Diagnostic uncertainties in medical imaging

Analysing, acknowledging and handling uncertainties in the diagnostic process

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Abstract
Diagnostics is a crucial tool in health care's endeavours to help people, and tremendous progress has been made in the field. Nonetheless, there are a wide range of uncertainties involved in all aspects of diagnostics – uncertainties that are important for scientific improvement, for quality of care, for practicing medicine, for informing patients, and for health policy making. In this chapter we analyse a wide range of uncertainties presenting in the various steps of diagnostic imaging. For each step we describe the main concern and suggest measures to reduce and handle the various kinds of uncertainty. Overall, we provide 9 specific measures to reduce uncertainty in the diagnostic process. Moreover, we analyse ethical issues related to the various types of uncertainty presenting at each step and end the chapter with five specific questions framed to raise the awareness of uncertainty in diagnostic imaging, as well as to reduce and to handle it. Thereby we hope that this chapter will provide practical measures to acknowledge and address diagnostic uncertainty.

Introduction

Diagnoses are crucial tools in order to help people with their existing or future suffering. However, diagnostics is not certain. There are many types of diagnostic errors (Balogh et al. 2015), which have many sources and causes (Pinto and Brunese 2010), and a wide range of consequences (Norman and Eva 2010; Singh et al. 2017).

Defining and measuring diagnostic error is challenging (Zwaan and Singh 2015; Hansson 2009). One crucial source of diagnostic error is diagnostic uncertainty. Therefore, this chapter will analyse and discuss various forms of uncertainty in diagnostics, their epistemic and ethical challenges. Identifying diagnostic uncertainties is a first step in increasing awareness of diagnostic fallibility and to improve the quality of care and the health of individuals and populations in the long run. Moreover, we need practical advice to how to address them. Accordingly, we will provide five key questions and nine specific measures to address and handle the various types of uncertainties.

Types of uncertainty in the diagnostic process

There are many ways to classify and study uncertainty in the sciences in general (Halpern 2017; Hansson 2016) and in the health sciences in particular (Hatch 2017). In this chapter we will follow the diagnostic process in clinical practice to illustrate the various types of diagnostic uncertainty. Table 1 provides an overview over the various steps in the ordinary diagnostic process in radiology, the main concern with each step, the corresponding issues with respect to uncertainty, and the relevant measures to reduce uncertainty.

Table 1 Uncertainties, main concerns, and relevant measures to reduce uncertainty related to the various steps of the diagnostic process. Some of the uncertain issues identified at one step are also relevant for the subsequent steps.

Steps	Main concern	Related uncertainty issues	Measures to reduce uncertainty
1. First encounter between patient and clinician	Appropriateness of referring	• Uncertainty about the benefits and risks involved in specific diagnostic examinations • Uncertainty about the existence and relevance of referral guidelines • Clinicians uncertainty of skills in clinical examinations • Unclear involvement of the patient in the decision-making process (patient autonomy, shared decision making)	• Education and training of professionals
2. The referral is received in the radiology department	Appropriateness of accepting test requests	• Uncertainty related to unclear or missing information in the referral • Unclear who is responsibility for vetting of the referral and justification of the examination • Radiologists and radiographers may be uncertain about the existence or relevance of referral guidelines • Uncertain pathways for communication with referring physician	• Improve communication between referrer and performer. • Clarify responsibility. • Train professionals.
3. The examination is planned and carried out	Appropriateness of test methods	• Uncertainty of choice of imaging modality and procedure • Unclear what responsibility the radiographer or radiologist has to supplement/correct referral information • Unclear if patients informed consent can or should be obtained	• Education and training of professionals. • Clarify responsibilities.
4. Review of image quality	Sufficiency of image quality	• Uncertainty whether retakes are needed, due to variation in perception of image quality • Uncertainty about applicable post processing	• Education and training of professionals.
5. Interpretation of the images	Accuracy of diagnostic findings	• Uncertainty of the accuracy of the examination (sensitivity, specificity) • Uncertainty about the meaning of abnormalities, e.g., if very small abnormalities represent pathology (indeterminacy) • Uncertainty about pre-test probability and prevalence, and hence about the predictive value of a test result • Prognostic uncertainty (will it matter?) • Uncertainty due to intra-observer and inter-observer variability.	• Improving test quality • Improve interpreter skills • Clarify disease definitions • Restrict testing with low pre-test probability • Increase knowledge about disease progression

