General introduction and research questions
Diagnostic reasoning and diagnostic error in medicine

Diagnostic error

When a patient arrives at the hospital with symptoms and complaints, the first important task of the physician is to establish a correct diagnosis. The diagnosis has to be established before the course of treatment can be determined. While sometimes determining the diagnosis can be a straightforward task, often it involves a series of tough choices and complex decisions. For the vast majority of the patients, the diagnosis established by the physician is correct. In some cases however, a diagnostic error occurs. A diagnostic error is defined as a diagnosis that was unintentionally delayed (sufficient information was available earlier), wrong (another diagnosis was made before the correct one), or missed (no diagnosis was ever made), as judged from the eventual appreciation of more definitive information.1 When a diagnosis is missed, late or wrong, it can have major effects on the course of the illness and can even lead to a patient’s death.2-4

International studies demonstrate that 15% of the diagnoses are not entirely correct.5 In post-mortem studies this percentage is even higher, 30%.6, 7 Various studies on the diagnostic process show that diagnostic error is often a combination of organizational and cognitive factors, although cognitive errors alone also underlie a large number of the diagnostic errors.1, 7

Since the report ‘To Err is Human’ from the Institute of Medicine revealed that many patients are harmed or even die due to medical errors8, there has been an increase in research on patient safety. Although diagnostic errors have severe consequences and are represented the most frequent in malpractice claims,9, 10 relatively little research has been conducted on diagnostic error. Only recently, there is more attention for diagnostic error and diagnostic reasoning. In 2009 the JAMA published an article that indicated diagnostic error as the new frontier of patient safety.11

Studying diagnostic reasoning and diagnostic error is difficult. Diagnostic reasoning occurs in the physician’s head and it is therefore hard to find out in retrospect why they made certain decisions. Besides studying the outcomes, such as diagnostic errors and patient harm, it is also important to study the reasoning process. How does diagnostic reasoning occur? What are common error types? And most importantly, what should be done to successfully prevent diagnostic errors?
The diagnostic process

The patient’s complaints and symptoms need to be investigated by examining the patient’s history, conducting a physical examination and by a series of tests and images. After this information-gathering step is completed and a picture of the patient’s condition is formed, a number of possible diagnoses can be considered. These possible diagnoses represent a set of hypotheses that need to be tested further until they are narrowed down to the single most likely diagnosis. Subsequently, the physician needs to consider the possible co-morbidity and then an appropriate treatment plan can be determined and the treatment can start.

Theoretical framework: Signal Detection Theory (SDT)

In practice, the diagnostic process is more complex than the simplified description presented above. Patients often have many symptoms, complaints and abnormalities in laboratory values and images. Not all of the symptoms and abnormalities are relevant for finding the main diagnosis of a patient. However, it can be difficult to separate the relevant information needed to diagnose the patient, from the irrelevant information. Essentially, the diagnostic task of the physician can be compared to the task of a sonar-operator who tries to detect an enemy submarine from the background of noise. Such problem of detecting a signal from a background of noise has been widely investigated in cognitive psychology and human factors for the last 40 years. To formally describe this problem a theory called the signal detection theory (SDT) was developed. The SDT is a model of how people make decisions under conditions of uncertainty.12, 13 This theory assumes that under conditions of uncertainty the important information (signal) that the operator needs to detect is embedded in the irrelevant information (noise). Therefore, as in the task of a sonar-operator, it is not always clear whether the signal is present or not. Based on the available evidence the operator has to make a decision about whether the signal is present in the noise.12 In medicine, the SDT has commonly been applied to determine the specificity and sensitivity of diagnostic tests and to determine the optimal decision criteria for these tests.14, 15 Examples of the use of the SDT in medicine involve looking for the presence of a disease in radiology images or to determine the optimal cut-of value for a laboratory test.16, 17

Besides specific diagnostic decisions within the diagnostic process, SDT also applies to the diagnostic process as a whole. In that case, the signal is the pattern
of symptoms that matches a specific disease. The noise on the other hand, consists of other symptoms that are coincidental or can be related to another disease (i.e. co-morbidity). Before a physician decides to establish a diagnosis and start the treatment, a substantial amount of evidence consistent with the diagnosis has to be present. When a patient has all the typical symptoms for a certain diagnosis and no symptoms that cannot be explained by this diagnosis (i.e., the signal to noise ratio is high), it will be easy to correctly diagnose the disease. However, when the presentation of the disease is atypical and many other symptoms are present (i.e. the signal to noise ratio is low) it is more difficult to establish the correct diagnosis.

