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Cost-effectiveness of a clinical decision support system for rare disease diagnosis

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Tiivistelmä

Harvinaissairaudet voivat olla vaikeita diagnosoida, mikä johtaa usein pitkiin ja kalliisiin viiveisiin diagnoosissa ja hoidon aloittamisessa. Potilas voi joutua käymään monella eri erikoislääkärillä ja kärsiä oireistaan pitkän aikaa. Vaskuliitit ovat harvinaissairauksia, joissa verisuonien seinämät tulehtuvat. Ne ovat usein parannettavissa, mutta myös vaikeita diagnosoida, jolloin ne saatetaan diagnosoida vasta, kun potilas on teholla jonkin elimen vajaatoiminnan takia.

Tämän tutkimuksen tavoite oli selvittää, kuinka paljon rahaa voitaisiin säästää käyttämällä algoritmia, joka etsii mahdollisia vaskuliittipotilaita ja nopeuttaa heidän diagnosointiaan. Kustannussäästöt laskettiin summaamalla kaikki potilaiden kulut kolmen kuukauden ajalta ennen diagnoosia. Tutkimuksessa selvitettiin myös diagnoosikustannuksiin vaikuttavia tekijöitä regressioanalyysin avulla ja analysoitiin keskimääräistä diagnoosipolkua. Tutkimuksessa käytettiin 2306 HUS:ssa diagnosoidun vaskuliittipotilaan kustannus-, diagnoosi- ja potilastietoja. Lopuksi tutkimuksessa pohdittiin suosituksia algoritmin käyttöön asiantuntijahaastattelujen perusteella.

Tutkimuksen mukaan potilaiden diagnosoiminen kolme kuukautta aikaisemmin olisi säästänyt keskimäärin 1 308 243€/vuosi tai 7375€/potilas. Miesten diagnosointi oli keskimäärin 26% naisia kalliimpaa, ja kustannukset kasvoivat eksponentiaalisesti iän myötä. Eri diagnoosit vaikuttivat myös merkittävästi kustannuksiin. Keskimääräisessä diagnoosipolussa oli 10 potilaskontaktia, jotka koostuivat puheluista, käynneistä ja lähetteistä eri osastoille.

Tulosten perusteella voidaan päätellä, että algoritmin käyttö voisi merkittävästi vähentää kustannuksia aikaistamalla vaskuliitin diagnosointia ja vähentämällä potilaskontakteja. Aikaisempi diagnoosi voisi myös parantaa potilaiden elämänlaatua, sillä aikaisemmin aloitettu hoito ennaltaehkäisisi elinten vajaatoimintaa ja muita vakavia komplikaatioita.

Avainsanat päätöstukijärjestelmät, harvinaissairaudet, kustannusvaikuttavuus, vaikuttavuusperusteinen terveydenhuolto

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Abstract

Rare diseases can be difficult to diagnose, leading to lengthy and expensive diagnostic processes and delays in treatment. This can be particularly unpleasant for patients who may need to visit multiple specialists and endure their symptoms for an extended period. Vasculitides, a group of rare diseases characterized by inflammation of the blood vessel walls, are often curable but also challenging to diagnose. They are often not diagnosed until the patient is already in the hospital for organ failure.

The aim of this study was to calculate the potential cost savings of using an algorithm to spot patients with vasculitis and expedite their diagnosis. To do this, the study summed all the costs occurring during the last three months before the diagnosis. The study also examined the factors that affect diagnostic costs using regression analysis and analyzed the average diagnostic path of a vasculitis patient. The data used in the study were the cost-, patient-, and diagnosis data of 2306 patients diagnosed with vasculitis at HUS. Finally, the study discussed suggestions for using the algorithm based on interviews with an expert.

The study found that, on average, diagnosing patients three months earlier could have saved 1,308,243€/year or 7375€/patient. Men were, on average, 26% more expensive to diagnose than women, and diagnostic costs increased exponentially with age. Different diagnoses also greatly impacted costs. The average diagnostic path for a vasculitis patient included 10 contacts with healthcare professionals, including calls, visits, and referrals to different departments.

This study suggests that the use of the algorithm could result in significant cost savings by expediting the diagnosis of vasculitis and reducing the number of patient contacts. Earlier diagnosis could also improve the quality of life for patients by allowing treatment to begin sooner and potentially preventing organ failures and other severe complications.

Keywords decision support systems, rare diseases, cost-effectiveness, value-based healthcare

1. Introduction

The first chapter starts with a discussion of the background and motivation of this study. Then, it presents the research questions and defines the scope and structure of the thesis.

1.1 Background and motivation

Healthcare costs are rising, and rare diseases are exceptionally costly (Tisdale et al., 2021). When combined, they are not that rare, over 300 million people worldwide suffer from a rare disease. Rare diseases are difficult to diagnose, leading to lengthy and costly diagnostic journeys and causing suffering to patients (Tisdale et al., 2021). Tisdale et al. (2021) claimed that it could take years for many patients to find a diagnosis, and in different studies, rare diseases can account for over 10% to 50% of healthcare costs in some systems.

One solution to improve rare disease diagnostics is the use of clinical diagnosis support systems. Faviez et al. (2020) described these in the context of rare diseases as systems helping clinicians to improve their treatment by, among other things, reducing their misdiagnosis, diagnostic delay, and costs. They stated that there are already many promising clinical diagnosis support systems for rare diseases from which several have proven effective and are already in use.

eCare for Me is a project consortium conducted by HUS (Hospital District of Helsinki and Uusimaa) that seeks to develop artificial intelligence methods to improve diagnostics and treatments (Business Finland, 2019). Its project for rare diseases is conducted with an international IT and consulting company Tietoevry. The project aims to develop an artificial intelligence algorithm to reduce diagnostic delays and the costs of rare diseases. The algorithm uses the HUS Data Lake, which includes comprehensive health data on HUS patients including diagnoses, investigations, and treatments performed. It processes the data, points out possible patients with certain rare diseases, and informs the clinicians that make the final decision about their diagnoses. The algorithm is expected to make rare disease diagnostics 10-20% faster (Business Finland, 2019).

This thesis aims to determine the cost-effectiveness of using the algorithm and estimate the potential savings resulting from earlier diagnoses using its clinical decision support.

1.2 Research questions

As Tisdale et al. (2021) stated, rare diseases are often complex and expensive to diagnose, which causes unnecessary costs and human suffering.
Therefore, the two research problems in this study are:

RP1: How can rare disease diagnosis be expedited?
RP2: How much would the costs be reduced with earlier diagnoses?

The studied algorithm can currently search for three diseases: vasculitis, myositis, and glomerulonephritis, but this thesis concentrates only on vasculitis. When testing the studied algorithm with retrospective data, it could spot the diseases even several years before the doctors had diagnosed them in the patients (Ryyppö, 2021). However, it is suggested that the last months before the diagnosis are usually the most expensive ones (Seppänen, 2022). Vasculitis is often diagnosed when the patient is already in a severely deteriorated physical condition and may even have developed organ failures and irreversible damage to organs (Seppänen, 2022). Therefore, expediting the diagnosis by a few months would already be a significant improvement that would save a lot of human suffering and money. Hence, it was decided to study the patient path and related costs three months before the diagnosis. This is because even though the algorithm can likely spot the diseases earlier, its prediction is more accurate closer to the diagnosis. A prediction three months before is accurate and can show its cost-saving potential reliably. Therefore, the first research question is:

RQ1: How much would the costs be reduced if vasculitis was diagnosed three months earlier with the algorithm?

- **RQ1.1**: What is the cost structure of the last three months of patients' diagnostic path for vasculitis?
- **RQ1.2**: Which patient factors influence the total costs of the treatment path?
- **RQ1.3**: How is the average treatment path of a vasculitis patient during the last three months before diagnosis?

Even though the algorithm might have an excellent cost-saving potential, it can only be achieved by planning its use carefully and considering its possible disadvantages and risks. Thus, the second research question is:

RQ2: How should the algorithm be used to improve the production system of vasculitis' diagnosis and prevention?

1.3 Scope and structure of the thesis

This study was conducted from the healthcare provider's perspective, meaning that only the costs incurred for HUS were considered in the cost calculations. Other costs like societal costs and productivity losses were excluded. The health economic evaluation was conducted as a cost-minimization analysis, a cost comparison usually used in comparing two interventions with the same outcomes. In this thesis, the cost savings due to earlier diagnosis were calculated. An earlier diagnosis most probably affects the outcomes in addition to the diagnostic costs by reducing the treatment costs and improving the life quality of patients. However, these outcomes are likely positive, and calculating the savings in diagnostic costs could already prove the algorithm's effectiveness. The costs of using the algorithm were estimated so low that they are not likely to affect the results.

Each patient's diagnostic path during the last 90 days before the diagnosis was reviewed, and its costs were calculated. Ninety days timeframe was chosen because, according to Ryyppö (2021), the algorithm has been proven to recognize vasculitis patients with a high level of accuracy for even longer timeframes, and a three-month earlier diagnosis would already bring significant cost savings. The studied algorithm was developed to search for three rare diseases, but to limit the scope of this thesis, only vasculitis was included in the analysis.

In this chapter, the background and motivation of the study were introduced, and the research problems and questions were formed.

The second chapter is a literature review that first discusses rare diseases in general and vasculitis in more detail. Then it describes the different forms of economic evaluation, how it can be done in the healthcare field and how the results of a health economic evaluation should be used in practice.

The third chapter describes the rare disease diagnosis and treatment at HUS. The diagnostic path of a rare disease path is discussed, including its problems. Also, the third chapter introduces the studied decision support system, how it works, and how it could be used at HUS.

Chapter four introduces the data and methods used in this research. The data collection and patient sample are described, and the methods for answering each research question are discussed.

In chapter five, the results of the study are presented, and the first research question is answered.

Chapter six is the final, concluding chapter of the study, where all the research questions and their results are discussed. Also, the limitations of this study and future research are considered. The chapter ends with a conclusion of the study.

2. Literature review

In this chapter, the theoretical background of this thesis is discussed. First, rare diseases and common problems related to them are described. Then, the health economic evaluation is discussed, including the different methods and how to use the results. Finally, the patient delay and misdiagnosis are described, and solutions to reduce them are introduced, concentrating primarily on decision support systems.

2.1 Rare diseases

According to Richter et al. (2015), there are various definitions of rare diseases, but rare diseases generally have only a few cases per 10,000 people. For example, the European Medicines Agency defines a rare disease as less than 5 cases per 10,000 people (Richter et al., 2015). Among the 2.2 million people in the HUS area (HUS, 2022), this would mean less than 1100 cases. Even though a single rare disease affects only a few individuals, they are important because, as Richter et al. (2015) stated, there are 5000-8000 reported rare diseases affecting 27-36 million people in the EU.

Rare diseases are often chronic diseases that are difficult to treat and diagnose because, due to their rareness, the doctors are not as experienced in diagnosing them as more common conditions (Faviez et al., 2020).

Therefore, rare diseases are often diagnosed late, leading to complicated treatment paths and costs. Ronicke et al. (2019) stated that many patients have unusual symptoms for a long time and get various misdiagnoses before their condition is diagnosed correctly. According to them, after the first symptoms, it took, on average, six years and 7.3 visits to different physicists to find the correct diagnosis for rare disease patients. Rare diseases are also frequently expensive to treat. The sooner a disease is diagnosed, the sooner the treatment can be started, and the more cost-effective the treatment is (Willmen et al., 2021).

According to Taimen (2021), vasculitides are a group of diseases where inflammation in the blood vessel walls damages the blood vessels. They state that the symptoms can be minor, like rash, numbness, and weakness, but the condition can also cause more significant problems like a stroke, heart attack, or kidney failure. They stated that vasculitis can be caused, among other things, by an infection or disease, or drug usage, but the cause is also often unknown. The disease can be diagnosed by biopsy and imaging, but the diagnosis is often difficult and expensive. Depending on the type of vasculitis and the study, the average diagnostic delay may vary between a few days and months to several years. In their study, Taimen (2021) found out that the longer the diagnostic delay was, the higher the medical costs were both before and after diagnosing a vasculitis patient. The most significant cost factors were the number of days in hospitalization, laboratory tests, and medication. Hyyrynen (2019) stated that yearly over a thousand people are diagnosed with vasculitis in Finland.

2.2 Health economic evaluation

Healthcare costs in Finland are rising, and in 2019, 22 billion euros were spent on healthcare which was 3% more than the previous year (Matveinen, 2021). As Porter (2009) states, rising healthcare costs cannot be sustained forever as the population ages and new medical advances are developed. He suggests that it is not enough to minimize the costs, but we should concentrate on the value we create for the patients. Porter (2009) defined this value as the 'health outcomes achieved per dollar spent. Therefore, when measuring value in healthcare, we need to consider the achieved outcomes and not only how many patients were treated.

To manage the rising healthcare costs, it is necessary to compare the costs and outcomes of different medical interventions using limited resources. According to Rudmik and Drummond (2013), this kind of comparison is called economic evaluation. It is used, for example, when a surgeon must decide whether a new device should be used if it is more expensive than the old one yet more effective. The most straightforward form of economic evaluation is cost-minimization analysis, where the costs of two interventions with the same outcomes are compared. Rudmik and Drummond (2013) stated that when the consequences of two interventions are the same, it is enough to find the intervention with the lowest costs without considering other factors. However, this does not work in most cases. Therefore the authors suggested using other methods like cost-effectiveness analysis (CEA) which also considers the outcomes of the interventions. They described CEA as an evaluation that compares different interventions and their clinical outcomes as "natural units," like gained length of life in years or days without symptoms.