6. Writhing the radiology report	Relevance of findings to report	• Uncertainty of the clinical relevance of incidental finding • Unclear if this relevance should be determined by the radiologist or the clinical referrer	• Increase knowledge about disease progression • Personalize medicine • Clarify responsibility • Align objectives of referrer and executor of the examination
7. Providing and communicating the results to the patient	Appropriateness of communicating the findings	• Unclear if informing the patient is a task for the referring physician or the radiologist (and in some cases radiographer)? • Uncertainty about what "findings" to include in the information, all vs. those of clinical relevance • Deciding what is "clinical relevance"	• Patient autonomy, informed consent • Shared decision-making • Professional autonomy and integrity

1. Uncertainties in referring

In the first encounter, the health professional may be uncertain whether the patient has a disease, what disease the patient may have, and which diagnostic test would be appropriate. Moreover, patients and clinicians may be unaware of benefits and risks involved in specific diagnostic examinations (Hollingsworth et al 2019). Clinicians may also be uncertain of the existence and relevance of referral guidelines (Greenhalgh 2013). Additionally, clinicians may be uncertainty of their own skills in clinical examinations (Espeland and Baerheim 2003, Morgan, Jenkins, and Ridsdale 2007), and thus refer to radiological examinations more often than relevant. There may also be uncertainty with respect to patient involvement in the diagnostic decision-making process, relating patient autonomy and shared decision making (Rogers 1919).

Hence, in the context of the initial encounter between health professional and patient the diagnostic uncertainty is related to disease status, relevance and justification of a specific examination, and related to the diagnostic skills of the referring health professional. The main measure to reduce the uncertainties of this part of the diagnostic process is to educate and train professionals.

2. Uncertainties in accepting test requests

The process of assessing the referral and deciding on what to do is subject to several types of uncertainty. First, there is uncertainty related to unclear or missing information in the referral (Davendralingam et al. 2017, Matthews and Brennan 2008). Second, it may be unclear who is responsible for vetting of the referral and for assessing justification of the examination (Vom and Williams 2017). Third, radiologists and radiographers may be uncertain about the existence or relevance of referral guidelines (Greenhalgh 2013). Fourth, there may be uncertain pathways for communication with the referring professional (Lysdahl, Hofmann, and Espeland 2010). All these aspects may result in diagnostic uncertainty with respect to whether to make an examination and (in case) which examination to make.

The main measures to reduce the uncertainty related to referral assessment is to improve communication between referrer and performer, clarify responsibility, and train professionals.

3. Uncertainties in testing methods (finding the right examination)

When it is decided that an examination is warranted, the next decision is on the right examination, e.g., the imaging modality and procedure (Djulbegovic, Hozo, and Greenland 2011). This decision may be hampered by uncertainty of the effectiveness and efficiency of a specific modality for this particular patient. The responsibility of the radiologists and radiographer with respect to supplementing/correcting referral information may also be unclear (Egan 2003), and it may be unclear if patient's informed consent can or should be obtained(Berlin 2014). To reduce these uncertainties, increase the quality of the imaging services, and the ethical standards, education and training of professionals is a crucial measure as is clarifying the responsibility of professionals.

4. Uncertainties about image quality

Prior to diagnosing, there may be uncertainty with respect to whether the image or examination quality is good enough for the task. There may for example be questions about whether retakes are needed due to image quality or variation in perception of image quality. Retake rates are surprisingly high (Andersen et al. 2012; Waaler and Hofmann 2010; Hofmann et al. 2015), illustrating that this is a

real problem. Correspondingly, there may be uncertainty about whether and what post processing is applicable (Decoster, Mol, and Smits 2015).

