

Temporal uncertainty in disease diagnosis

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Abstract:

There is a profound paradox in modern medical knowledge production: The more we know, the more we know that we (still) do not know. Nowhere is this more visible than in diagnostics and early detection of disease. As we identify ever more markers, predictors, precursors, and risk factors of disease ever earlier, we realize that we need knowledge about whether they develop into something experienced by the person and threatening to the person's health. This study investigates how advancements in science and technology alter one type of uncertainty, i.e., temporal uncertainty of disease diagnosis. As diagnosis is related to anamnesis and prognosis it identifies how uncertainties in all these fields are interconnected. In particular, the study finds that uncertainty in disease diagnosis has become more subject to prognostic uncertainty because diagnosis is more connected to technologically detected indicators and less closely connected to manifest and experienced disease. These temporal uncertainties pose basic epistemological and ethical challenges as they can result in overdiagnosis, overtreatment, unnecessary anxiety and fear, useless and even harmful diagnostic odysseys, as well as vast opportunity costs. The point is not to stop our quest for knowledge about disease but to encourage real diagnostic improvements that help more people in ever better manner as early as possible. To do so, we need to pay careful attention to specific types of temporal uncertainty in modern diagnostics.

Key words: diagnosis, anamnesis, prognosis, uncertainty, ethics, epistemology

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Introduction

Diseases are phenomena that throughout history have been considered to occur in time and space (location) (Evans, Lucas, & Kerry, 2016; Whitbeck, 1977; White, 1926). The *space* of disease has been studied extensively in the history of medicine where diseases have been identified in body fluids in terms of humoral imbalances (Hippocrates, Galenos), in organs (Giovanni Battista Morgagni, 1682–1771), tissues (Xavier Bichat, 1771–1802), cells (Rudolf Virchow, 1821–1902), biomolecules (genes) and other places (Hofmann, 2001, 2017b).

Correspondingly, disease is studied in *time*, e.g., in terms of its temporal extension (lasting in time) (Hofmann, 2002). Historically, the temporal aspects of disease have been studied in terms of the ancient concepts of *Chronos* and *Kairos* (Bergmann, 2003). *Chronos* has been crucial in studying the chronological development of disease, and *Kairos* has traditionally been a key term for studying the right time for treatment.

In modern (preventive) medicine time has become ever more important, e.g., in terms of detecting and treating disease as early as possible. In particular, a wide range of screening programs have been implemented and early detection has become part of clinical care. Moreover, the development of biomarkers and use of artificial intelligence (machine learning and deep learning) and BigData are envisioned extensively to preempt disease (Ginsburg & Willard, 2009; Young, 2021).

However, there seems to be a profound paradox in modern medical knowledge production: The more we know about disease development, the more we know about the uncertainties of disease diagnosis, i.e., the more we know that we (still) do not know. Nowhere is this as visible as in early detection of disease. Novel knowledge about predictors, precursors, and risk factors reveals the urgent need for knowledge about whether such indicators develop into something that will be experienced by the person and threatening to the person's health (Welch, Schwartz, & Woloshin, 2011). That is, while the vast advances in science and technology have identified a wide range of (bio)markers, signs, signals, findings, red flags, and alarms that are associated with disease, oftentimes we do not know whether they will develop into something that will ever bother the examined, monitored, or tested person, i.e., that will result in pain, dysfunction, or suffering in individuals (Hofmann & Welch, 2017).

Hence, while science and technology vastly has expanded our knowledge about temporal aspects of disease (such as disease mechanisms and progression), they also have revealed how much more there is still to know. This increase in *temporal uncertainty* poses basic epistemological and ethical challenges as it can result in overdiagnosis, overtreatment, unnecessary anxiety and fear, useless and even harmful diagnostic odysseys, as well as vast opportunity costs.

Accordingly, the objective of this article is *to investigate the temporal uncertainty that results from advancements in diagnostic science and technology*. The research question is: *how do advancements in science and technology alter temporal uncertainty in disease diagnosis in modern medicine?* As the uncertainties of diagnosis are closely connected to anamnesis and prognosis, relevant aspects of anamnesis and prognosis will be addressed together with the temporal uncertainty of diagnosis.