The third form of economic evaluation described by Rudmik and Drummond (2013) is Cost-Utility Analysis (CUA). They stated that CUA is very similar to CEA, but instead of natural units, CUA uses a utility score from 0 to 1, where zero means death and one means perfect health. The effectiveness of the outcomes is measured in quality-adjusted life-years (QALY). In both CEA and CUA, the comparison of different interventions is calculated as the "Incremental Cost-Effectiveness Ratio" (ICER), which is the additional costs of an intervention divided by the additional benefits.

Rudmik and Drummond (2013) recommended combining these methods with net monetary benefit calculation, where the policymakers' willingness to pay for one additional unit of a health outcome is considered when deciding whether a medical intervention is worth using. The last method for economic evaluation that Rudmik and Drummond (2013) listed is cost-benefit analysis (CBA), where both the costs and benefits of an intervention are given a monetary value. However, the authors state that it can be difficult to measure the monetary value of a health benefit.

Once the economic evaluation is done, the least costly and most effective interventions should be chosen. However, as Rudmik and Drummond (2013) stated, it is not always that simple because an intervention can be less costly but less effective or more costly but more effective than another intervention. In these cases, the ICER and the willingness to pay for the benefits should be considered. As Lillrank et al. (2019) argued, for digital healthcare technologies, it is not enough to show that they work as intended but also to prove that they create value for the system. However, it can be more challenging to measure the created value by digital solutions because they may have several stakeholders and complicated paths to the outcomes. Lillrank et al. (2019) stated that to be helpful and become more common, a digital healthcare solution needs to have substantial proof of its effectiveness. Often the best way to test a solution is a randomized controlled trial, but it can be expensive and might not work in a real-world context with many variations in different healthcare contexts.

To help digital health technology companies analyze their solutions' cost-effectiveness and gather evidence of it, Lillrank et al. (2019) created a tool called the PROVE-IT model. The PROVE-IT model uses CIMO logic described by Denyer et al. (2008), a framework used to solve real-world problems by applying scientific research and information. In CIMO logic, the subject consists of a context (C) where an intervention (I) causes an outcome through a mechanism (M). Denyer et al. (2008) stated that using the CIMO logic makes it possible to create effective propositions in certain situations while understanding why they work.

The PROVE-IT model created by Lillrank et al. (2019) consists of the CIMO logic adapted to the healthcare context by applying specifying questions to each aspect of the logic. In the PROVE-IT model, context (C) describes the organization where a digital health intervention is implemented, its stakeholders, and the different perspectives from which the context can be considered. The value a digital health intervention creates is information and has three parts: gathering information, processing it, and displaying the output to the end-user. Therefore the intervention (I) aspect clarifies how these three parts are implemented in a digital health intervention. So that the intervention creates the desired outcome, the actor needs to have the resources, knowledge, and willingness to execute it, which is covered by mechanism (M). Finally, the outcome (O) means the differences in the state of a patient's health and costs. The PROVE-IT model is illustrated in figure 1. Lillrank et al. (2019) stated that the actual costs of an intervention can be difficult to estimate monetarily as things like pain and discomfort cannot be directly measured, so the cost-effectiveness must be calculated by considering measures like the number of sick days, visits to the doctor, and self-documentation. The costs caused to the provider can be estimated using the provider's databases and nationally defined standard costs for specific interventions.

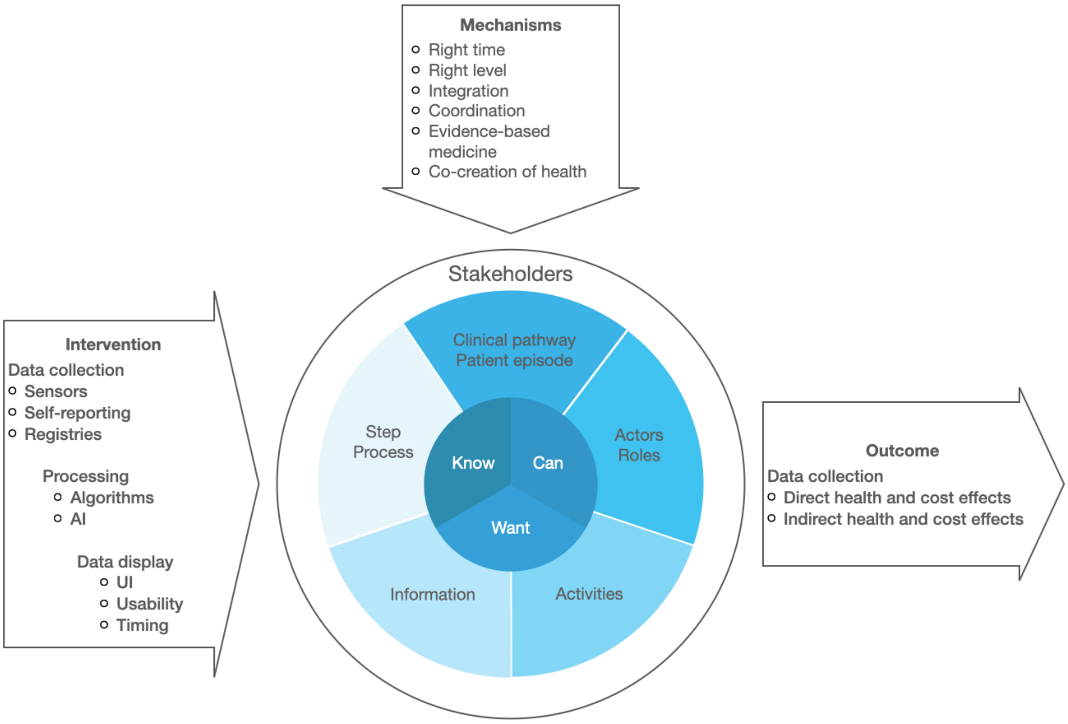

Figure 1. The PROVE-IT model (Adapted from Lillrank et al., 2019)

The main focus of this thesis through the PROVE-IT model is to find out how much the costs can be reduced (O) when an algorithm is used to support the diagnosis of rare diseases (I) and what causes these cost savings (M). The algorithm is developed by HUS rare diseases department and Tietoevry for expediting rare diseases diagnoses (C).

To perform an economic evaluation, it is essential to understand the different cost components that an intervention causes during its care cycle. According to Drummond et al. (2015), the cost components considered in healthcare are costs of healthcare and other sectors, costs that the patient and their family have to pay, and productivity losses due to the intervention. They stated that it depends on the chosen perspective, which cost components are included in an evaluation, and listed three main perspectives: societal, provider and payer.

In healthcare, the cost structure of an intervention can be quite complex as there are many cost drivers to consider. Therefore, Lievens et al. (2003) recommended using activity-based costing (ABC), a cost accounting tool that focuses on all the identified activities in a care cycle and their costs. They argued that ABC is more accurate in cost computation than the traditional tools that consider the interventions as a whole instead of recognizing the costs of each step and calculating them separately. The different activities are placed on a process map to illustrate how each activity relates to the costs and calculate an intervention's total costs. In the radiotherapy example of Lievens et al. (2003), the activities included radiotherapy deliveries, follow-up appointments, general management, and IT support.

According to Drummond et al. (2015), after recognizing the different activities, their resource consumption should be measured in measurable units like the number of visits. They suggest that the information can be derived, for example, from a hospital database, existing literature sources, and interviews. Lievens et al. (2003) stated that the costs can be divided into direct costs caused directly by the care delivery, like the physician fees, and indirect costs caused by supporting activities like department management and building rents. They claimed that many studies ignore indirect costs, but they can be calculated by allocating a particular share of the total costs for each interest group. One of their examples was assigning resources based on bed days. To calculate the total costs of an intervention, each activity is evaluated by its natural units. According to Drummond et al. (2015), this can be done by using the market prices of the hospital that delivered the intervention.

To make costs incurred in different years comparable, Drummond et al. (2015) stated that the costs should be discounted. The later a cost incurs, the better because the saved money can be invested for profit.

This is taken into account in the discount formula that calculates the present value P in the year n with the discount rate r (Drummond et al., 2015):

$$P = \sum F_n(1 + r)^{-n}$$

In the formula, F_n is the cost incurred in year n. According to Drummond et al. (2015), 3-5% is usually used as the discount rate r. In this study, all the costs were discounted with a discount rate of 3%.

2.3 Patient delay and misdiagnosis

The National Academies of Sciences (2015) report stated that misdiagnosis is one of the worst medical errors, as it can lead to dangerous and costly consequences such as incorrect treatment and delayed correct treatment. The report also noted that misdiagnosis is a relatively common problem, with most patients experiencing it at least once in their lifetime. As Newman-Toker et al. (2021) pointed out, the rate of misdiagnosis varies significantly depending on the disease. They found that the diagnostic error rates varied between 2.2% and 62.2%, with the highest rates observed in rare diseases.

National Academies of Sciences (2015) conceptualized a diagnostic process model starting from a patient having problems with their health and looking for help in the healthcare system. After the patient contacts the healthcare system, their condition is studied through interviews, exams, and seeking information on their clinical history. This gathered information is integrated and interpreted, and a working diagnosis is formed. This process can be repeated until the diagnostic team thinks they have a diagnosis that accurately matches the patient's health problem. Then the diagnosis is communicated to the patient, and the treatment is started. National Academies of Sciences (2015) stated that clinicians must not be sure about the diagnosis to start the treatment. However, they need to have sufficient certainty and consider the risks of implementing the treatment and postponing it to gather more information. After the clinicians receive feedback from the treatment, they can go back to the iterative loop to refine the diagnosis and seek better treatment if needed. The diagnostic process is illustrated in figure 2.

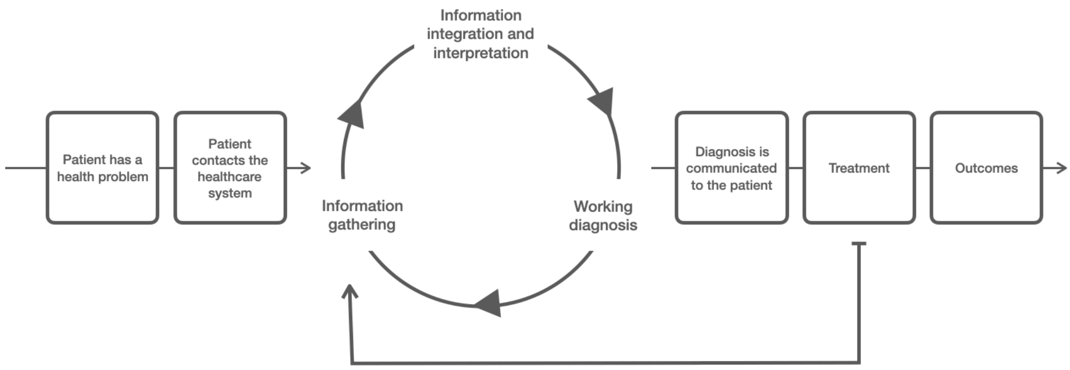

Figure 2. Diagnostic process (Adapted from National Academies of Sciences, 2015)

Walter et al. (2012) explained the five types of delay defined in the General Model of Total Patient Delay. 'Appraisal' and 'illness delays' happen when a person takes time to notice that their symptoms need professional care and decide to seek medical help and 'behavioral' and 'scheduling delays' refer to the time that it takes the person to seek help and get to an appointment with a medical professional. This work focuses on the 'treatment delay' that Walter et al. (2012) defined as the time it takes to get treatment after the first appointment.

2.3.1 Reducing patient delay and misdiagnosis

National Academies of Sciences (2015) stated that diagnostic processes should be improved and listed recommendations for developing them. The recommendations included better communication between the stakeholders to make the patients feel more comfortable, increase awareness of different diseases among healthcare professionals, and learn from diagnostic errors. The organization also argued that the research on the diagnostic process should get more funding, and health information technologies should be developed to support the diagnostic process.

In this work, we are interested in health information technology and primarily clinical decision support systems, which the National Academies of Sciences (2015) described as systems that arrange and filter large amounts of data so that it helps healthcare professionals to make accurate diagnoses. As they explained, the idea of a decision support system is not to make decisions but to support the decision-making while the final decision is always made by a human that also has other information available. The final decision can be used as feedback to the system, creating a loop that trains the system to make better suggestions. The feedback loop is illustrated in figure 3.