The decision whether a disease is present or absent can be illustrated using the two distributions presented in Figure 1. The distribution presented by the black line represents the situation in which a specific disease is present (signal), while the distribution presented by the dashed line represents the situation in which the disease is absent (noise). During the diagnostic process, the physician is accumulating evidence in terms of gathering symptoms that match the diagnostic hypothesis (x-axis in Figure 1). At a certain point enough evidence is collected for the physician to conclude that the disease is present. The amount of evidence that a physician considers to be sufficient in order to make a decision that a disease is present is called ‘the criterion’ and is located on the x-axis.

**Figure 1.** The two distributions of the Signal Detection Theory
The overlap between the two distributions illustrates the difficulty of making a diagnostic decision (see Figure 2). When the distributions overlap to a large extent (meaning that the patient has no clear pattern of symptoms), there is little discriminability and more diagnostic errors will occur (left part of figure 2). When the distributions overlap only slightly few diagnostic errors will be made, because the pattern of symptoms and complaints more clearly stands out compared to other possible diseases (right part of Figure 2). In the situation illustrated in Figure 2, the disease is difficult to detect since there is a substantial overlap between the ‘disease present’ and the ‘disease absent’ distributions.

![Figure 2](image.png)

**Figure 2.** The discriminability of the distributions

**Outcome parameters**

When making a decision regarding a diagnosis there are four possible outcomes: 1) the disease is correctly diagnosed (hit), 2) the disease is correctly ruled out (correct rejection), 3) the disease is diagnosed while it is actually absent (false alarm) and finally, 4) the disease is ruled out while actually present (miss), see Table 1. In decision making research the outcomes are described as the sensitivity and the specificity. Sensitivity is defined as the proportion of people with a disease that are also classified to have the disease according to the diagnostic test (proportion hits). Specificity is the proportion of people who do not have the disease and are correctly classified by the test as not having the disease (proportion correct rejections).
Table 1. The four possible types of response in the Signal Detection Theory

<table>
<thead>
<tr>
<th>Decision \ Reality</th>
<th>Disease present</th>
<th>Disease absent</th>
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<tr>
<td>Disease present</td>
<td>Hit</td>
<td>False alarm</td>
</tr>
<tr>
<td>Disease absent</td>
<td>Miss</td>
<td>Correct rejection</td>
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Decision criterion

As can be seen from Figure 1 the criterion is a very important factor in determining the pattern of diagnostic outcomes. The criterion is the amount of evidence a physician considers to be sufficient for reaching a decision about a certain diagnosis. However, the criterion does not have a fixed location, but the location of the criterion depends on many factors. When the criterion is located exactly in between the two distributions (neutral criterion), a maximum number of the diseases are correctly diagnosed. However, the number of false alarms is the same as the number of misses, which is not always desirable. First, the costs of an incorrect diagnosis (incorrect treatment) have to be considered (i.e. the costs of a false alarm). A physician might start a treatment even with little convincing information, if a treatment does not do any harm to the patient in case it turns out to be incorrect. This leads to many false alarms, and only few misses and is called a liberal criterion. The sensitivity is high and the specificity low. However, if the treatment for a diagnosis is considered to be invasive and contains severe possible side-effects, the physician might need more convincing information before establishing the diagnosis and starting the treatment. This leads to few false alarms, but many misses and is called a conservative criterion, the specificity is high and the sensitivity is low.

