a short explanatory video and is then guided on to the questionnaire. If the AI system determines a certain suspected diagnosis, then the user receives a unique code and a contact list of more than 120 neurologists in Germany. There is an offer to receive further information by a hotline phone number and to be supported by an appointment service at a neurological doctor's office. A short video clip shows how to proceed after completing the questionnaire.

The ARTIS project was launched on 1 November 2020 and, since then, 3122 users have completed the questionnaire. Of the 3122 questionnaires, 510 were incomplete, leaving 2612 response samples that could be evaluated. Table 3 includes the amount of suspected diagnoses in each case. In total, the AI system generated 853 unique codes, representing 33% of the 2612 evaluable response samples.

Table 3. Unique code statistics.

	Diseases	Amount	Relative Amount
1	Muscular dystrophy	164	19%
2	Morbus Pompe disease	151	18%
3	Spinal muscular atrophy	51	6%
4	Amyotrophic lateral sclerosis	33	4%
5	Polyneuropathy, HMSN	66	8%
6	Other neuromuscular disease	207	24%
7	Glycogenosis type V	104	12%
8	Multifocal acquired demyelinating sensory chronic inflammatory demyelinating polyneuropathy multifocal acquired demyelinating sensory and motor	15	2%
9	Myasthenia gravis	42	5%
10	Inclusion body myositis	20	2%
	Total amounts	853	853/2612 → 33%

The software of the NeuroSys company offers a number of other medical services for the patients of a doctor's office, such as pain diaries, tablet service, and health checks. A special option includes a software interface for the AI system. The results of the evaluation

[1] The ARTIS project was founded by the Sanofi-Aventis Deutschland GmbH (SSA_2020_010569).

[2] The NeuroSys GmbH, Ulm, supported the ARTIS project by technical advice and by its "PatientConcept APP"

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of the questionnaires in the case of a suspicion of one of the 10 modeled neuromuscular diseases are displayed to the physician.

4. Discussion

In principle, the high computing power of modern computers enables an AI-based evaluation of digital questionnaires. The scientific development of such a medical questionnaire for neuromuscular diseases exploits the personal disease knowledge and experience of many patients and requires extensive preliminary work. If patients with an already confirmed diagnosis fill out such a questionnaire, then response patterns emerge with which an AI system can be trained. Conversely, new response patterns without a diagnosis can be easily evaluated with these data models using mathematical recall methods, because the computational effort required for recall is low.

The results of the field studies impressively showed that people with different rare diseases share commonalities in the pre-diagnostic phase, and therefore, rare disease recognition can be supported by history-based phenomenon detection. For the ten neuromuscular diseases modeled, the modal response patterns for the questionnaire had different shapes, so the AI system was able to recognize the diagnosis.

Patients confirmed both the high quality and easy handling of the electronic questionnaires. Browser-based realization allows versatile use in medical institutions for the special project ARTIS or online on any PC or smartphone and, therefore, at any place. Every physician that knows the patient's unique code is offered the possibility of receiving a diagnostic hint within seconds after filling out the questionnaire, to check it critically and possibly to steer the subsequent diagnostics in this direction. For example, the diagnosis of the rare disease "Morbus Pompe" requires a simple and inexpensive dry blood test in advance, which can be ordered immediately by the physician if the AI system provides a corresponding diagnostic hint. This could potentially enormously shorten the latency period, reduce the suffering time of patients, and allow the start of therapies earlier.

Quite fundamentally, the digitalization of medicine offers many opportunities to improve the healthcare system. The support of diagnostics by AI methods makes a particularly effective contribution to this. What is innovative about this project is the use of experience-based questionnaires in conjunction with a combination of data mining and AI methods, the exceptionally high reliability of the server-based system, and the user-friendly application on commercially available computers and smartphones. The software of the AI diagnostic system is available as a browser-based version and can be accessed free of charge via the link: https://www.patientconcept.de/artis. We encourage everyone to try out the AI system and, of course, we would be pleased to receive corresponding feedback (kontakt@kimedi.de).