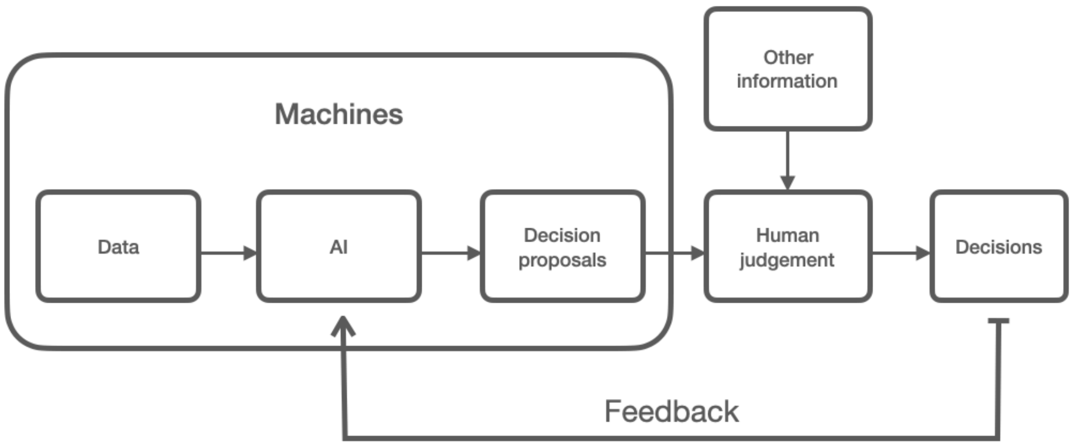

Figure 3. Decision support system feedback loop

Decision support systems often use different forms of artificial intelligence, which Ilhan et al. (2021) defined as machines having human-like behavior and intelligence. They stated that as computers have become more and more efficient in processing large amounts of data, algorithms that detect diseases even better than human experts are developed. It is possible due to the computer's ability to process data from various information sources more efficiently than a human brain and detect small details that the human eye cannot see. According to the authors, clinical decision support systems using artificial intelligence to detect cancers from images are examples of such systems performing better than human experts. However, the National Academies of Sciences (2015) warned that even though the decision support systems are promising, they still need much development and the experts have to be careful not to trust them too much.

Sutton et al. (2020) discussed the pitfalls of clinical decision support systems. They stated that it is essential to make them easy to use so that no special computer skills are needed to use them and that they do not disrupt the clinician workflow. They also claimed that if the system makes too many alerts, it can cause alert fatigue, make clinicians distrust the system, and even ignore the alerts making it useless. On the other hand, Sutton et al. (2020) pointed out that a well-working decision support system can make the users rely on it too much, affecting their skills negatively and causing risky situations if an expert does not double-check the decisions. The authors also stated that it is crucial to keep in mind that the system and the data it uses must be maintained well, which can be expensive and result in bad results if not done properly. Finally, Sutton et al. (2020) warned that there is a lack of research on the cost-effectiveness of clinical decision support systems, and the existing analyses have had mixed results. They stated that developing a new system, setting it up, and continuously training new staff to use it can result in high costs, and cost savings can be challenging to measure.

2.3.2 Existing decision support systems for rare disease diagnosis

According to Faviez et al. (2020), there are already many clinical decision support systems for rare diseases, and studies about them have increased in recent years. In their review, the authors analyzed articles about these systems and found a variety of prototypes and more advanced tools. They stated that 52% of the studies claimed to have developed a functioning system, but most were not tested in real-life scenarios. To prove the usefulness and accuracy of any decision support system, not only retrospective but also prospective assessment seems mandatory. Most of the approaches were based on artificial intelligence and used health data such as images or knowledge acquired from experts, existing literature, and databases. Faviez et al. (2020) stated that the systems generally found the correct diagnosis, but it was difficult to compare the results due to a lack of standardized evaluation metrics. The authors divided the systems into two categories defined earlier by Montani and Striani (2019): knowledge-based and data-driven systems. Knowledge-based approaches use knowledge derived from existing literature or experts in a top-down fashion. The human experts report how they solve problems and this knowledge is formalized into a software. On the other hand, data-driven systems work in a bottom-up fashion processing big amounts of data to find patterns in it and for example, make predictions. Montani and Striani (2019) state that both types have their own limitations; knowledge-based systems cannot process large amounts of data and they need a lot of effort to develop, but data-driven approaches require a lot of data and computing power.

One promising knowledge-based decision support system for rare diseases mentioned by Faviez et al. (2020) and developed by Ronicke et al. (2019) is Ada DX. According to Ronicke et al. (2019), it is an application that clinicians use to search for symptoms and diagnoses and to add new cases to the system's knowledge base. The application uses its reasoning engine to match symptoms with possible diagnoses and then ranks the diagnoses by probability and how well they fit with the symptoms. All common and hundreds of rare diseases are modeled in the Ada DX knowledge base created by acquiring information from existing literature reviewed by experts. Ronicke et al. (2019) stated that in 54% of the cases, the correct diagnosis was in the application’s top 5 fit suggestions earlier than the clinical diagnosis. The accuracy of Ada DX was also relatively high, as at the time of clinical diagnosis, its top suggestion was correct in 89% of the cases. However, Faviez et al. (2020) pointed out that the application still needs further development and better validation before it can be used in real-life situations.

More mature, already usable knowledge-based tools are, for example, PubCaseFinder (Fujiwara et al., 2022) and GDDP (Genetic Disease Diagnostic based on Phenotypes) (Chen et al., 2019). Both are online tools that aim to improve the diagnostics of rare genetic diseases and have an interface where a user can input the phenotype of a patient. Then, the system suggests possible diagnoses according to the input. To develop PubCaseFinder, Fujiwara et al. (2022) combined different disease definition databases and created a matching algorithm that compares similarities between the patient and disease phenotypes. The authors tested the algorithm with actual case reports, and in 55% of the cases, the system listed the correct diagnosis in the top 10 suggestions. Fujiwara et al. (2022) state that since its release in 2017, PubCaseFinder has become more popular each year, and in 2021, more than 10 000 queries were made to it. GDDP, developed by Chen et al. (2019), is a very similar system to PubCaseFinder, using official disease and phenotype definitions from databases and searching for similarities and overlaps with the patient phenotypes. When tested, the correct diagnosis was in the system's top 10 suggestions in 60% of the simulated cases and 30% of the real cases.

Shen et al. (2018) developed an entirely data-driven system for rare disease diagnosis. Unlike many other systems, their approach does not match patients with diseases but instead looks for similarities in different patients' symptoms and classifies them. To do this, the system uses electronic medical records and medical literature. The idea was similar to the technology used in e-commerce, where customers are suggested to buy more products according to other similar customers' purchase histories.

Basel-Vanagaite et al. (2016) developed another data-driven system that recognizes Cornelia de Lange syndrome, a rare genetic disease, from patients' facial images. The system analyses images by locating their different facial points and computing facial properties like distances between the points. Images of people with different genetic syndromes were used in training, and the system used the images to create a classifier for Cornelia de Lange syndrome. The classifier could score new images according to their similarity to the syndrome phenotype. The system was tested with new images, and it classified correctly 87% of them while human experts' detection rate was 77%.

Barnhart-Magen et al. (2013) combined both data-driven and knowledge-based approaches to find a way to reduce the diagnosis costs of a rare disease called thalassemia. They stated that expensive tests are needed to diagnose the disease, and there was no effective way to screen it broadly from routine blood counts. Their system uses artificial neural networks to process relevant blood sample parameters picked by experts and points out the patients that might have thalassemia. When tested with patients with thalassemia and a control group, the system reached a specificity and sensitivity of 0.9-1, depending on which types of the disease were included. Barnhart-Magen et al. (2013) stated that the system could be used for screening a larger population to avoid doing unnecessary and high-cost tests for so many people. Table 1 summarizes the discussed decision support systems.

The algorithm developed by HUS and Tietoevry is based on both knowledge and data. Expert knowledge was used to develop the algorithm, and the HUS patient data was used to train it. Recognition of patients with rare diseases was developed with supervised learning, and general characteristics of the patient groups were explored with unsupervised learning. Compared to other clinical decision support systems, the studied algorithm has access to a considerably large amount of real patient data. It is also different from most of the solutions developed with English data as it uses the HUS patient data in Finnish.

Table 1. Summary of the described clinical decision support systems

System	Knowledge-based	Data-driven	Accuracy	Used technologies/ methods	Used data
Ronicke et al. (2019)	x		89 %	Probabilistic reasoning engine	Diseases modeled to the knowledge-database by experts and literature
(Fujiwara et al., 2022)	x		Correct diagnosis in top 10 suggestions 55 %	User-weighted matching algorithm	Disease definitions from existing databases
(Chen et al., 2019)	x		Correct diagnosis in top 10 suggestions 30% / 60%	Semantic similarity, weighted overlapping	Disease and phenotype definitions from databases
Shen et al. (2018)		x		Collaborative filtering, data fusion	Patient symptoms from medical records
Basel-Vanagaite et al. (2016)		x	87 %	Automated facial recognition, statistical models	Images of people with genetic syndromes
Barnhart-Magen et al. (2013)	x	x	Sensitivity 0.9-1 Specificity 0.97	Artificial neural networks	Data from blood sample and parameters chosen by experts

2.3.3 Increasing cost-effectiveness with decision support systems

Many of the studies of decision support systems aiming to expedite diagnosis concentrate on the sensitivity and specificity of the systems and whether they spot the diseases earlier than an expert. However, it should also be studied what effects the earlier diagnosis has and, especially in the scope of this thesis, how much costs can be saved with decision support system expedited diagnoses.

Barnhart-Magen et al. (2013) claimed that the system they developed for diagnosing thalassemia could save diagnostic costs by reducing the need for expensive tests, but they did not specifically study that. Willmen et al. (2021) measured the costs that could be saved using the decision support system Ada DX presented by Ronicke et al. (2019). Willmen et al. (2021) analyzed 76 patient cases of a rare inflammatory disease and documented all the disease-related diagnostic measures from the beginning of the symptoms to the diagnosis. They used the prices defined in a German healthcare remuneration system to assign a price for each diagnostic measure to calculate the total costs of the diagnoses. The potential savings from having used Ada DX were calculated by summing the costs incurred after the assumed timestamps of the system displaying the correct diagnosis in its top-5 or top-1 suggestion. The patient data was not run through the system, but they used the timestamps defined by Ronicke et al. (2019). According to Willmen et al. (2021), 49-32% of the total costs could have been saved if Ada DX had been used early in the studied cases.

3. Rare diseases diagnosis at HUS

This chapter starts with an overview of HUS (until 2023, Hospital District of Helsinki and Uusimaa, from 2023 onwards HUS Group, The Joint Authority for Helsinki and Uusimaa) including its University Hospital and how rare diseases are diagnosed and treated in it. The second part of this chapter describes the decision support system developed for rare disease diagnoses.

Finland’s largest hospital district HUS (2022), employs 27 000 people and has 2.2 million people in its catchment area. It takes care of Finland's most complex medical care, including many rare diseases. HUS is one of the best hospitals in Europe, providing rare disease knowledge, and it uses 18% of its annual budget on rare disease treatment (HUS, 2021). HUS has a center for rare diseases that, according to Seppänen (2019), does not admit patients but works as a centralized rare disease support center that helps to remit patients to the correct clinics and find the correct expert, diagnosis, and treatment. Seppänen (2019) stated that the center develops digital services that provide, among other things, peer support for patients and their families and consultation for experts. The center collaborates with different rare disease organizations, and HUS (2021) is a member of 23 European Reference Networks (ERN) networks that connect different rare disease experts in Europe. Seppänen (2019) explains that the rare disease center also researches rare disease treatment paths, costs, and quality.

3.1 Diagnostic path of a rare disease patient at HUS

Patients with rare diseases are often the most expensive ones to treat and treating them accounted for 18% of the overall costs of HUS specialty care, three times more than the costs of other patients. As rare diseases are complex to diagnose, the patients may need to visit numerous clinicians and even go back and forth between the same wards several times before getting the correct diagnosis. The complexity can be seen in figure 4, which illustrates a path of a typical rare disease patient. The nodes in the figure represent the wards the patient visited, and the edges illustrate how the patient was transferred from one ward to another. The wards that the patient visited multiple times are marked with red nodes.

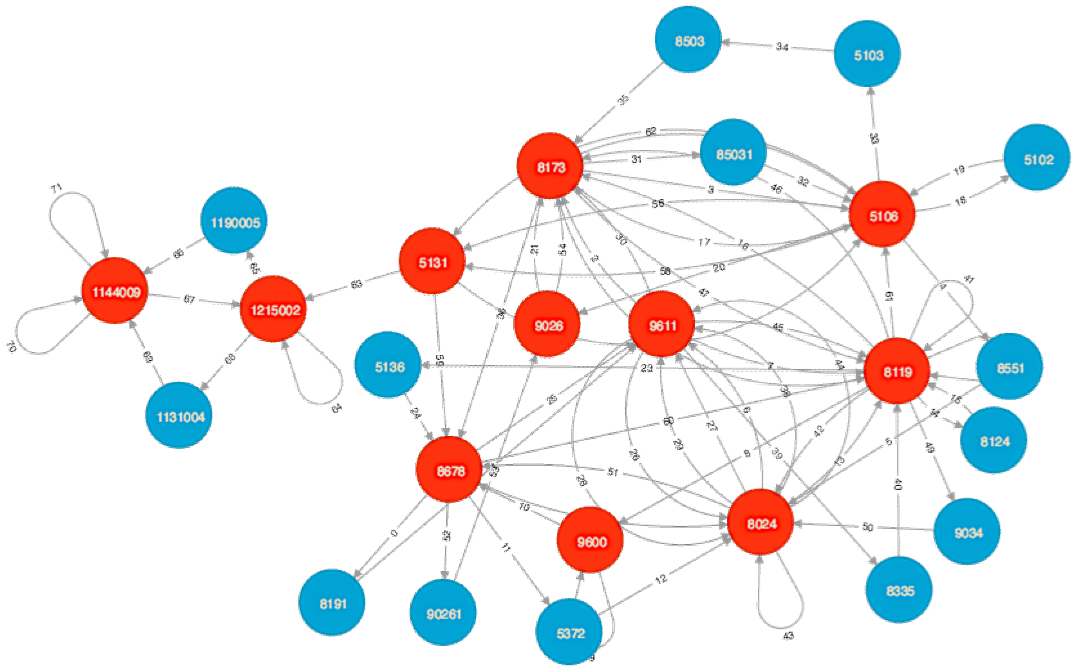

Figure 4. A typical diagnostic path of a rare disease patient

Some transfer loops might be normal and expected as the patient may need, for example, a laboratory test not provided by the referring ward. However, there are probably many unnecessary referrals due to errors like clinicians not knowing the best place to refer the patient. Numerous visits to different wards and long waiting times are expensive and negatively affect the patient's life. They must wait for the diagnosis, and their condition may worsen while the correct treatment is delayed.