Consequently, it is important to set the criterion correctly based on available information about the consequences of a miss or a false alarm. Unfortunately, even when the location of the chosen criterion is correct, a diagnostic error can occur. Generally, there is no location for the criterion in which no false alarm nor misses occur. With the same amount of evidence for a diagnosis, sometimes the patient has the diagnosis and sometimes the patient does not. In these cases, a diagnostic error can occur, however the diagnostic process was not necessarily incorrect. The signal detection theory shows that it is not always possible to establish a correct diagnosis and therefore it is important to distinguish between the process and the outcomes (such as diagnostic error or patient harm) when studying diagnostic error.
Heuristics and biases

One of the factors that might contribute to an incorrect reasoning process and/or diagnostic error are heuristics and biases. Physicians constantly use heuristics during the diagnostic process. Heuristics are shortcuts in the reasoning process and are usually associated with fast diagnostic reasoning. In most cases the use of heuristics will lead to the correct diagnosis. However, sometimes the use of heuristics can lead to cognitive biases. A cognitive bias is a flaw in the judgment due to cognitive factors such as memory and information processing.\textsuperscript{18,\textsuperscript{19}} One example of a bias is the confirmation bias. A confirmation bias occurs when a physician mainly gathers information that supports his/her hypothesis.\textsuperscript{20} The information that does not match the hypothesis is ignored. This can lead to missing information and therefore a different interpretation of the patient’s symptoms, which can lead to a diagnostic error. Other examples of cognitive biases that occur in diagnostic reasoning are representativeness bias, base-rate neglect and availability bias (see Table 2). These biases have an effect on the way information about symptoms is gathered (i.e. insufficient information-gathering) and the interpretation of the symptoms (the criterion in the SDT). The criterion for the diagnosis that the physician thinks is likely is reached faster than for the other possible diagnoses. Availability bias occurs when someone estimates what is more likely by what is more accessible in memory, which is biased toward unusual patients. This bias might lead to a more liberal criterion towards those cases, meaning that the physician needs less evidence before determining that the patient has the disease.
Table 2. Frequently occurring biases in diagnostic reasoning

<table>
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<tr>
<th>Bias</th>
<th>Description</th>
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<td><strong>Availability bias</strong></td>
<td>the disposition to judge things as being more likely, or frequently occurring, if they readily come to mind.</td>
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<td><strong>Base-rate neglect</strong></td>
<td>the tendency to ignore the true prevalence of a disease, either inflating or reducing its base-rate.</td>
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<td><strong>Confirmation bias</strong></td>
<td>the tendency to look for confirming evidence to support a diagnosis rather than look for disconfirming evidence to refute it, despite the latter often being more persuasive and definitive.</td>
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<td><strong>Framing effect</strong></td>
<td>how diagnosticians see things may be strongly influenced by the way in which the problem is framed, e.g. perceptions of risk to the patient may be strongly influenced by whether the outcome is expressed in terms of the possibility that the patient might die or might live.</td>
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<td><strong>Omission bias</strong></td>
<td>the tendency toward inaction and rooted in the principle of non-maleficence. In hindsight, events that have occurred through the natural progression of a disease are more acceptable than those that may be attributed directly to the action of the physician.</td>
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<td><strong>Overconfidence bias</strong></td>
<td>a universal tendency to believe we know more than we do. Overconfidence reflects a tendency to act on incomplete information, intuition, or hunches. Too much faith is placed in opinion instead of carefully gathered evidence.</td>
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<td><strong>Premature closure</strong></td>
<td>accepting a diagnosis before it has been fully verified.</td>
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<td><strong>Representativeness bias</strong></td>
<td>the diagnostician is looking for prototypical manifestations of disease. This leads to atypical variants being missed.</td>
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**Personal and circumstantial factors**

Besides the heuristics and biases, personal and circumstantial factors also play a role in the diagnostic process. Circumstantial factors, such as workload, time pressure and high-risk situations have an influence on people’s decisions. When physicians find themselves in situations of high workload and time-pressure and they have to make diagnostic decisions with high-risks for the patient, this affects their information processing. It is known that when people work faster (due to e.g. workload and time pressure) more errors are made (i.e. speed accuracy trade-off). In addition, not only high levels of the time pressure and workload affect performance, also the perception of a high workload or time pressure can affect performance in decision tasks.