In order to address the research question, the article will follow four steps. In the first step, the concepts of diagnosis, anamnesis, and prognosis will be briefly defined. Second, basic temporal uncertainties in anamnesis, diagnosis, and prognosis will be investigated. The third step will investigate how disruptive science and technology have altered basic temporal elements of medical knowledge production and application and how this can enhance or introduce new types of uncertainties. The fourth step is based on the analysis in the previous steps and argues that advances in science and technology have (over time) have resulted in a closer connection between diagnosis and prognosis and increased our prognostic uncertainty for a wide range of diagnosed conditions, weakening the epistemological standing of diagnoses.

Anamnesis, diagnosis, and prognosis

Anamnesis is the medical history of a patient. The word stems from new Latin and Greek (anámñēsis “remembrance,” equivalent to ana(mi)mné(skein) “to remember” or “to call to mind”). The anamnesis presents the development of disease as experienced by the patient, i.e., the development of illness. Based on the anamnesis health professional aims to reach a diagnosis of a disease and a treatment plan (Sadegh-Zadeh, 2012). Hence, anamnesis tracks the disease backwards in time in order to identify it in the present (diagnosis) and to predict its temporal course (prognosis) and to influence the progression of the disease, where possible (treatment).

The term *diagnosis* stems from New Latin and from Greek (diágnōsis, “a distinguishing, means or power of discernment”). The meaning has changed throughout history, but one traditional meaning seems to be “discerning by knowledge” (Liddell, Jones, & Scott, 2011). Diagnosis has been considered to be categorical or conjectural statement about specific conditions in the world, a label (idiom) (Sadegh-Zadeh, 2012), and a value-laden (Stempsey, 1999) social construct (Brown, 1995). Moreover, it has been used as a classificatory category (Jutel, 2011) and the name of a process (Blaxter, 1978) and, relatedly, as nosographic and pathophysiological types (Chiffi & Zanotti, 2017). According to one definition diagnosis is “a hypothesis about the nature of a patient’s illness, one that is derived from observation derived by the use of inference” (Kassirer, 1989). In the context of this study, the term diagnosis both refers to a (disease) label given at a specific time and the temporal process of giving such a label.

Prognosis is “[t]he likely outcome or course of a disease; the chance of recovery or recurrence.” (National Cancer Institute, 2015) The term stems from Late Latin and Greek prógnōsis “foreknowledge.” As such it is knowledge about the progression of a disease in time, or more precisely the prediction of the progression of a disease (or condition) in time. Moreover, prognosis involves two types of predictions, i.e., what will happen with and without intervention (Sadegh-Zadeh, 2012), and as such is imbued with uncertainty (Chiffi & Zanotti, 2017).

Hence, while anamnesis looks *backward* in time, prognosis looks *forward*. Anamnesis points towards a diagnosis at a given time. Nonetheless, diagnosis is not a-temporal as it develops through a process and points to a prognosis (depending on the knowledge about the disease).

Temporal uncertainties in anamnesis, diagnosis, and prognosis

Paul Han and colleagues have mapped a wide range of sources of uncertainty (probability, ambiguity, complexity), uncertainty issues (scientific, practical, personal), and identified loci of

uncertainty (patient, clinician, and researcher) (Han, Klein, & Arora, 2011). A recent systematic review by Bhise and colleagues uncovers a rich literature on diagnostic uncertainty and concludes that “diagnostic uncertainty” lacks a clear definition (Bhise et al., 2018). Correspondingly, a wide range of errors (causing uncertainty) have been identified in diagnostics and prognostics (Balogh, Miller, Ball, National Academies of Sciences, & Medicine, 2015; Mark L Graber, 2013; M. L. Graber, Franklin, & Gordon, 2005; Newman-Toker & Pronovost, 2009; Geoffrey R Norman & Eva, 2010; G. R. Norman et al., 2017; Pinto & Brunese, 2010; Smith, White, & Arnold, 2013). This study adds to the existing literature in looking more narrowly at the temporal uncertainty involved in disease diagnosis.

In the *anamnesis*, the main temporal uncertainty is of a historical kind, e.g., related to remembering past events, such as symptoms, health-related events, medications etc. Accordingly, there may be recollection error, confirmation bias, lack of attention, or lack of knowledge (health illiteracy). Additionally, there is uncertainty with respect to whether the various identified previous health-related issues are relevant for the present situation. Hence, the temporal uncertainty of anamnesis stem from *ignorance* (of important events, factors, and preconditions) and uncertainty of the *relevance* (of such factors).