However, the diagnostic paths of different patients vary a lot, and this is also the case with vasculitides. The Director of the HUS Rare Diseases Center, Seppänen (2022), stated that they are often unpredictable, and one patient can be fine for years, while another may get an organ failure after a few weeks. According to them, many vasculitis patients must visit many specialists seeking help for problems in different parts of their bodies. However, often every specialist treats only the problem concerning their area of expertise and gives temporal relief to the patient without noticing that a more significant underlying condition causes all the odd symptoms.

Therefore, as Seppänen (2022) pointed out, many vasculitis patients end up with organ failure before they get the correct diagnosis. According to Seppänen (2022), the last months before diagnosis are often the most expensive. Diagnosing a vasculitis patient just a few months earlier could save millions of euros and prevent organ failure. Seppänen (2022) stated that vasculitides are usually diagnosed from blood samples, biopsies, or by a specialist who can see them from a patient's medical history.

3.2 Decision support system for rare disease diagnosis

One of the research projects of the HUS rare disease center is the CleverHealth Network's eCare for Me, which develops solutions to improve the diagnosis and treatment of rare diseases, acute leukemia, and home dialysis patients. The rare disease project aims to develop an algorithm using artificial intelligence to recognize patients with rare diseases. Currently, the algorithm is trained to identify three disease groups that are frequent, expensive to diagnose but possible to treat, and have high failure demand: vasculitides, myositides, and glomerulonephritides.

The algorithm processes health data derived from the HUS data lake that includes, for example, disease-specific ICD-10 codes, laboratory results, and text from patient visits and charts written by clinicians. To identify patients with rare diseases, the algorithm uses residual neural networks, which He et al. (2016) described as normal neural networks where it is possible to skip layers by additional shortcut connections. One challenge is that due to their rarity, the amount of data from rare diseases is smaller than from more common conditions, and to work properly, artificial intelligence-supported decision support systems need large amounts of data. Therefore, the algorithm uses ”collaborative filtering,” a process described by Shen et al. (2018). According to them, a collaborative filtering system concentrates on classifying patients into different possible disease groups rather than finding an exact diagnosis. The algorithm can accurately spot patients with certain rare diseases by combining collaborative filtering with patient paths, previous diagnoses, and expert judgment. It also uses the typical diagnostic closures found in previous studies in its judgment. Ryyppö (2021) stated that when tested with retrospective data, it could identify the diseases almost six years before the original diagnosis with 78.9-87.1% sensitivity depending on the disease. The results were even better closer to the original diagnosis date reaching 82.5-89.4% sensitivity 30 days before the original diagnosis.

The algorithm is novel due to its use of collaborative filtering, typical diagnostic closures, and patient paths together with expert judgment. It also has access to a large amount of data that is the same as the data the clinicians use in their daily work. Because of this, the algorithm can be tested as if it was in a real-life clinical setting. In addition, it is geographically unique as it is developed to work with data in Finnish.

The goal is that in the future, the algorithm could be used in processing patient data and spotting patients that might have vasculitis. This information could be used for examining these patients and diagnosing them earlier than without the intervention of the algorithm. Currently, the algorithm is still in development, and some changes in law must happen before it can be taken into use. For example, it would be illegal to contact a patient spotted by the algorithm, making it difficult to invite these patients to further examinations. Furthermore, the user interface of the algorithm and workflows for reacting to its notifications are not yet designed.

4. Research data and methods

This chapter describes the data used in the research and how it was collected. Also, the patient sample and its selection are presented, and the research methods for answering each research question are described.

4.1 Data collection

This study used the data derived from the HUS data lake that contains all the clinical data from the patients of HUS. The data includes patient information like previous diagnoses and electronic patient records and information related to patient visits such as investigations and treatments given to the patients. The data lake is based on the cloud computing software Microsoft Azure® which is an environment used, for example, for managing applications and large amounts of data through the data centers of Microsoft. The data in the HUS data lake can be structured, unstructured, and binary, like images and audio.

This study utilized data from the HUS data lake, including costs and diagnoses related to vasculitis patients' contacts with HUS as well as the general demographic information of these patients. The data were anonymized so that each patient was marked with a number and individualizing information such as name and social security number were not accessible. The patient sample is described further in chapter 4.2.

To understand the cost structure of the diagnostic process of vasculitis and the path of vasculitis patients, semi-structured interviews were conducted with the Director of the HUS Rare Diseases Center Mikko Seppänen. The goal of the interviews was to get a professional opinion for selecting the costs to be included in the cost calculation. Seppänen also gave their points of view on how the algorithm could be used in the production system of diagnosing rare diseases.

The data sources used in this study are summarized in table 2. The data were imported from the data lake to the AzureML environment in the virtual HUS researcher's workspace. There it was analyzed in the computing platform Jupyter using the programming language Python.

Table 2. Data sources used in the study

Data source	Description
Cost data	The costs related to patient visits, procedures and treatments
Diagnosis data	Patients' contacts to HUS and the diagnoses given on every contact.
Patient data	Demographic data including the age, gender and location of every patient
Expert interviews (Seppänen, 2022)	Vasculitis and its diagnosis, costs related to different stages of vasculitis and how an algorithm could be used to expedite vasculitis diagnosis

Each patient was assigned a diagnosis and diagnosis date by choosing the first vasculitis diagnosis and its date in the diagnosis data. Each patient's cost data was filtered by including the cost data rows whose start or end date was within the three months before the diagnosis. Some rows in the cost data had abnormal end dates years after their start dates. Most of these rows were minor procedures costing less than 1000€, so the end dates were probably mismarked. Therefore, the end dates of these low-cost rows were changed to be equal to their start dates. On more expensive rows, the end dates were changed to a maximum of one year after the start date.

4.2 Patient sample

The diagnosis and patient data contained all the HUS patients diagnosed with vasculitis between 2/1/2004 and 23/8/2022. In total, there were data from 3170 patients. However, the cost data only contained the data from 13/12/2008 to 31/12/2021. Therefore, to calculate the costs three months before diagnosis, the patients diagnosed before 13/3/2009 or after 31/12/2021 were excluded. In total, there were 2306 patients in this study, of which 1185 (51.4%) were female and 1121 male. There were patients of all ages; the average age was 42 years. The most common age of diagnosis was around 3-9 years, and the number of patients also increased slightly after the age of 60. The age distribution can be seen in figure 5, and the age distribution by gender can be seen in figure 6.

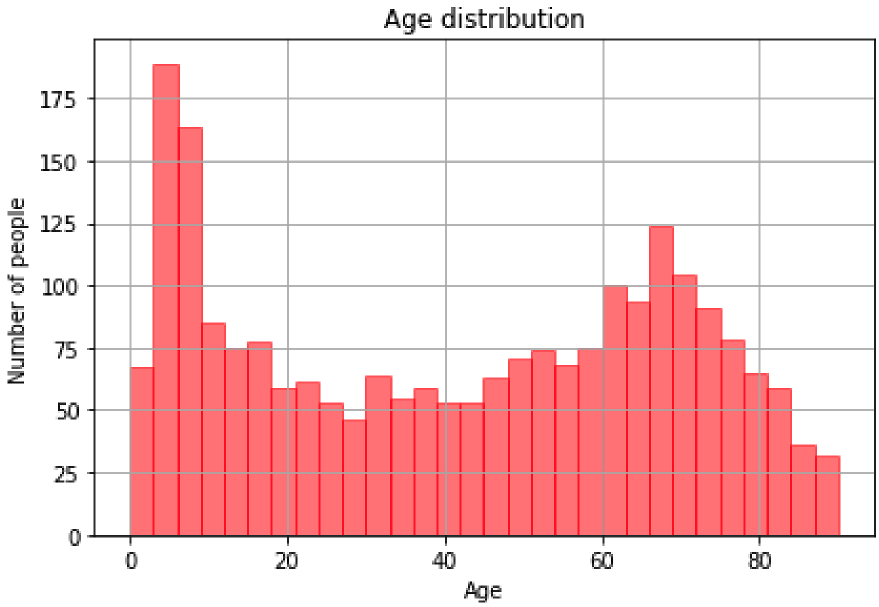

Figure 5. Age distribution

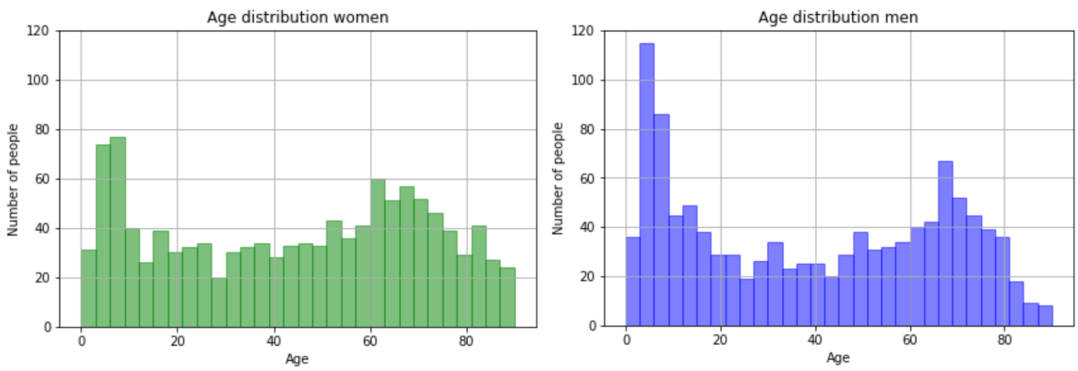

Figure 6. Age distribution by gender

The patients were grouped by their first vasculitis diagnosis in their medical history. The most common diagnosis was allergic purpura which was the diagnosis for 61.9% of the patients. The diagnoses are listed in table 3.

Table 3. Vasculitis diagnoses

ICD-10 diagnosis code	Diagnosis	Number of patients (n=2306)
D69.0	Allergic purpura	1428 (61.9%)
M31.3	Granulomatosis with polyangiitis	426(18.5%)
M30.0	Polyarteritis nodosa	169 (7.3%)
M31.7	Microscopic polyangiitis	157(6.8%)
M30.1	Polyarteritis with lung involvement - Strauss syndrome	65(2.8%)
M31.4	Aortic arch syndrome - Takayasu's arteritis	61(2.6%)

4.3 Research design and methods

4.3.1 Cost calculations

To understand the cost structure of vasculitis's diagnostic process and answer RQ1.1, real patient data from HUS and municipal registries was used. The diagnostic paths of every patient were reviewed 90 days prior to their diagnosis, and the costs were calculated. Initially, the plan was to review diagnostic paths from the first contact with healthcare to the diagnosis, but due to the difficulty of defining the first contact for every patient, a period of three months prior to diagnosis was chosen. Patients with vasculitis are often diagnosed late, and they may already be in poor condition by the time of diagnosis, which leads to more treatment close to the diagnosis making the last months the most expensive. As Seppänen (2022) stated, undiagnosed vasculitides often lead to organ failures that cost millions of euros to treat and cause unnecessary human suffering. He claimed that diagnosing a vasculitis patient three months earlier would allow doctors to start the correct treatment before organ failure and prevent it. According to Ryyppö (2021), the algorithm can recognize vasculitis patients with high certainty 90 days before the diagnosis. By reviewing the costs of that period, it was already possible to study the algorithm's potential for cost-saving in this thesis.

As recommended in ABC (Lievens et al., 2003), each activity on the path was assigned a cost, and the total costs of each patient's diagnostic process were calculated as a sum of these activity costs. In the cost data, one activity meant one patient contact with HUS that could last more than one day. The cost calculations included all the patient contacts that were even partly in the 3-month analysis period. The costs were not filtered according to whether they were related to the vasculitis diagnosis, so the calculations were made using all the costs from the patient contacts with HUS.

The cost data consisted of all the patient contacts with HUS. Each of these contacts was assigned a cost that was then categorized into one of 25 categories. The categories were divided further into direct and indirect costs, as seen in table 4.

Table 4. Cost groups

Cost group	Cost categories
Direct costs	1. Physiological examination 2. Neurophysiological examination 3. Inpatient consultation 4. Surgical procedures 5. Medical treatment 6. Inpatient care 7. Outpatient care 8. Outpatient visits 9. Rehabilitation 10. Laboratory 11. Blood products 12. Pathology 13. Imaging 14. Aids and equipment 15. Expensive equipment 16. Outpatient care in another hospital district 17. Inpatient care in another hospital district 18. Services related to special healthcare bought from outside of HUS 19. Extra visits (no cost to HUS) 20. Pharmacy services and medicine delivery
Indirect costs	21. Transportation 22. Pharmacy services and medicine delivery 23. Vouchers 24. Correcting invoicing 25. Translation 26. Other costs

Direct costs are directly related to patient care. They include patient examination and procedures and treatments performed on the patient. Services bought from other hospital districts are also included in the direct costs as they occur directly in patient care. Indirect costs consist of any other costs that are not directly related to patient care. These costs include invoicing, translation, transportation of people, equipment, and medicine.