Author Contributions: Conceptualization, methodology, validation, formal analysis, investigation, and project administration, L.G., W.L., and F.K.; software, writing—original draft preparation and writing—review and editing, W.L. All authors read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of the Medical University Hannover for studies involving humans.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The database of all answer patterns can be obtained by an email request (kontakt@kimedi.de).

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Questionnaire for neuromuscular diseases.

Q[1]: Are you able to lift a heavy object (e.g., beverage crate) from the floor without any problems?
Q[2]: Do you feel more weak and tired compared to other phases of life?
Q[3]: Is it comfortable for you to open a fizzy drink bottle by hand?
Q[4]: Have your liver values ever been elevated without being able to explain it?
Q[5]: Do you often stumble when walking because one foot gets caught somehow?
Q[6]: When lying down, can you lift your legs and keep them just above the ground at the same time?
Q[7]: Do you feel pain after physical activity?
Q[8]: Do you have difficulty jumping over small puddles?
Q[9]: Can you comfortably stow a piece of luggage at head height?
Q[10]: Do you sometimes notice muscle twitches that occur all by themselves?
Q[11]: Do others often refer to you as lazy to move?
Q[12]: When you lose your balance, are you unable to counteract quickly enough?
Q[13]: Is it true that after several days of physical rest, your muscle strength deteriorates significantly?
Q[14]: Does constant back pain accompany you?
Q[15]: Do you have any kind of joint hypermobility?
Q[16]: Have you been diagnosed with an increase in CK (creatine kinase, a muscle enzyme)?
Q[17]: Can/could you splay one leg sideways in a standing position without any problems?
Q[18]: Is it true for you that you often want(ed) to but can't during sports activities?
Q[19]: Do you often take longer to get back on your feet after illness?
Q[20]: When you turn onto your side (or from your stomach to your back) while lying down,
do your movements differ from others?
Q[21]: Can you easily lift and hold your head while lying down?
Q[22]: Do you find it extremely difficult to walk uphill?
Q[23]: Is it true that you prefer seats with armrests,
because you can push yourself off by using your arms when you stand up?
Q[24]: Do you sometimes fall for unexplained reasons?
Q[25]: Do you have difficulty getting up from a squatting position?
Q[26]: Can you be said to throw your legs outward when walking?
Q[27]: Do you find it difficult to work above head height (e.g., hanging laundry or hammering a nail)?
Q[28]: Were you rather unable to keep up in quite a few sports when you were young?
Q[29]: Is it true that you have difficulty speaking (e.g., slurred speech, lisp)?
when speaking?
Q[30]: Have you noticed a significant decrease in muscle strength, e.g., arms or legs?
Q[31]: When you cross your legs while sitting, do they usually support this movement with your hand?
Q[32]: Can you pick up loads from the floor rather with momentum only?

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Q[33]: Is it true that you find it difficult to button your shirt?
Q[34]: Does simply jumping up from a standing position cause you difficulty?
Q[35]: Do you feel that individual limbs (e.g., legs or arms) are losing mass (become smaller, shrink, seem to melt)?
Q[36]: Can the smallest bumps in the floor make it difficult for you to walk safely?
Q[37]: Do you find sports that involve spontaneous development of force, such as jumping, throwing, sprinting, tend to be very difficult for you?
Q[38]: Do you often hear that you have a typical or noticeable gait?
Q[39]: When you want to put your legs up, do you sometimes need the support of your arms to lift them?
Q[40]: Is it true that you were suddenly unable to do things you had learned in sports?
Q[41]: Can you comfortably hold a full water bottle by your outstretched arm at your side?
Q[42]: Do you suffer from muscle cramps?
Q[43]: Do you find it rather difficult to carry loads, such as full shopping bags?
Q[44]: Do you have protruding shoulder blades (so-called angel wings)?
Q[45]: Can it be said that during strenuous activities you switch to other muscle groups or movement patterns?
Q[46]: Have you noticed that without noticeable weight gain you have become you have gained a bigger belly?

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