Education and training of professionals are appropriate measures to reduce such uncertainties.

5. Uncertainty about diagnostic findings

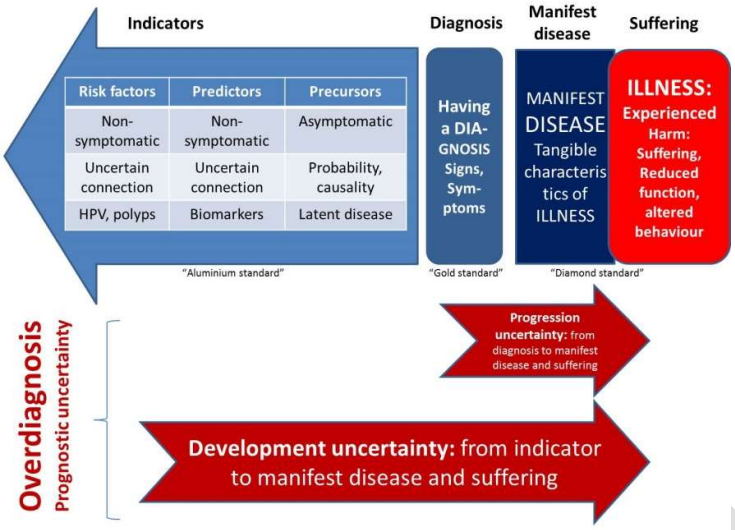
Once the examination is carried out, and its quality is found acceptable, a wide range of uncertainties emerge. There is uncertainty with respect to the meaning of findings, e.g., whether very small abnormalities represent pathology. This is a matter of how findings are defined, i.e., a conceptual type of uncertainty also called *indeterminacy* (Wynne 1992). This is an uncertainty about how to define disease (Djulbegovic, Hozo, and Greenland 2011) and about using vague concepts in the description of the findings (Korsbrekke 2000).

Then there is uncertainty with respect to the accuracy of the examination (sensitivity, specificity), also called *diagnostic accuracy efficacy* (Fryback and Thornbury 1991). This is a question of whether the test can find abnormalities that could be found by other means (gold standard). However, even when diagnostic accuracy is known there may be uncertainty about pre-test probability and prevalence, making the predictive values of a test result uncertain. Hence, we do not know whether a positive test actually means that a patient has the disease (positive predictive value) or whether a negative test means that the person does not have the disease (negative predictive value).

However, even if the test is accurate and the test correctly identifies an underlying condition, it is not clear that this will influence the health of a person. That is, we do not know whether what we correctly find will matter in terms of causing pain and suffering. For example, if we correctly identify a precursor of disease, it is not clear that this will develop into symptoms, manifest disease, suffering, and eventually death if not detected and treated. This problem is frequently recognized as overdiagnosis (Hofmann 2014). This type of uncertainty occurs in the relationship between indicators, precursors, risk factors, disease manifestations, suffering, and death. It occurs because we do not know how these factors develop. This type of uncertainty is called prognostic uncertainty because it is temporal, and it results in overdiagnosis (Hofmann 2019a; Hofmann 2019b; Hofmann 2017).

Prognostic uncertainty may have two components, *development uncertainty* and *progression uncertainty*. Progression uncertainty occurs because we do not know whether the condition which we (correctly) identify in terms of signs and symptoms actually develops to manifest disease and/or death (if not detected and treated). Development uncertainty occurs because we do not know whether the risk factors, predictors, and precursors that we identify develop into signs and symptoms, manifest disease, and suffering. Figure 1 gives an overview of these kinds of uncertainty.

Figure 1 The relationship between progression uncertainty and development uncertainty. Adopted from (Hofmann 2019a)



As the uncertainties with respect to diagnostic findings are diverse, so are the measures to reduce them. First and foremost, we should clarify disease definitions (Pandharipande et al. 2016), i.e., reduce indeterminacy. Then we should improve test quality and interpreter skills. Additionally, we should restrict testing with low pre-test probability and increase knowledge about disease progression. Then it is crucial to align interpreters' performance to reduce intra-observer and inter-observer variability (Korsbrekke 2000).