The (temporal) uncertainties from anamnesis may influence diagnostics, e.g., with respect to deciding which examinations to make, which tests to take, and to estimate the pre-test and post-test probability of a specific disease (Hofmann & Lysdahl, 2021). The uncertainty depends on the outcomes of each diagnostic step and varies throughout the diagnostic process (Seely, 2013). For example, each step in diagnostic imaging has its own sources of uncertainty (Hofmann & Lysdahl, 2021). Hence, “diagnostic uncertainty is dynamic and changes with time.” (Bhise et al., 2018) The uncertainties in the process of *diagnosis* are related to the accuracy of the test, i.e., whether the test misses cases of disease (due to low sensitivity) and diagnoses cases of non-disease (due to low specificity). Correspondingly, positive and negative test results may be wrong (due to low predictive values). Moreover, diseases may have undiscovered variants (due to *ignorance*) and their signs have unknown probability distributions (*fundamental uncertainty*) or be defined ambiguously (*indeterminacy*) (Hofmann & Lysdahl, 2021; Wynne, 1980, 1992).

In sum, uncertainty varies throughout the diagnostic process depending on uncertainties about the test characteristics, test context, significance of symptoms, signs, findings, and test results. Moreover, even for categorical diagnosis, where the question is whether the person has a specific diagnosis or not, there is temporal uncertainty, for example for asymptomatic and presymptomatic conditions there is uncertainty with respect to whether the person will develop symptoms and manifest disease.

In *prognosis* there is temporal uncertainty with respect to how the diagnosed condition (mostly a disease) will progress. This *progression uncertainty* stems from the fact that (instances of) diseases develop differently. Some may develop rapidly, others slowly, some may stop progressing, and some even regress. Moreover, diagnoses are not the same as diseases. As clearly stated in the ICD (from ICD-10 in 1989 and onwards) many diagnoses are not labels of diseases, but of health-related problems and risk-factors. Moreover, the term “diagnosis” is used for discerning conditions that are explicitly not considered to be diseases. One example of this is when professionals are “diagnosing pregnancy” (Cohen & Teal, 2022). Hence, one type of temporal uncertainty is whether what is

identified (and labelled) with a diagnosis will (ever) progress to something that is recognized as a (manifest) disease and experienced by the person as pain, dysfunction, and/or suffering (Hofmann, 2017a; Hofmann, 2019a).

Thus, three types of temporal uncertainties can be identified in the process from anamnesis to prognosis. First, there is uncertainty with respect to the recollection and relevance in the anamnesis. Second, there are uncertainties in each step of the diagnostic process. Thirdly, partly based on uncertainties in anamnesis and diagnosis and partly on limited knowledge and evidence, there is uncertainty with respect to prognosis, i.e., whether findings will develop into manifest and experienced disease. Table 1 provides an overview of various types of uncertainty related to anamnesis, diagnosis, and prognosis.

Table 1 Uncertainties related to anamnesis, diagnosis, and prognosis. For details, see (Hofmann & Lysdahl, 2021).

	Anamnesis	Diagnosis	Prognosis
Temporal relevance	Backward-looking	Based on past and expecting future events Process	Forward-looking
Types of uncertainty	Recollection Relevance	Uncertainties in each step of the diagnostic process: <ul style="list-style-type: none"> • Risk • Fundamental uncertainty • Ignorance • Indeterminacy 	Prognostic uncertainty: <ul style="list-style-type: none"> • Progression uncertainty • Development uncertainty
Sources of uncertainty	Recollection error Lack of knowledge, lack of attention	Lack of information over time due to: Diagnostic accuracy Inappropriate test Unknown probability distribution Unknown events Ambiguity, complexity	Lack of knowledge (about mechanisms and development) Ignorance
Type of temporal uncertainty	About the meaning of symptoms and reported experiences	About the meaning of signs, findings, and test results	About whether findings will develop into something relevant for the person's experience of pain, dysfunction, and/or suffering

Disruptive technologies

As technologies have changed medicine since the invention of the uroscope and the stethoscope (1816) (Keers, 1981), a wide range of novel technologies have been claimed to be disruptive to medical practice and knowledge production. Artificial intelligence (AI) including Machine learning (ML), BigData, come together with precision medicine (Ho et al., 2020; Nayarisseri et al., 2021;

Santosh & Gaur, 2021) and are envisioned to totally change medicine. The same goes for genetic screening (and gene editing).