4.3.2 Regression models

To understand better the cost structure and variables affecting the total costs and to answer RQ1.2, a regression analysis was conducted. The total costs per patient three months before diagnosis were assigned as the dependent variable in the regression model. The independent variables were patient age, gender, and diagnosis. Age was a continuous variable, and gender and diagnosis were categorical variables. The model was assessed by analyzing the numbers describing the fit of the data and visualizing them.

4.3.3 Qualitative analysis

To form the different patient paths over the last three months before diagnosis and to answer RQ1.3, the diagnosis data was used. One vasculitis diagnosis group was selected, and the distribution of the number of patient contacts and their total costs were studied. The patient with an average number of contacts and the total costs closest to the average was selected to describe the average path of a vasculitis patient.

To answer RQ2, the best way to use the algorithm in the production system of vasculitis diagnosis and prevention to maximize its benefits was discussed. In addition to the suggestions for the best use, also the risks were considered. The analysis was done by using the PROVE-IT model (Lillrank et al., 2019) and the opinions given by an expert. The possible cost-cut points were identified, and a suggestion for using the algorithm was created.

5. Results

The research results are presented in this chapter, and the research questions are answered. First, the costs of the last three months before diagnosis and the regression analysis are presented. Then, the average path of a vasculitis patient is formed.

5.1 Cost savings and the structure of the diagnostic process of vasculitis

Table 5 presents the costs incurred in the last three months before diagnosis. On average, the costs were 7375€ per patient. The costs for male patients were, on average, around 26% higher than those for female patients. The total costs were 17 007 159€, which averages out to 1 308 243€ per year when divided by the 13 years covered in the sample data.

Table 5. The costs of the last 3 months before diagnosis (discounted)

Measure	All patients (n=2306)	Women (n=1185)	Men (n=1121)
Average (€)	7375	6293	8519
Median (€)	1259	1096	1388
Total costs (€)	17 007 159	7 457 459	9 549 700

There were differences between the average costs per patient depending on the year. The cheapest year was 2019, with an average of 6118€, and the most expensive was 2015, with an average of 8459€. 2015 had the least number of patients(119), while 2010 had the highest number of patients(247). On average, there were 177 patients per year. The yearly average costs are presented in figure 7.

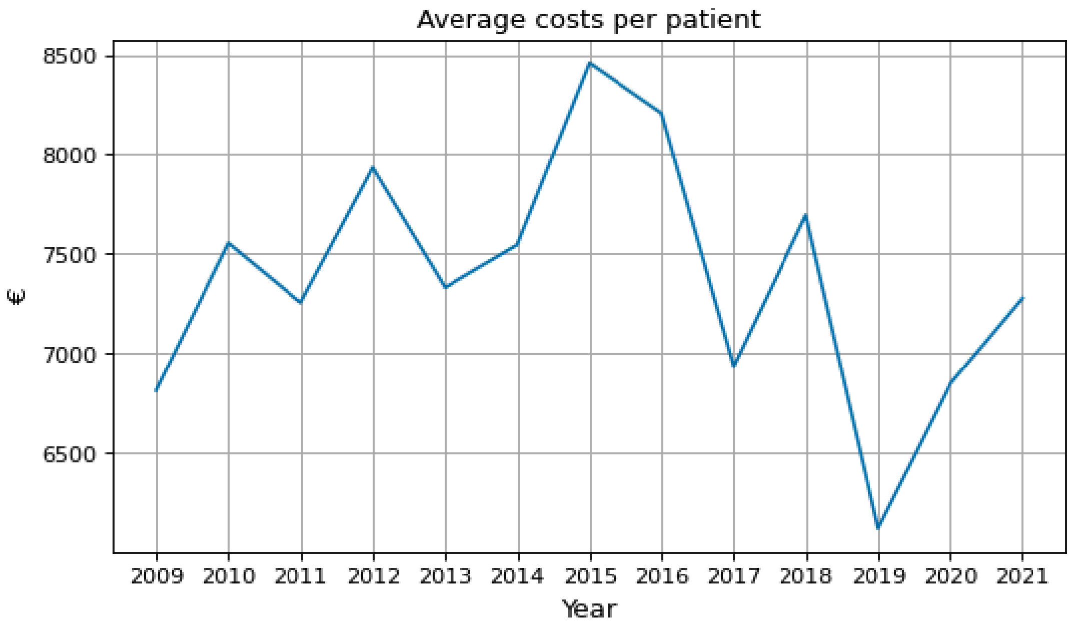

Figure 7. Average costs by year (discounted)

Table 5 shows that the median of the total costs was much smaller than the average. Therefore, most patients had relatively low costs, while a small number had very high costs. Total costs varied between 50€ and 209,570€. Half of the patients had costs of 1259€ or less, and 80% 8664€ or less. The percentiles are shown in figure 8.

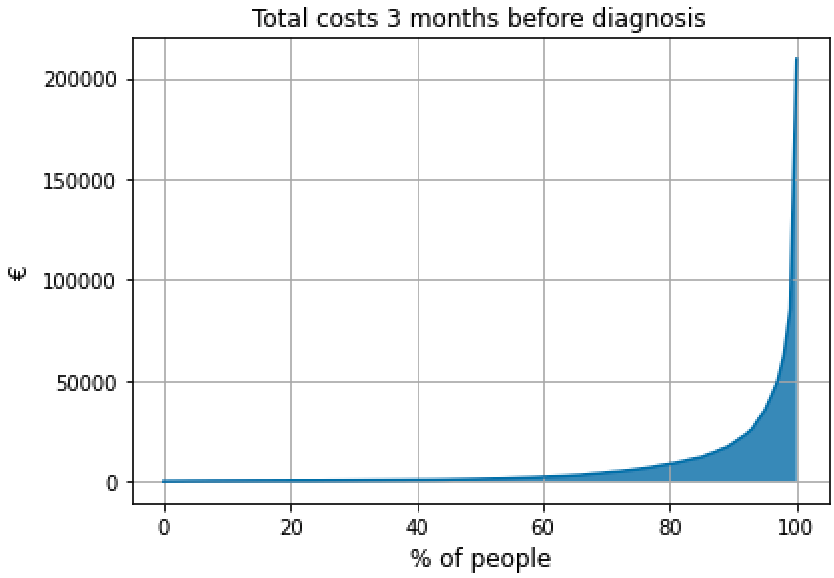

Figure 8. Percentiles of the total costs per person (discounted)

The average costs accumulated quite steadily during the last three months before the diagnosis until the last two days when the costs peaked. These days were, in general, costly for many patients, but also, many patients had no costs until the last days. The cumulative costs can be seen in figure 9.

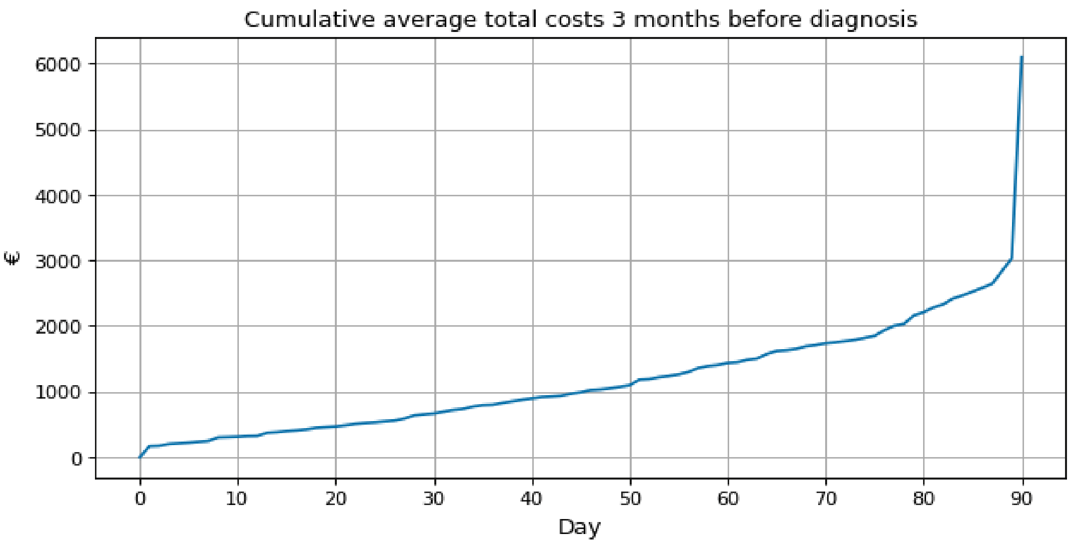

Figure 9. Cumulative costs (discounted)

All the most important cost categories were direct medical costs. The most expensive category was inpatient care which formed almost half of the costs of an average patient. The second most expensive categories were outpatient visits, surgical procedures, and outpatient care, all around 10% of the total costs. If outpatient care and visits are combined, they become the second biggest group forming 20.6% of the total costs. The cost structure can be seen in figure 10.

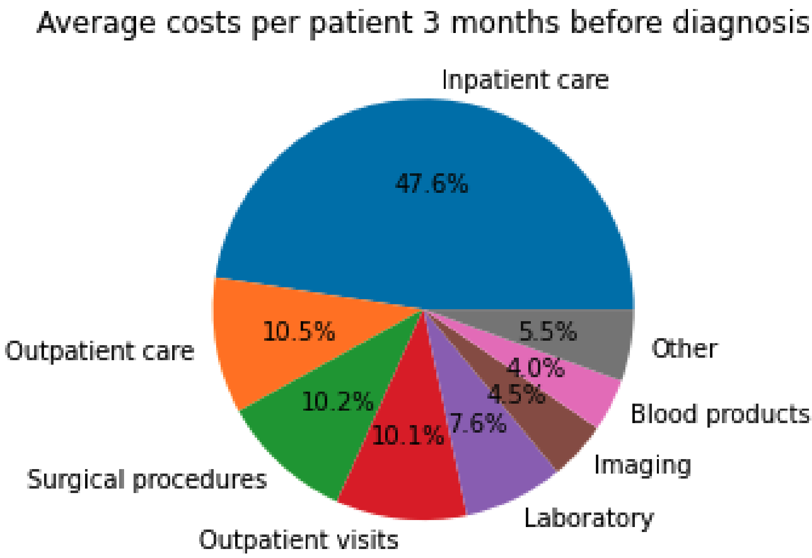

Figure 10. Cost structure (discounted)

The most expensive categories are explained below in the context of vasculitis patients. All these costs include the costs of hospital rooms, staff labor, and other fixed hospital costs.

1. Inpatient care: In inpatient care, the patient is already in very bad condition, and the correct treatment for them is searched. Their body functions are monitored to keep them alive and react fast if something changes.
2. Outpatient care: If a patient is sick but not yet in a critical condition, the procedures can be done as outpatient care sending the patient home afterward.

3. Surgical procedures: Surgical procedures are needed, for example, when a patient is in the intensive care unit for too long and cannot breathe anymore on their own. These procedures can also be part of the diagnostics, like taking tissue samples or opening a patient to see the problem inside them.
4. Outpatient visits: Outpatient visits are the same as outpatient care but do not include invasive operations. They are more just talking with a doctor that might, for example, prescribe medicine or refer the patient forward.
5. Laboratory: The laboratory is used for tests like looking for infections or antibodies. These tests can be, for example, blood culturing.
6. Imaging: All kinds of imaging methods are used in vasculitis diagnosis. Some used methods are x-rays, ultrasound, and radioisotopic imaging.
7. Blood products: Vasculitis patients need different blood products, for example, when they are anemic because of kidney problems or if they are done some procedure that requires blood products to be safe.

There were differences in the costs of different vasculitis diagnoses. M31.7 and M31.3 were the most expensive diagnoses, both with average total costs of over 16 000€. M30.0, M30.1, and 31.4 were all 8000-9000€ on average, and D69.0 was the cheapest diagnosis with an average of 3047€. The average costs of the diagnoses can be seen in figure 11.