Every physician is different, they all have had different experiences, different patients and different teachers, and therefore they might interpret findings differently. For example a physician who worked in a hospital with a certain specialty, might overestimate the prior probability of those specific diseases when working in a general hospital. In addition, the amount of work experience and the level of fatigue direct physicians’ diagnostic decisions (i.e. the criterion for establishing a diagnosis). Fatigue is another type of personal factor that might influence physicians’ work. Physicians, indicate to experience negative effects of sleep deprivation and fatigue in both their personal life and work.
The negative effect of fatigue on performance has been shown particularly in routine tasks.\textsuperscript{24, 25} It is important to realize that personal and circumstantial factors are always present and can affect the diagnostic process.

Diagnostic reasoning strategies
Another important factor that affects the diagnostic process is the diagnostic reasoning strategy of physicians. Two main reasoning strategies are distinguished in the literature: (1) hypothetico-deductive reasoning and (2) pattern recognition.\textsuperscript{26} Hypothetico-deductive reasoning is a falsification process of possible diagnoses.\textsuperscript{23, 27} From a list of possible diagnoses usually the most severe and the most likely diagnoses are examined first. If those diagnoses do not include the correct one, subsequent possibilities are examined until the correct diagnosis is determined. The other diagnostic strategy, pattern recognition, is based on previous experiences.\textsuperscript{28, 29} If the patient’s complaints and symptoms resemble a pattern that the physician has seen before, then the physician will try to verify that diagnosis. Research has shown that hypothetico-deductive reasoning occurs more often in physicians with little work experience. They have a lot of knowledge, but have not yet seen enough patients to recognize certain patterns of symptoms and complaints. More experienced physicians on the other hand have seen many patients and can therefore rely on pattern recognition.\textsuperscript{23} However, pattern recognition is seen in straightforward cases, for the difficult cases experienced physicians also rely on hypothetico-deduction reasoning because it is harder to recognize the pattern.\textsuperscript{29} Pattern recognition can also be viewed as a heuristic; with little information a diagnosis is determined. With pattern recognition it is usually faster to diagnose a patient than with hypothetico-deductive reasoning. Although it is known from experimental research that more experienced physicians perform better in diagnosing their patients\textsuperscript{26, 30}, this does not necessarily mean that pattern recognition is always the better strategy. When a physician quickly recognizes a pattern of symptoms in a patient and diagnoses the patient, it could happen that not all necessary information was obtained. The symptoms and abnormalities that were not gathered might have indicated another diagnosis. If this happens, this affects the distribution in the signal detection theory since for some diagnoses not all available information is obtained and therefore it is less likely that the criterion is reached and the diagnosis is established. If due to this a diagnostic error occurs, this can be attributed to a reasoning bias.
Given that diagnostic reasoning is a complex process, evidence-based guidelines are developed in order to support physicians when diagnosing a patient. These evidence-based decision rules are defined by the Institute of Medicine as: systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. Those evidence-based decision rules basically indicate which information should be gathered by the physicians and which criterion should be used to decide to diagnose a patient with a specific disease. Over the last years, more and more evidence-based guidelines are developed and implemented. Guidelines that have been proven to be effective can improve the quality of care and the consistency of care, which is beneficial for the patient. For physicians, evidence-based guidelines can provide support when difficult decisions are made. There is also criticism on the use of evidence-based guidelines. Not all guidelines are of high-quality, sometimes guidelines might even turn out to be invalid. This occurs when guidelines are inflexible and lack room for tailoring in specific cases. The use of invalid guidelines can have adverse effects on patients, and can hurt the physician’s credibility. When examining the diagnostic reasoning process and diagnostic error, it is important to take the use of evidence-based guidelines into account as well.

How to study diagnostic reasoning and diagnostic error?
This introduction illustrates that sometimes diagnostic errors are not due to faults of the physician. Sometimes it is just not possible, even when all the accurate information is gathered and interpreted correctly, to establish the correct diagnosis. In other cases, the process was incorrect leading to a diagnostic error. Therefore it is important to study both the diagnostic reasoning process as well as the outcomes, of the process i.e. diagnostic error and patient harm.