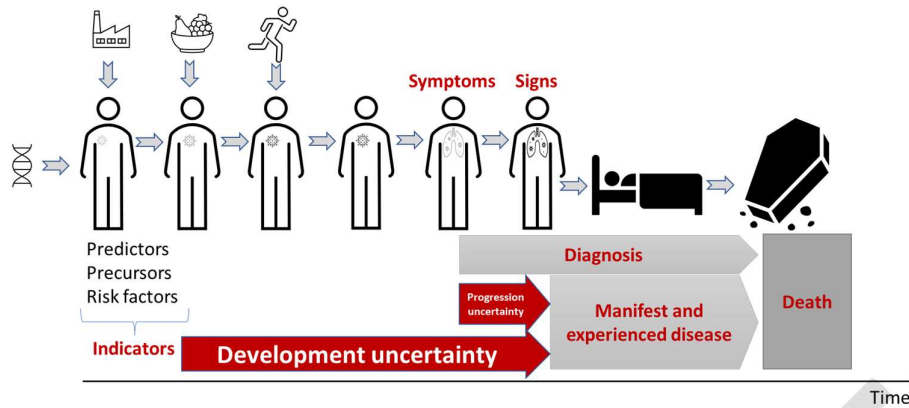
With BigData analysis of large health data as well as behavioral data by various types of AI/ML it is expected that we will get new and unforeseen information about people's health. This will provide crucial input for prevention and early intervention, but also result in false alarms and unnecessary diagnostic and therapeutic odysseys (Hofmann & Welch, 2017). The point here is not to go into the details of how these technologies change medicine, but to use them as examples of how they can influence the temporal uncertainty in disease diagnosis and how this relates to uncertainties in anamnesis and prognosis.

Technology reducing and enhancing temporal uncertainty

As acknowledged, the role of science and technology is ambiguous and ambivalent. Science and technology have made diseases more fine-grained, knowledge of disease mechanisms and etiology ever more advanced, and the gathering, evaluation, and exchange of evidence better, resulting in reduced temporal uncertainty and improved diagnosis and prognosis.

At the same time, science and technology have identified a wide range of predictors, risk factors, precursors, preconditions, and biomarkers of disease (here collectively called "indicators") where we do not know whether they will temporarily evolve to manifest disease and suffering (if they were not detected or treated). This has generated a new type of temporal uncertainty: *development uncertainty*. Development uncertainty is uncertainty of whether what is detected by an indicator will develop into anything that is experienced by the person, such as pain, dysfunction, suffering, manifest disease, or death (Hofmann, 2019b). Development uncertainty is different from *progression uncertainty*, which is an uncertainty about how a condition diagnosed (based on symptoms and signs) will progress to manifest and experienced disease. Together development and progression uncertainty make up *prognostic uncertainty*. Figure 1 illustrates the relationship between progression uncertainty and development uncertainty.

Figure 1 The relationship between progression uncertainty and development uncertainty, who together make up prognostic uncertainty. Symbols above person indicate environmental and lifestyle factors (food and exercise). Symbol left of person indicates genetic makeup. Symbols inside person indicates biomedical changes that can be detected (by indicators) and that may develop to symptoms, signs, and manifest and experienced disease. For more details, see (Hofmann, 2019a).



When science and technology have revealed clear connections between various indicators and manifest disease or verified disease mechanisms, this has contributed to reducing progression uncertainty and development uncertainty. However, as the connections are not clear (or verified) and the mechanisms at best oftentimes are weak, the opposite occurs: prognostic uncertainty increases. In general, the number of biomarkers has increased rapidly, but their connection to what matters to people (pain, dysfunction, and suffering) is ever weaker.