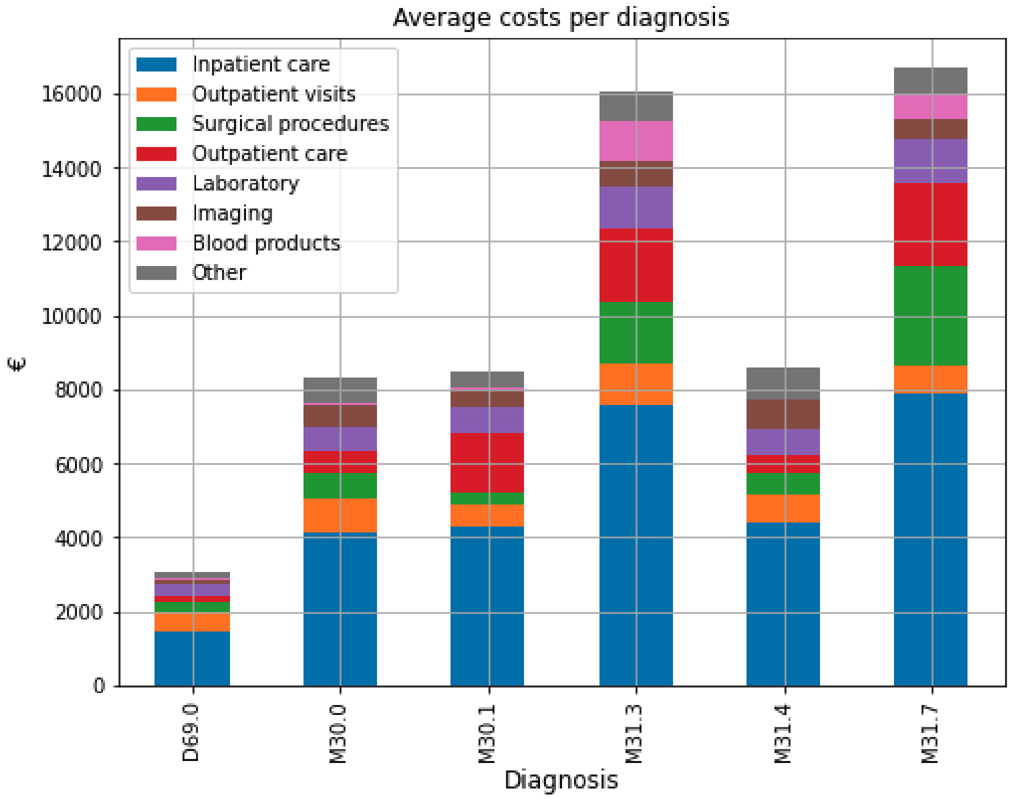

Figure 11. Diagnosis costs per diagnosis (discounted)

5.2 Factors affecting the total costs of the treatment path

To answer RQ1.2, a regression analysis was conducted. The dependent variable was the total costs three months before diagnosis. Age, gender, and diagnosis of the patient were independent variables. The variables are presented in tables 6 and 7.

Table 6. Continuous variables

Variable	Mean	Median	Min	Max	Standard deviation
Total costs (€, discounted)	7375	1259	50	209 569	17 311
Age (years)	41.7	44.0	0	94	27.1

Table 7. Categorical variables

Variable	Number of patients (n= 2306)
Gender (Female)	1185 (51.4%)
Gender (Male)	1121 (48.5%)
Diagnosis (D69.0)	1428 (61.9%)
Diagnosis (M31.3)	426(18.5%)
Diagnosis (M30.0)	169 (7.3%)
Diagnosis (M31.7)	157(6.8%)
Diagnosis (M30.1)	65(2.8%)
Diagnosis (M31.4)	61(2.6%)

The diagnosis D69.0 had the highest negative correlation (-0.31) with the total costs, while the diagnosis M31.3 had the highest positive correlation (0.27) with total costs. These two diagnoses also had a significant negative correlation (-0.61) with each other. The correlation between age and total costs was 0.18. The correlation matrix between the variables can be seen in figure 12.

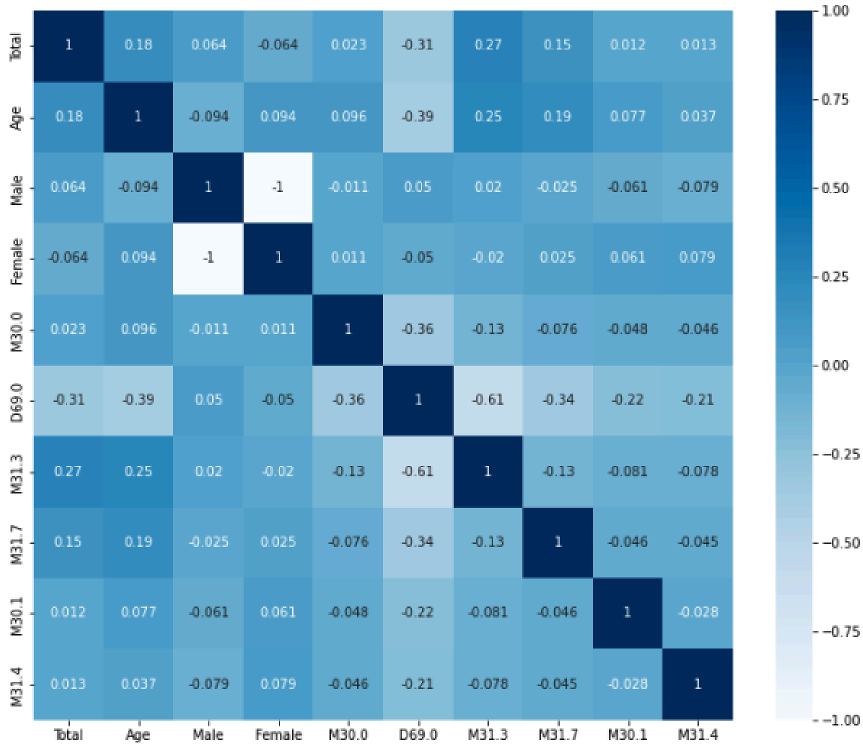

Figure 12. Correlation matrix

First, a linear regression model (OLS) was used to study the relationship between the patient characteristics and the total costs 3 months before the diagnosis. The model was tested for linearity, heteroskedasticity, and outliers. As the Q-Q plot in figure 13 indicates, the linear model did not seem to fit the data very well. Other diagnostic plots also showed some problems with heteroskedasticity and outliers.

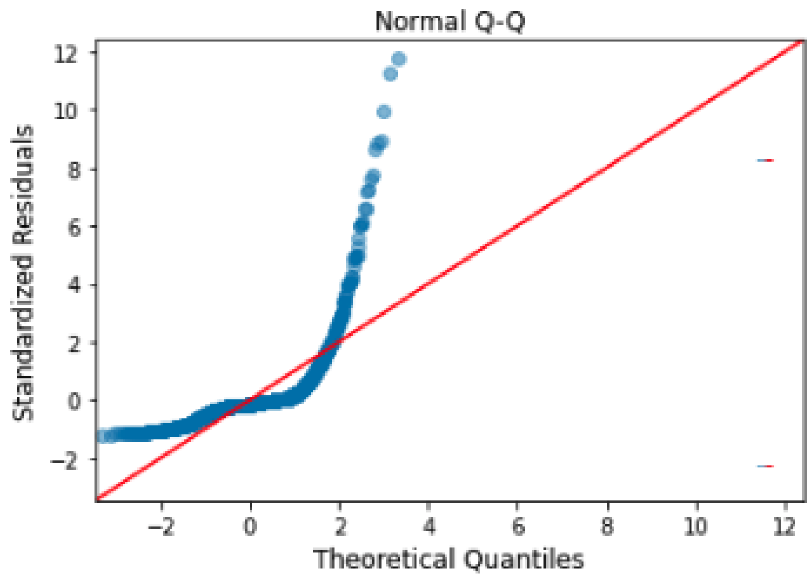

Figure 13. Q-Q plot of the linear regression model

The relationship between age and costs seemed to grow in a non-linear way, more specifically exponentially (see figure 14). Therefore, the data were fitted with a model where the dependent variable was log-transformed. Also, heteroskedasticity robust standard errors were used.

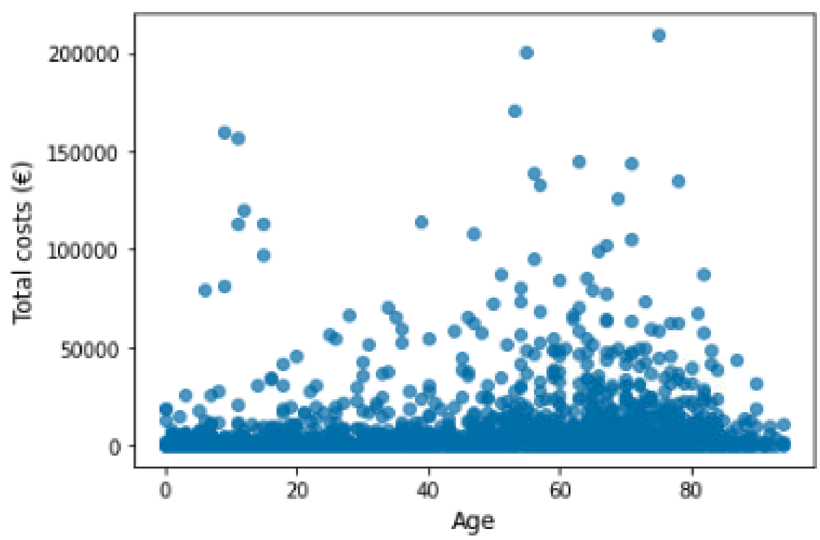

Figure 14. Total costs by age (discounted)

The results of the log-transformed regression analysis are presented in table 8. When tested for linearity, heteroskedasticity, and outliers, the log-transformed model works much better than the linear model. Figure 15 shows the diagnostics of the log-transformed model. Diagnosis D69.0 was selected as the reference category because, as seen in figure 11, it was the least expensive diagnosis.

Table 8. Regression of log-transformed total costs

	Coefficient	Std. error	z-value	p-value
Intercept	6.7501	0.050	135.057	0.000
Age	0.0104	0.001	8.648	0.000
Gender (female)	-0.3268	0.058	-5.610	0.000
Diagnosis (M30.0)	0.8575	0.126	6.798	0.000
Diagnosis(M30.1)	0.8685	0.200	4.332	0.000
Diagnosis(M31.3)	1.4792	0.093	15.895	0.000
Diagnosis(M31.4)	1.1683	0.207	5.634	0.000
Diagnosis(M31.7)	1.4725	0.144	10.254	0.000

n=2306, $R^2 = 0.255$

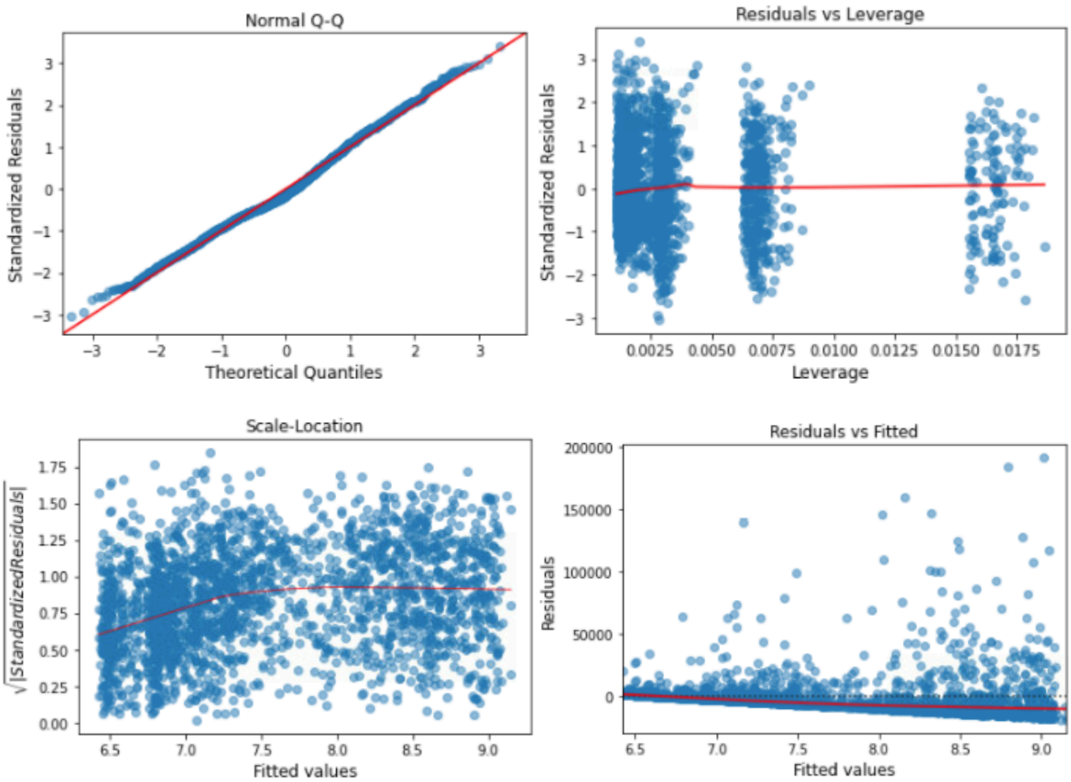

Figure 15. Diagnostics of the logarithmic regression model

Also, a generalized linear model (GLM) with Poisson regression was tested. Table 9 shows that the coefficients are close to the coefficients of the logarithmic model presented earlier in table 8. Log-transforming dependent variable is not ideal due to the problems related to interpreting the coefficients in the original metric. By using GLM with log-link, the issues associated with log-transforming the dependent variable are avoided. Poisson regression produces consistent estimates for the exponential model (Rönkkö et al., 2022). Thus, it was decided to proceed with the GLM, using heteroskedasticity robust standard errors.

Table 9. Regression of total costs with GLM

	Coefficient	Std. error	z-value	p-value
Intercept	7.9517	0.099	80.036	0.000
Age	0.0072	0.002	2.874	0.004
Gender (female)	-0.3522	0.093	-3.786	0.000
Diagnosis (M30.0)	0.9202	0.179	5.142	0.000
Diagnosis(M30.1)	0.9424	0.224	4.216	0.000
Diagnosis(M31.3)	1.5408	0.134	11.486	0.000
Diagnosis(M31.4)	1.0242	0.191	5.353	0.000
Diagnosis(M31.7)	1.5380	0.177	8.683	0.000

n=2306, Log-likelihood=-15541000

The coefficients in table 9 are static approximations, but actually, their non-linear effect is relative and dynamic and depends on the values of age and other variables. According to these approximations, one additional year in age accounts for a 0.72% increase in a patient's total costs three months before diagnosis. Therefore, a 50-year-old patient is estimated to be 7.44% ($1.0072^{10} = 1.0744$) more expensive than a similar 40-year-old patient. Likewise, the costs of female patients three months prior to the diagnosis are estimated to be 35.22% cheaper than those of male patients.