6. Reporting uncertainty

When the diagnosis is made, we still face with uncertainty with respect to how much and how the findings should be reported. First, there is uncertainty of the clinical relevance of certain findings, such as incidental findings (Rosenkrantz 2017; Brown 2013) or whether the findings will make any difference in subsequent diagnostics and treatment (Djulbegovic, Hozo, and Greenland 2011). Then, it is unclear who should determine the relevance of a finding, i.e., if this relevance should be determined by the radiologist or the clinical referrer. It is a challenge for the radiologist to communicate the various types of uncertainties to the referring physician in the radiology report (Bruno, Petscavage-Thomas, and Abujudeh 2017).

In order to reduce *reporting uncertainty*, we need to increase knowledge about disease progression (in order to reduce the uncertainty related to findings, such as incidental findings) and to increase knowledge about disease progression, i.e., to personalize medicine. To reduce reporting vagueness, it is important to align reporting language (Korsbrekke 2000). Moreover, it is important to align the objective of the examination of the referrer and the radiologist (e.g., where they are on the Receiver Operator Characteristic (ROC) curve.

7. Communication uncertainty

There are several types of uncertainties related to providing and communicating results to the patient. First, it can be unclear if informing the patient is a task for the referring physician or the

radiologist (and in some cases radiographer). Second, there may be uncertainty about what "findings" to include in the information, all vs. those of clinical relevance, for example how much to inform patients about incidental findings (Phillips et al. 2015; Kang et al. 2016). Third, there is uncertainty in deciding what is "clinical relevance," i.e., what is important. This is a type of indeterminacy, as discussed above.

As before, the ethical principles of beneficence and non-maleficence are relevant to avoid harm and ascertain the best interest of the patient. Moreover, communication uncertainty involves patient autonomy and informed consent. However, it also encompasses professional autonomy and integrity.

To reduce communication uncertainty, we may clarify responsibilities, as well as core concepts such as "clinical relevance." Additionally, shared decision-making (SDM) may be a valuable tool (Berlin 2014; Birkeland 2016; Lumbreras et al. 2017). Moreover, strengthening professional integrity and communication skills is of utmost importance. However, it is important that referrers (GPs and others) and performers (radiologists and others) may have different goals. A referring physician may want to rule out a certain condition while a radiologist may be eager not to miss any pathology (Korsbrekke 2000). Hence, the uncertainty stemming from different goals may be mitigated by clear communication between referrer and performer.

Relevance and implications

Above we have presented various types of uncertainty related to the diagnostic process. We have also highlighted the issues related to each step, and various measures to reduce uncertainty. There are of course many other ways to classify and discuss diagnostic uncertainty in radiology. Our framework is by no means the only or the best way to do so, but it is chosen because of its familiarity to clinicians. Moreover, it can easily be related to other frameworks, which we will show in the following Thereafter we will present different perspective and conceptions of uncertainty in which diagnostic uncertainty is situated. Finally, we will address ethical issues and principles relevant for addressing diagnostic imaging uncertainties.

Frameworks for uncertainty

One framework for analysing uncertainty differentiates between risk, fundamental uncertainty, ignorance, and indeterminacy (Van Asselt 2000; Wynne 1992). *Risk* is when you know certain outcomes and the chance that they occur. Given certain findings on the image, you know the risk that the patient has a given diagnosis. With *fundamental uncertainty* (also known as severe or Knightian uncertainty) you still know about the outcome (e.g., a given diagnosis) but you do not know the probability (distribution). *Ignorance* are unknown factors that are relevant for the diagnostic process, but which the health professional is not aware of. *Indeterminacy*, which formally is a type of model validity uncertainty, is uncertainty stemming from different ways to classify the conditions to be diagnosed.

Table 2 gives an overview of these four types of uncertainty applied to the diagnostic process discussed above.

Table 2 Four types of uncertainty classified according to outcomes and risks. Adapted from (Stirling 2010).