The reasoning process has been studied previously by thinking-aloud-protocols, observations and by experiments. The outcomes (diagnostic error and patient harm) have been studied by reports of errors by physicians, analysis of malpractice claims, reviews of autopsy reports and patient record reviews. All of these methods provide valuable information and insights in diagnostic reasoning or diagnostic error. However, in order to obtain information on the error types, biases and circumstances that lead to diagnostic error and patient harm, it would be necessary to link the reasoning process to the outcomes of the process. In order to establish such a link, a combination of different methods to gather data is needed. It is further useful to gather data in a specific and thus more homogenous patient group. The data should be gathered during the
reasoning process, but in addition information about the patient’s hospital stay and the outcomes of care is needed.

If the entire diagnostic process as well as diagnostic error is studied, factors such as personal and circumstantial factors or organizational aspects (e.g. use of evidence-based decision rules) should be taken into account as well. The development of a study that combines different methods may lead to interesting exploratory results about the factors in the diagnostic process that lead to diagnostic error and patient harm. In addition, a better insight into the effects of the main influencing factors such as selective information-gathering and information-interpretation and subjective workload. The present thesis describes the development and the results of a study on diagnostic reasoning and diagnostic error using combined research methods. The studies aim to describe the incidence and consequences of diagnostic errors as well as reasoning errors and reasoning strategies as well as circumstances contributing to these diagnostic errors. In addition, the use of an evidence-based diagnostic decision rule aimed to optimize the diagnostic process is studied.

Research questions of this thesis
1. What is the incidence rate of diagnostic adverse events and how do the consequences and the preventability compare to other AE types?
2. What are the most common faults that occur in the diagnostic reasoning process?
   a. Where in the process do reasoning faults occur?
   b. What are the causes of those faults?
   c. What are the (possible) consequences of diagnostic reasoning errors?
3. Does selective information use relate to diagnostic errors and patient harm?
4. Are adverse outcomes in the diagnostic reasoning process related to subjective workload and work experience?
5. How are evidence-based diagnostic decision rules applied to diagnose a patient?

Content of the Thesis
The present thesis aims to provide insights into the diagnostic reasoning process and diagnostic error. These insights will reveal weaknesses of the diagnostic process and indicate where in the process it can be helpful to start interventions. In addition, we examined some of the weaknesses of the diagnostic reasoning process into more detail.
In chapter 2 diagnostic adverse events are examined using a large, population based, retrospective record review study of 7926 patient records. The adverse events that were classified as diagnostic adverse events were selected for the analyses. The incidence, causes and consequences of diagnostic adverse events were examined and compared to other adverse event types.

In chapter 3, the design of a study focused on the diagnostic reasoning process is described. It involves a record review in combination with obtaining additional information during the diagnostic process. With a Delphi method, the optimal diagnostic process for patients with shortness of breath (dyspnea) was determined. Based on the optimal diagnostic process a questionnaire was developed which was used to review the patient records of the dyspnea patients. In addition, information about the reasoning process, workload and work experience were gathered.

Chapter 4 describes the results of the study on faults in the diagnostic reasoning process, diagnostic error and patient harm. The overlap between faults in the diagnostic reasoning process, diagnostic error and patient harm is described. In addition, the causes and (possible) consequences are examined. The data presented in this chapter are gathered according to the research protocol described in chapter 3.

In chapter 5, the occurrence of selective information-gathering and information-processing in diagnostic reasoning is examined. Since selectivity is needed to diagnose a patient within a reasonable amount of time and without conducting too many unnecessary tests, we examined how selectivity relates to diagnostic error and patient harm. The data were gathered according to the research protocol in chapter 3.

In chapter 6, personal and circumstantial factors, i.e. subjective workload and work experience are related to the occurrence of diagnostic error and patient harm. The data on subjective workload were gathered concurrently to the diagnostic process according to the research protocol in chapter 3. Furthermore, by observations, the work factors influencing subjective workload (e.g. number of patients) were examined.

In chapter 7, the diagnostic process of the disease pulmonary embolism is examined. It is known that pulmonary embolism is a difficult diagnosis to establish and is often missed. There are well-known and validated criteria to diagnose pulmonary embolism. In this chapter the use of those criteria in clinical practice is examined.

In chapter 8 the results and conclusions as well as the research methods used in this thesis are discussed and interpreted using existing theoretical models.
General introduction and research questions

Reference List

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