An adjusted prediction plot was created to describe better the non-linear relationship between the variables and the total costs. The prediction plot was calculated by adjusting the gender and diagnosis variables and using the GLM to predict the total costs in relation to age. The adjusted prediction plot can be observed in figure 16. It can be seen in it that the total costs depend highly on the diagnosis, increasing exponentially with the patient's age. The highest costs were for men whose diagnosis was M31.3 or M31.7. These diagnoses were also the most expensive in figure 11, and men were also more expensive in table 5. The exponential growth with age was steeper in these groups than in females and other diagnoses. However, women with M31.3 and M31.7 were the next most expensive groups, and the costs also grew quite steeply with age. On the other hand, in the cheapest diagnosis, D69.0, the growth was relatively moderate in both genders.

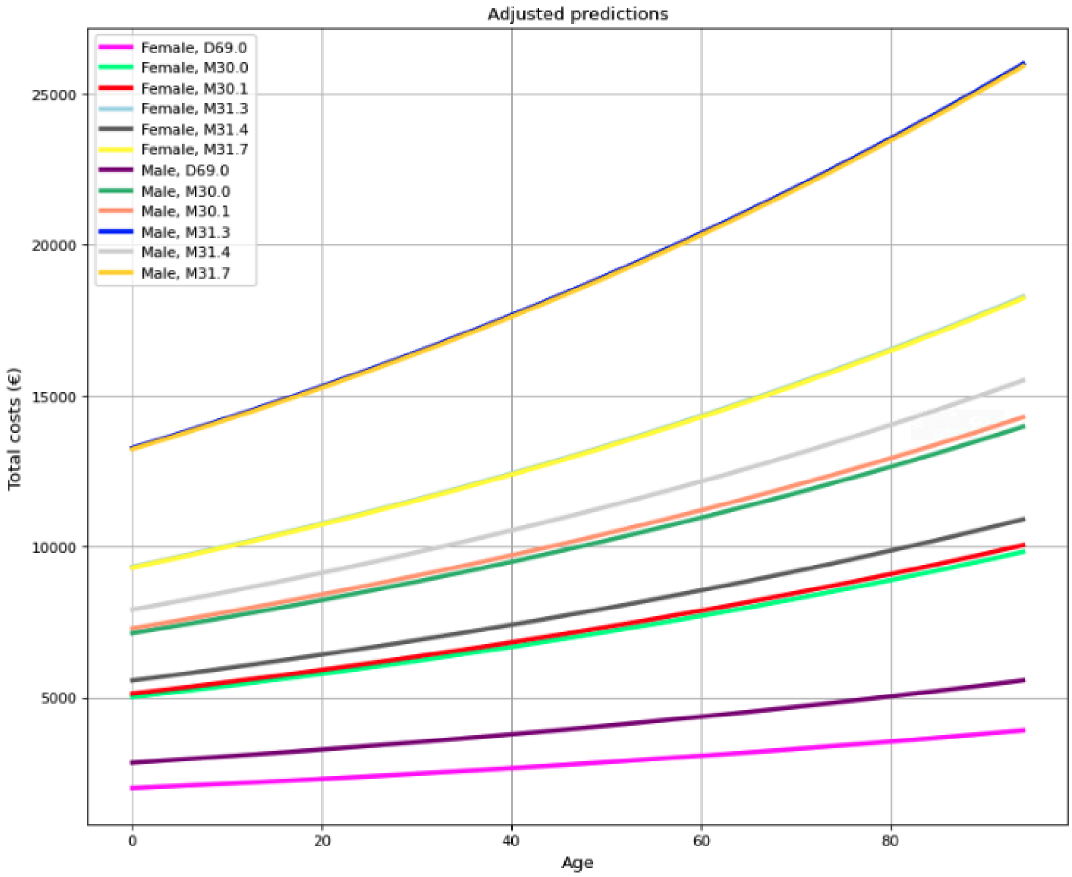

Figure 16. Adjusted predictions of the total costs of different genders and diagnoses

The model performed well in estimating total costs for low-cost patients, but its accuracy decreased when predicting costs for high-cost patients. This can be observed in Figure 17, where the true observations are plotted against the adjusted predictions. The adjusted predictions were only accurate for costs less than 30 000€, but there were cases where patients had total costs exceeding 200 000€. However, these were extreme cases and most patients had significantly lower total costs. As seen in chapter 4.3.1, 80% had total costs of less than 8 664€.

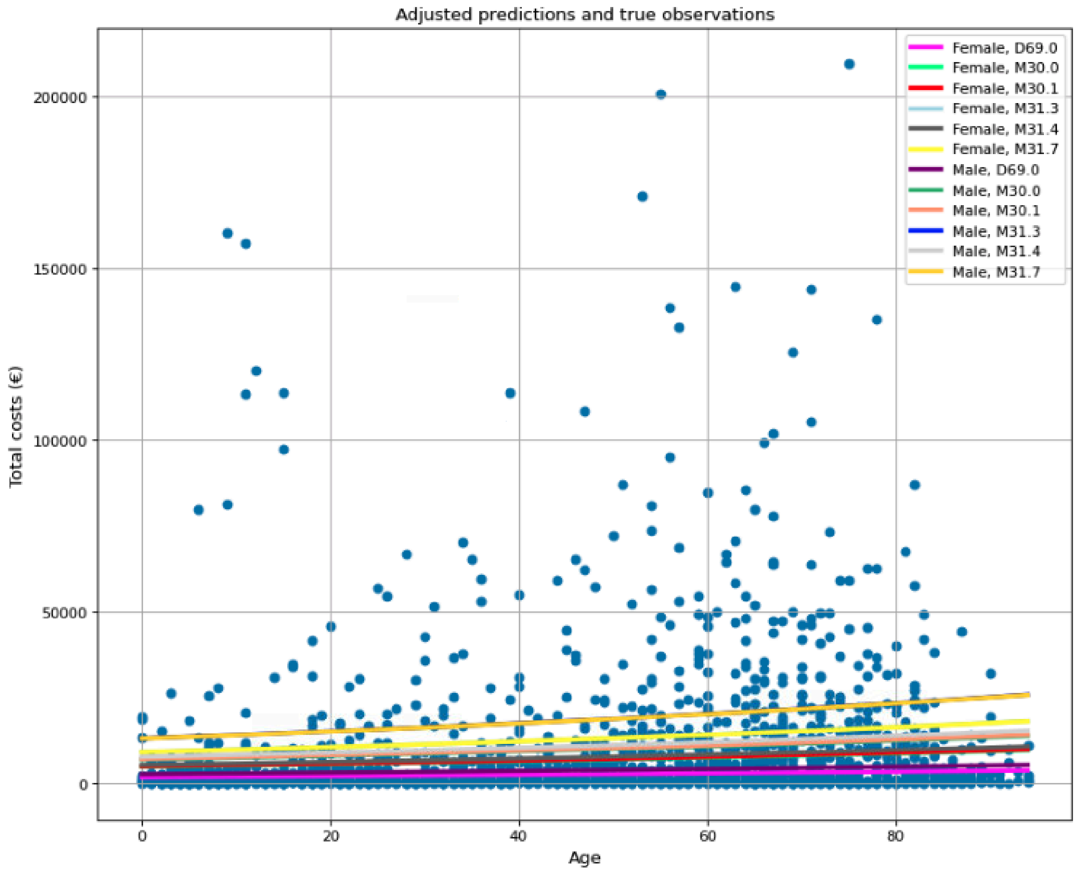

Figure 17. Adjusted predictions of different genders and diagnoses with true observations

5.3 Average treatment path of a vasculitis patient

To illustrate an average treatment path of a vasculitis patient during the last three months before diagnosis, granulomatosis with polyangiitis (M31.3) patient with average costs and an average number of patient contacts was selected. A patient with diagnosis number M31.3 was selected because it was the second most common diagnosis after allergic purpura (D69.0). D69.0 would not have represented a common treatment path because it is a special case of vasculitis and, as seen in figure 11, is also a lot cheaper to treat than other diagnoses.

Figure 18 shows the number of patient contacts and the total costs of patients with diagnosis number 31.3 during the last three months before diagnosis. Most of the patients had less than 20 contacts, but there were also patients with several dozens of them. The average number was 10. Patient contact is defined as one row in the diagnosis data. Each row includes the type of contact, the working diagnosis that was the reason for the contact, and the department where the contact occurred.

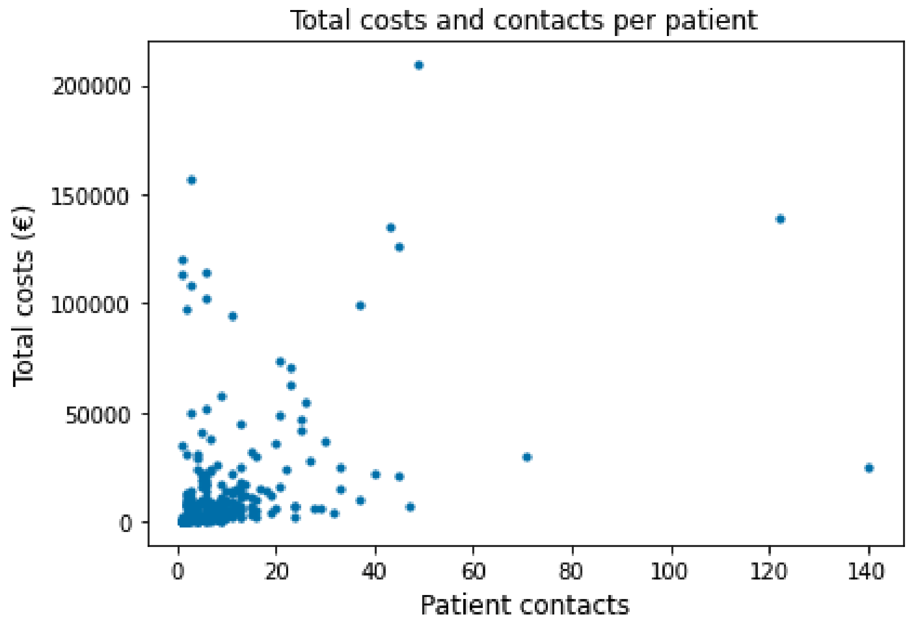

Figure 18. Number of patient contacts and total costs (discounted) per patient with diagnosis number 31.3

The selected average patient was the patient that had the average number of contacts and the total costs closest to the average(7375€). Thus, their number of contacts was 10, and their total costs were 7825€. Their treatment path during the last three months before their diagnosis is illustrated in figure 19. Each circle represents a patient contact and colors type of contact. Different departments are marked with boxes. Day 0 is the day of the diagnosis, and the arrows show the path between the contacts starting from the first day and ending with the date of diagnosis. The patient path started with several calls at the beginning of the three months. Twenty-eight days before the diagnosis, the patient visited the healthcare provider, and three days later, they were referred to another department. Then, they got a new referral from the earlier department six days before the diagnosis but ended up in inpatient care, where they were diagnosed with granulomatosis with polyangiitis. The costs of the activities starting on the day of the diagnosis were in total of 4876€, which is 62% of the total costs of the patient during the analysis period of three months.

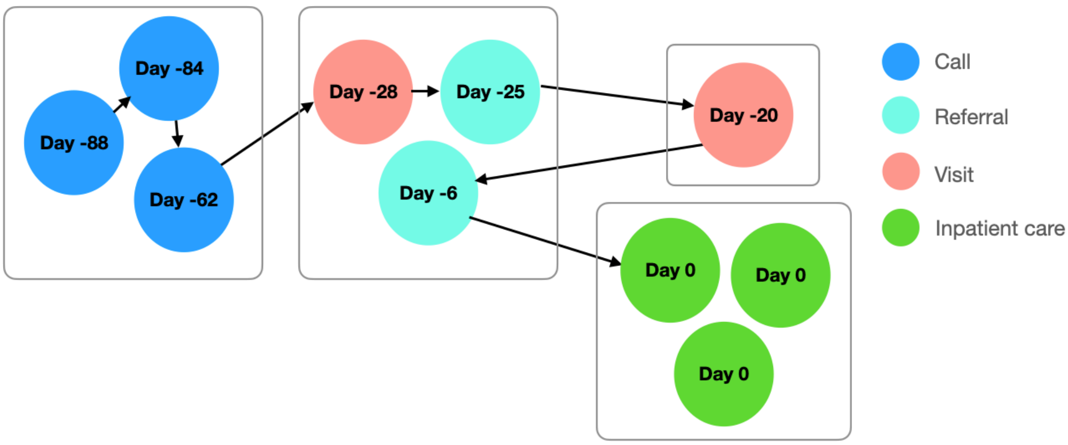

Figure 19. Average patient path during the last 3 months before diagnosis

6. Discussion

In this chapter, the results of this thesis are discussed. First, RQ1 and its subquestions are addressed by analyzing the cost calculations and qualitative analysis results. Then, the suggestions for using the algorithm are discussed, and the second research question is addressed. In the end, this study's limitations, future research, and conclusions are discussed.

6.1 Treatment path of a vasculitis patient and its costs

The first research question asked, how much costs could be saved with the algorithm. Its first subquestion was:

RQ1.1: What is the cost structure of the last three months of patients' diagnostic path for vasculitis?