One reason for this increase in prognostic uncertainty is that advances in science and technology have moved diagnosis ever earlier in time (increasing temporal uncertainty) and away from what matters to people (e.g., reduced the phenomenological relevance)(Aronowitz, 2009; Leder & Jacobson, 2014). In the latter case, science and technology has contributed to an increased (epistemological and ontological) gap between diagnosis and manifest disease. This development is characterized by two effects. First, diagnosis have become less labels of diseases and more characteristics of bodily or mental phenomena of relevance to health. As we are able to technologically detect and define phenomena that are considered to be relevant for peoples' health, these are prone to become diagnoses. This happens in various types of early diagnosis, such as in health surveillance and prevention (screening), but also in clinical practice in ordinary testing (including incidentalomas). Hypertension and hyperglycemia are but two examples. As expressed by Aldous Huxley: "Modern medicine has made such tremendous progress, that there is hardly a healthy human left." (Yudkin & Montori, 2014)

Second, the distinction between diagnosis and prognosis has become blurred as progression and development uncertainty have become relevant for diagnosis. That is, in addition to the temporal uncertainties of the diagnosis process, the temporal uncertainty of whether indicators will develop into something relevant for persons' health makes diagnosis even more subject to temporal uncertainty. More precisely, in addition to the uncertainty at each temporal step of the diagnostic process, uncertainty with respect to whether what the diagnosis indicates will occur is added.

Figure 2 illustrates the idealized disease trajectory, where indicators may detect a disease process early. However, they may also result in unnecessary anxiety, diagnostic odysseys, overdiagnosis, and overtreatment, as indicated in Figure 3.

Figure 2 Idealized disease trajectory indicating the relationship between anamnesis, diagnosis, and prognosis.

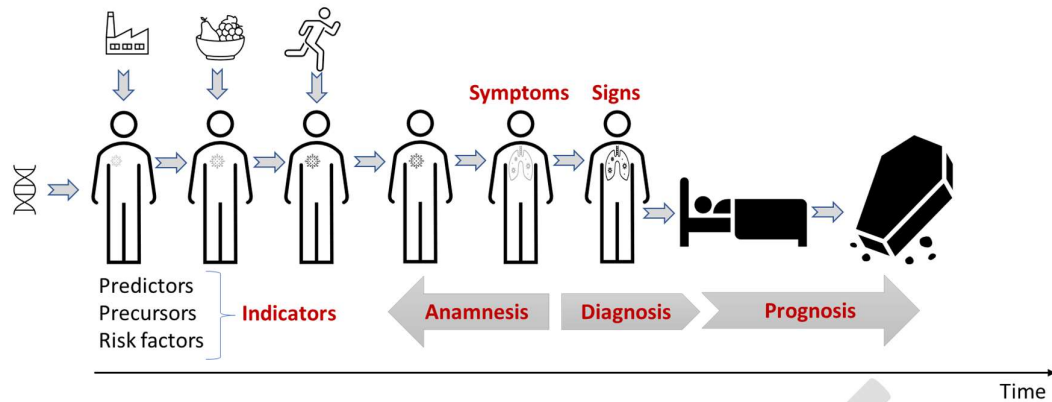
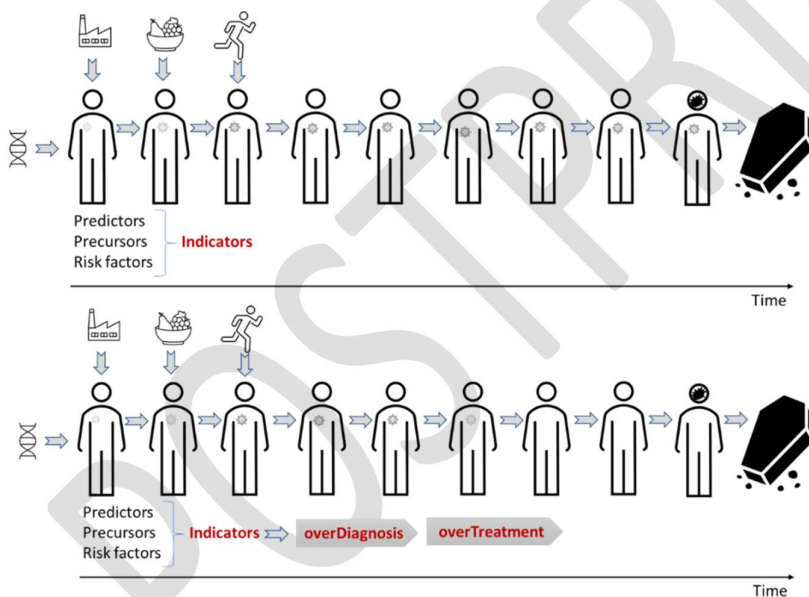


Figure 3 Early detection of indicators of conditions that can develop to disease, but that do not necessarily do so. Upper figure is when left untreated, where the person dies from other causes. Lower figure is when the person is diagnosed and treated, i.e., overdiagnosed and overtreated. In this case there may also be side effects from diagnostics and treatment in addition to experienced fear and anxiety from unnecessary diagnosis and pain and suffering from unnecessary procedures.