Possibilities **Probability**	**Known outcome**	**Unknown outcome**
Known probability	**Risk** Test accuracy (sensitivity, specificity, predictive values) for the various examinations in different contexts. Outcomes and harms of various examinations Knowledge about diseases	**Indeterminacy** (Ambiguity) How to define specific findings Defining disease entities Vagueness in description of findings or in reporting Defining clinical relevance
Unknown probability	**Fundamental** (Knightian) **Uncertainty** Prognostic uncertainty - Development uncertainty - Progression uncertainty Overdiagnosis, underdiagnosis Value of incidental findings	**Ignorance** Unknown meaning of certain markers for diagnosis or prognosis Unknown effects of ionizing radiation (good or bad) Unknown relevance of individual health data

Our classification of uncertainties also corresponds with Sven Ove Hansson's early framework (Hansson 1996), which distinguishes between four general types of uncertainty, i.e., uncertainty about i) alternatives, ii) consequences, iii) trustworthiness of information, and iv) about values and conceptions amongst decision makers. Uncertainty with respect to which alternatives and consequences with respect to which diagnostic method to apply is covered by our step 3 and 4. The issue of whether the information is trustworthy is covered in step 5. Uncertainty about values and conceptions amongst decision makers, Hanson's fourth type, is covered in our 2, 6, and 7.

Correspondingly, our diagnostic uncertainties also correspond to other conceptions of uncertainty in a clinical setting, such as discussed by Trisha Greenhalgh (Greenhalgh 2013). Greenhalgh specifically refers to uncertainty about the specific illness narrative, about case-based reasoning (our step 2), about what the guidelines show (step 1 and 2), what best to do in the circumstances (step 3-5), about multi-professional working (step 2 and 6), and how best to communicate and collaborate (step 2, 6, and 7).

Different perspectives on uncertainty

Our approach also is informed by the ways that uncertainty is conceptualized and investigated in various academic disciplines (Han et al. 2019). In behavioural economics many see uncertainty as an obstacle to rational decision making. In clinical medicine and health services research it may be an issue of optimal evidence-based care. Psychologists may think of uncertainty as a barrier or facilitator to the satisfaction of fundamental human needs, and cognitive scientists see it as a perceptual state, and in communication science uncertainty is a product of information exchange. Moreover, in anthropology and sociology it may be viewed as a socially constructed, negotiated, and shared understanding or set of meanings (Han et al. 2019).

Uncertainty is also scrutinized in terms of vagueness, and classified in terms of linguistic vagueness, epistemic vagueness, semantic vagueness, and ontic vagueness (Sadegh-Zadeh 2012).
Paul Han defines «uncertainty as the subjective consciousness of ignorance. As such, uncertainty is a "metacognition"—a thinking about thinking—characterized by self-awareness of incomplete knowledge about some aspect of the world." (Han 2013). Han provides an overview of different conceptions of uncertainty in medicine (Han, Klein, and Arora 2011), which is useful for setting diagnostic uncertainty in context. See Figure 2.

Figure 2 Different conceptions and sources of uncertainty from (Han, Klein, and Arora 2011).

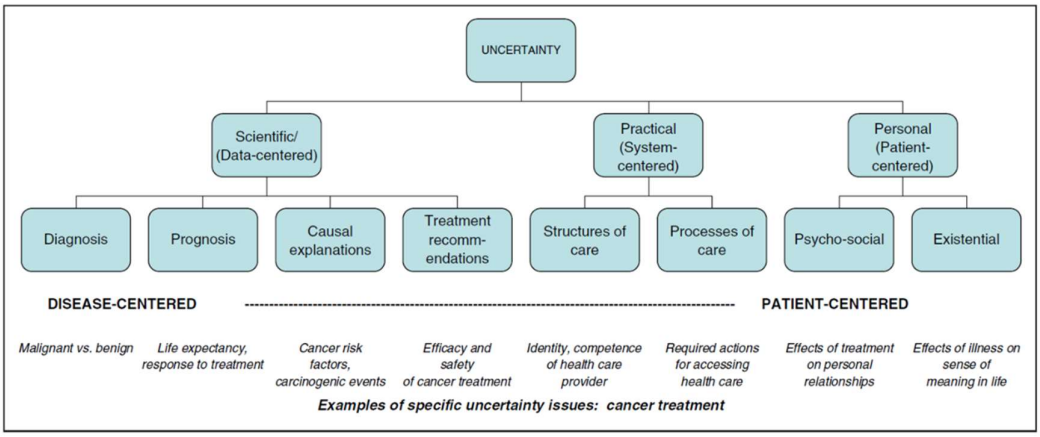


Figure 2. Issues of uncertainty in health care.