The average costs of the last three months of a vasculitis patient path were 7375€, and the costs of all vasculitis patients were 1 308 243€/year on average. These are the costs that could be saved if the algorithm was used and it would expedite the diagnosis by three months. Almost half of the costs were formed by inpatient care, and the following highest cost groups were inpatient care, surgical procedures, and inpatient visits, each forming around 10% of the costs.

The results from the cost calculations supported well the assumptions that Seppänen (2022) had in his interviews. It was found that the total costs, particularly inpatient care costs, were highest right before the diagnosis, indicating that many patients are not diagnosed until they are already in poor health and require inpatient care. Earlier diagnosis could prevent organ failure and significantly reduce costs and suffering. While Seppänen (2022) acknowledges that it may not be possible to eliminate the high peak entirely, as various imaging and examinations are required for diagnosis even with the help of the algorithm, the peak could be lowered and occur sooner as the gradual increase in costs would be halted earlier.

An earlier diagnosis could not only improve the quality of life for individual patients but also benefit the healthcare system by saving money and resources. These saved resources could be reallocated to areas where they are needed most, such as reducing long waiting times and improving the system's overall efficiency. Additionally, in the long term, these savings could help to mitigate the rising costs of healthcare.

The RQ1.2 was: Which patient factors influence the total costs of the treatment path?

Most patients had relatively small costs during the last three months before their diagnosis, but some had significantly higher costs. The most expensive patient had costs higher than 200 000€. These high-cost patients are particularly interesting as they have the greatest potential for cost savings. On average, men were 26% more expensive than women. The regression analysis and adjusted prediction plots showed that costs increased exponentially with the age of patients. The exponential growth of costs with age was particularly steep for the most expensive diagnoses (M31.3 and M31.7) and more moderate for the cheapest diagnosis (D69.0). One possible factor contributing to these differences is the age range of patients with these diagnoses. The median age of a D69.0 patient was 24 years, while for M31.3 and M31.7, the medians were 60 and 65 years, respectively. Older people may be more likely to have more frequent and serious health issues, which can make their care more expensive.

The cost calculations and regression model revealed that the most expensive group was older men with diagnoses of M31.3 or M31.7. This differs from the findings of previous research by Taimen (2021), who did not find a correlation between total costs and the age, gender, and diagnosis of vasculitis patients during the diagnostic period. According to Taimen, the number of inpatient days, laboratory tests, and days of diagnostic delay had a stronger correlation with total costs. However, the results cannot be directly compared as the diagnostic period was defined differently, the factors included in the analysis varied, and the sample size of Taimen's study was only 317 patients.

The RQ1.3 was: How is the average treatment path of a vasculitis patient during the last three months before diagnosis?

An average diagnostic path had ten patient contacts and included calls and visits in several different departments. More than half of the total costs were formed by inpatient care, which started on the day of the diagnosis. The path does not look as complicated as the average path of a rare disease patient in figure 4, but it shows how the patient has contacts with several departments and ends up in inpatient care. These contacts could have been avoided if the patient had been diagnosed three months earlier, saving money and the patient's time. Also, initiating the treatment earlier might have prevented, for example, organ failures and, therefore, the need for inpatient care.

6.2 Using the algorithm to improve the production system of vasculitis diagnosis

The second research question was:

RQ2: How should the algorithm be used to improve the production system of vasculitis' diagnosis and prevention?

Seppänen (2022) stated that artificial intelligence is great at handling enormous amounts of data, categorizing it, and finding anomalies in it. However, it lacks the intuition that an expert has after years of working in their expertise. An algorithm cannot make a diagnosis because it lacks the intuition of an experienced doctor, and it would even be illegal. Therefore, the algorithm should be only used as a decision support system that points out the patient that might have vasculitis, and a human expert would make the final decision of further actions.

In practice, the algorithm would frequently process all the patient data of those who have visited HUS in the last three months. This could happen, for example, every day at a certain hour. The algorithm could access the data in the data lake and analyze it automatically without human intervention. If the algorithm finds a patient that possibly has a rare disease, it alarms the designated experts at HUS, who decide how to act upon the notification. The staff responsible for monitoring the system would be a few rheumatologists who are experts in diagnosing vasculitis and can give a well-educated opinion on whether an alarm is true or false. The system shows them the patient's medical history, including patient visits, examinations, and medications, so that they can go through the information, possibly discuss it together and then decide if the patient should be examined in case they have vasculitis. If they decide to act upon the alarm, they contact the Finnish Institute for Health and Welfare (THL). THL contacts the patient’s regionally responsible doctor, who then suggests the patient should be remitted to in this case Rheumatology Department for further examinations because of a potentially serious disease.

It is essential to consider the possible risks of using a system like this. One of the possible risks that Sutton et al. (2020) listed is that the system might cause alert fatigue in the staff by making too many alerts. This should not be a big problem with the algorithm for vasculitis diagnosis because, for its rareness, there were only 177 vasculitides diagnosed on average every year in the HUS area between 2009-2021. Alert fatigue should be avoided by adjusting the algorithm's sensitivity so that most alerts are true positives. Seppänen (2022) suggested that the specificity and sensitivity of the algorithm should be set to 90% so that only every 10th alert would be unnecessary. There will also be false negatives, but they are not a serious concern as they will probably be detected just a bit later as their patient data increases. Seppänen (2022) was not worried about false positives and the costs they cause because an expert will revise all the alerts, and because with associated findings the patient may have some other serious disease. A further examination is performed only for those who probably have vasculitis. Furthermore, even if a patient is examined and it results in no vasculitis, they must be seriously ill. The tests might still reveal a similar condition so that the examination costs are not wasted money.

Sutton et al. (2020) were also concerned about the alert fatigue's reverse side: the staff starts to trust the system too much. This should be kept in mind when the use of the algorithm becomes routine, as the algorithm will never detect 100% of the cases. The algorithm has to be treated as an additional tool that detects the cases that the doctors have not yet found. A human expert always makes the final decision even if the algorithm has an opposite opinion. However, trusting too much of the system is not a likely risk in this case because more experienced practitioners are more likely to override the decisions made by a clinical decision support system(Sutton et al., 2020), and the staff checking the alerts will be experts in the field and eventually will be informed of the final diagnosis.

Another risk that Sutton et al. (2020) discussed was that the clinical decision support systems can be difficult to use, disrupting the clinician workflow. The algorithm must be designed with a user interface that has high usability and does not require much training. Engaging the experts that check the alerts is vital as if they find it too troublesome to use or distrust it, it will not be used, and the system will not reach its full potential.

The last concerns Sutton et al. (2020) listed were the data quality, maintenance, and cost-effectiveness of clinical decision support systems. The algorithm is proven to work with the data currently stored in the data lake with past and current IT systems. As time passes, the system must be maintained and secured to work also with future patient system updates. The system's cost savings were studied in this thesis, but the costs of developing, maintaining, and using the system should also be considered. Seppänen (2022) stated that as the algorithm is a product of TietoEvry and HUS is helping in the development, there are no costs for HUS from the algorithm itself. He stated that the highest cost will be the time the experts use for checking the alerts and training new experts to use the system.

Figure 20 summarizes how the algorithm creates value. The figure was configured using the questions in the PROVE-IT model (Lillrank et al., 2019). The intervention consists of an algorithm that uses the patient data in the HUS data lake. The algorithm processes the data with artificial intelligence and alarms the experts if it finds a patient that might have vasculitis. The experts can see the patient data in the alarm and analyze it to determine whether it is justifiable.

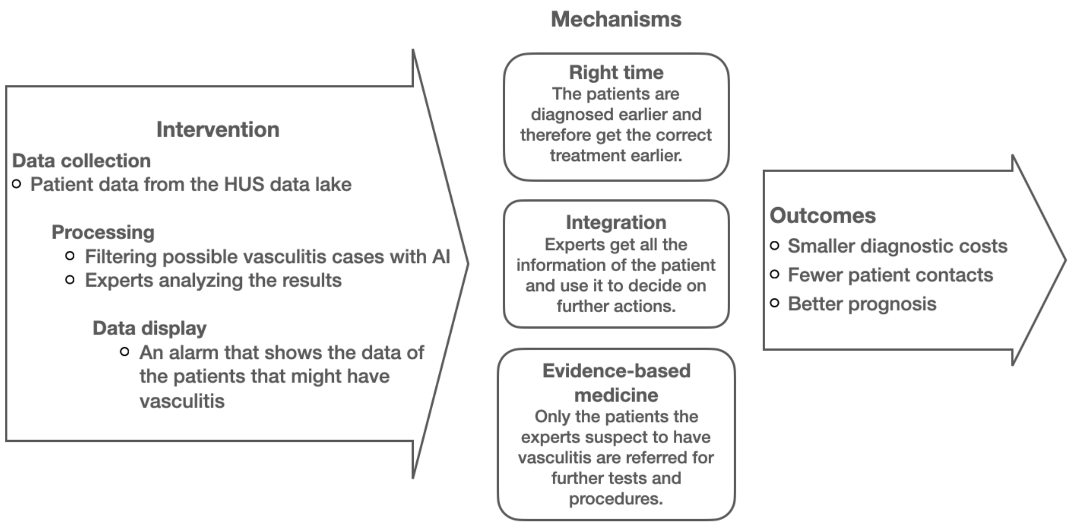

Figure 20. Value formulation of the algorithm

The three main mechanisms of value creation named by Lillrank et al. (2019) and identified in the algorithm are right time, integration, and evidence-based medicine. According to Lillrank et al. (2019), the right time means doing the actions at the optimal time, meaning not too late nor too early. The algorithm does this by expediting the diagnosis so that the treatment can be started earlier. The diagnosed patients are all sick and need treatment, so it is not likely to happen too early. Integration refers to that when making decisions about a patient's diagnosis and treatment, the doctor can see all the patient data and develop an integrated treatment plan that considers all the relevant aspects of a patient's situation (Lillrank et al., 2019). In the case of the algorithm, this works as the alarms made by it include all the patient data, and the experts can use it to decide further actions in the diagnosis and treatment of the patient. Finally, the algorithm is also evidence-based medicine, which Lillrank et al. (2019) describe as avoiding unnecessary and harmful procedures. The experts make well-educated decisions with the data provided by the algorithm; therefore, only those likely to have vasculitis are referred to tests and procedures. Furthermore, fewer procedures are needed due to earlier diagnosis.

The primary outcomes of using the algorithm are smaller diagnostic costs, fewer patient contacts, and better patient prognosis. As the patients are diagnosed earlier, less testing is needed to find the correct diagnosis. Furthermore, starting the correct treatment earlier can prevent the patient from getting into such a bad condition that they end up in inpatient care that is unpleasant for the patient and expensive to provide. Experts with all the needed data can refer the right patients to the correct treatments at the right time, saving money by decreasing patient contacts and preventing the most expensive procedures. Also, the patients' quality of life is improved as they get help earlier.

6.3 Limitations and future research

There are some limitations to consider in the results of this thesis. First, the data was limited to the patients living in the HUS area, so the results might not be generalizable to all of Finland. Also, having more demographic data like income and education about the patients could have made the regression model better. The comorbidities were neither considered as all the patient contacts were included in the cost calculations regardless of whether they were related to vasculitis. It is impossible to tell afterward whether a particular patient contact would have happened even if the patient did not have vasculitis.

To link the algorithm more to the research, it would have been better to use it on each patient and find out how many days before the actual diagnosis it would have detected vasculitis. This time could have been used as the analysis period instead of the three months used in the research. The possible cost savings are probably higher than stated in this research because the three months were used as a safe assumption of the algorithm's performance, and the algorithm can likely detect vasculitis earlier. Therefore, also more extended periods than three months could have been analyzed.

In the future, the costs should be calculated by using the algorithm to define the analysis period. The use of the algorithm in diagnosing diseases other than vasculitis would also be beneficial. It should be started with glomerulonephritis and myositis, as the algorithm is already working with them. The algorithm is still in development and could be developed to detect even more diseases in the future. If the algorithm is sold to other hospital districts than HUS, the cost benefits in the other areas should be studied as the population and hospital organizations may be different.

On average, the calculated costs for patients were 7375€ per patient, with 80% of patients incurring costs less than 8664€. While these numbers may not appear high, there were some patients who incurred extremely high costs. As shown in Figure 17, 18 patients incurred costs greater than 100,000€. Future research could investigate the characteristics of these patients and the reasons for their high costs.

6.4 Conclusions

In this thesis, the cost-saving potential of the algorithm for vasculitis diagnosis was studied. This was done by calculating the total costs of the last three months before the diagnosis of the vasculitis patients at HUS. Also, the factors affecting the total costs were studied by analyzing the effect of age on the total costs when the diagnosis and gender are adjusted. It was assumed that if a patient was diagnosed three months earlier with the help of the algorithm, these costs could be saved. In addition, suggestions for taking the algorithm into use were discussed.

The algorithm is still in development, and further organizational and legal changes are required before it can be implemented at HUS. The efficacy of the algorithm should be evaluated by assessing whether cost savings are achieved when it is tested in practice. Later, if the algorithm is found to result in cost savings and improved diagnostic processes, it may be expanded to detect additional diseases.

The study's results suggest that the use of the algorithm has the potential to bring significant cost savings. The exponential growth of costs with age indicates that the cost-saving potential is greater for older patients. These cost savings would be achieved by diagnosing vasculitis patients earlier, which would allow for more timely and effective treatment. Early diagnosis would also reduce the number of costly patient procedures and tests, and may lead to improved patient outcomes and quality of life.

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