Han's conceptions of uncertainty relate to other classifications of uncertainty, such as indeterminacy, ignorance, unreliability, parameter uncertainty, and inexactness (Strand and Oughton 2009).

Ethical issues in diagnostic uncertainties

The various types of uncertainty raise a series of ethical issues, which will briefly discuss in the following.
Two ethical principles that are relevant for all steps of the process and their related types of uncertainty are beneficence and non-maleficence (Beauchamp and Childress 2019). This should not come as a surprize as the overall aim of diagnostic imaging is to promote good for the patients and avoid harming them, and uncertainties in the diagnostic process may hamper or undermine gaining this goal. In the initial steps (1 and 2) uncertainty is mainly about whether or not the radiological examination is warranted i.e. justifiable. In step 3 and 4 decisions may be hampered by uncertainty of the effectiveness and efficiency of a specific modality or procedure or the sufficiency of the image quality for the particular patient (e.g. based on insufficient referral information). All such uncertainties can obviously lead to wrong decisions and cause suboptimal examinations, which in turn may compromise patients' benefit in terms of reduced probability of a correct diagnosis and subsequent treatment as well as exposing patients to unnecessary risks of harm, i.e., reduced safety. Uncertainties that occur later in the process may also fail to promote benefits to the patient and/or cause harm due to inaccuracy or irrelevant findings. False-negative finding are for instance the major contributor to patient injury compensation claims in radiology (Bose et al. 2019). Likewise, is it of crucial importance not to harm the patient by causing unnecessary subsequent examination or treatments, or anxiety due to irrelevant information. This means that the principles of beneficence

and non-maleficence urge us to avoid inaccurate, false or incidental findings, and overdiagnosis (Mendelson and Montgomery 2016), followed by inappropriate patient management and follow-up procedures that are invasive, risky and expensive (Burger and Kass 2009).

The principles of justice and solidarity are relevant as uncertainties here may lead to misuse, underuse and overuse of services. For example, uncertainties about appropriateness of referring the patient and accepting the referral (step 1 and 2), challenge justice and solidarity (see chapter: Overutilization of imaging tests and healthcare fairness). Justice is also relevant more indirectly in the rest of the process due to the incorrect decisions and the subsequent waste of resources based on uncertainties.

The principle respect for patients' autonomy and as well as dignity is relevant in step 1 regarding the uncertainties in involving the patient in decision-making process. This is a challenging task for the clinician as patients demand for imaging services is an important driver for inappropriate imaging (Hendee et al. 2010). The uncertainty may easily occur in cases when the patient wants an examination for other the strictly medical reasons and respecting the patient's autonomy and dignity becomes incompatible with following best practice. In step 3 the relevance of patient autonomy regards the radiographers' uncertainty about if and how informed consent can or should be obtained (Younger et al. 2019). Moreover, patient autonomy is also involved in step 5 and 6 because it is crucial to inform patients about the types of uncertainty that should be considered along the results (Hofmann and Lysdahl 2008).

Professional autonomy, responsibility, and/or integrity are relevant aspects in many steps in the diagnostic process for the obvious reason that professionals are the main actors in the process. For instance, in step 1 the uncertainties in skills in clinical examination (Espeland and Baerheim 2003, Morgan, Jenkins, and Ridsdale 2007) and ignorance about clinical referral guidelines (Gransjoen et al. 2018), clearly raise questions about professionals' integrity and responsibility. Adherence to guidelines may be perceived incompatible with professional autonomy. Similar arguments can be made for step 2: the uncertainties related to justification or examinations (Vom and Williams 2017) and communication challenges (Strudwick and Day 2014) call for the professionals' responsibility.

Correspondingly, uncertainty raise issues of professional integrity and autonomy in decision making in step 3 and 4 as well as issues of the distribution of responsibility between professionals, e.g. regarding improvement of the referral information (Lam, Egan, and Baird 2004) and determining sufficient image quality (Mount 2016).

In the final step of the diagnostic process, the radiologists bear a heavy load of responsibility for dealing with the uncertainty inherent in process of interpreting and reporting the radiological findings (Bruno 2017), for instance the challenges related to incidentalomas (Berlin 2013), and uncertainties in patient information responsibilities (Gutzeit et al. 2019).

Handling diagnostic uncertainty

We have provided an overview of the various ethical aspects and measures to reduce uncertainty at 7 steps of diagnosis. Summarising these (given in the right column of Table 1) gives us 9 specific measures to reduce uncertainty in the diagnostic process:

- Educate and train professionals, especially in performance and interpreting skills
- Improve communication between referrer and performer and to the patient.
- Clarify the responsibility for the various steps of the diagnostic process.
- Clarify definitions of findings, diagnoses, and diseases
- Be cautious when the prevalence is low and restrictive when the pre-test probability is low
- Increase knowledge about disease progression and individual variability
- Increase knowledge about disease prognostics
- Communicate uncertainty to patients and apply shared decision-making
- Strengthen professional integrity

One important topic expected to influence diagnostic uncertainties in diagnostic imaging and the way they can be handled is artificial intelligence (AI). This is a too big an issue to address fully in this chapter. Suffice here is to point out that AI may reduce the uncertainties discussed in steps 2-5, and subsequently also in 6 and 7. However, introducing AI in order to improve diagnostics and reduce uncertainty also introduces two important and related challenges: the black box problem and responsibility.

AI introduces algorithms that are non-explanatory ("the black box problem"), which makes it difficult to understand why a certain diagnosis or decision is reached. This then makes it difficult to distribute responsibility (Neri et al. 2020; Pesapane et al. 2018). Who is responsible for a decision based on an AI-provided diagnosis that turns out to be wrong? Is it the AI-constructor or vender? The provider of the data on which the AI-system is trained or used? The health care system implementing the AI-system? The professional using it? Or the patient consenting to its use? These issues merit a separate paper.

If we focus on the overall goal of diagnostics, i.e., to find the underlying and potentially modifiable cause of pain and suffering (in terms of disease) and thereby to help people, we can boil the advice to handle diagnostic uncertainty down to five key questions:

1. Is it right to test? (Appropriateness of testing)
2. Is it the right test? (Test appropriateness)
3. Is the test right? (Accuracy of result, trustworthiness)
4. Is the test clinically helpful? (Relevance of result)
5. Does the test result matter to the patient? (Importance of result)

Figure 3 presents the five steps to handle diagnostic uncertainty in practice.

Figure 3 Five basic issues and questions to ask in order to reduce diagnostic uncertainty. Adopted from (Hofmann 2018)

Addressing these questions will make it easier to handle uncertainty and improve diagnostics in radiology.

Conclusion

In this chapter we have analysed a wide range of uncertainties presenting in seven steps of diagnostic imaging. For each step we have described the main concern and suggested measures to reduce and handle the various kinds of uncertainty. Overall, we have provided 9 specific measures to reduce uncertainty in the diagnostic process. Moreover, we have analysed ethical issues related to the various types of uncertainty presenting at each step of the diagnostic process and discussed the ethical principles relevant for addressing these issues. We have also demonstrated how the uncertainties presented and discussed in this chapter relate to the general literature on uncertainty and briefly indicated how AI may change and challenge diagnostic uncertainty. We ended this chapter with five specific questions framed to raise the awareness of uncertainty in diagnostic imaging, as well as to reduce and to handle it. Thereby we hope that this chapter provide practical measures to acknowledge and address diagnostic uncertainty.

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