Diagnosis and prognosis over time

Three important lessons can be drawn from this. First, technology is a game-changer. At the same time as it makes it possible to increase our knowledge about disease mechanisms and developments, and thereby can reduce (prognostic) uncertainty, technology can increase this uncertainty by detecting indicators of conditions that *can* develop into disease ever earlier, but without knowledge of whether they actually *will* do so. While early identification certainly can save lives, it can also result in overdiagnosis, overtreatment, unnecessary anxiety, and fear, as well as vast opportunity costs (Welch, 2015; Welch, Schwartz, & Woloshin, 2011). The reason for this is that the earlier and the more indicators of disease technology identifies, the more uncertain it may be whether they are of any relevance.

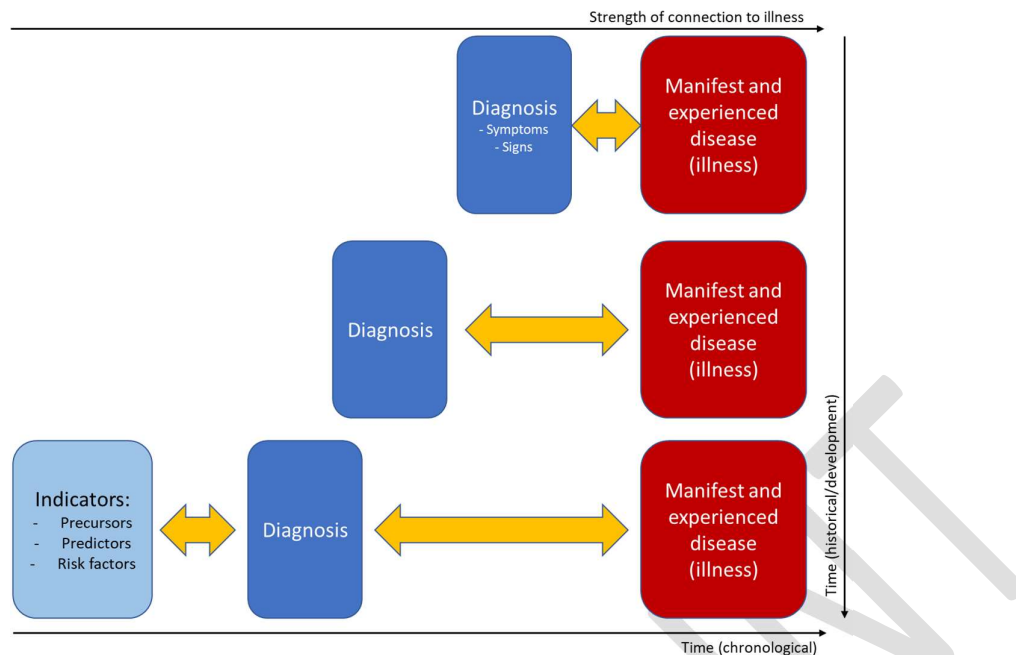
Second, the traditional relationship between anamnesis, diagnosis, and prognosis is changed. Anamnesis may (partly) be replaced by algorithm-based alarms and tests for indicators. Where the validity of pretest probability increases, this is certainly a good thing. However, this may not be the case as validation of indicators, such as biomarkers, is not an easy task (Bossuyt, 2011; Mohanty, Mohanty, Rout, & Pani, 2021; Rodríguez et al., 2021). Moreover, diagnosis may be made based on indicators, and less on anamnesis, symptoms, and traditional signs. This may increase the gap between diagnosis and what matters to people, i.e., pain, dysfunction, and suffering. We get what Aronowitz has called "symptom-less and sign-less disease" (Aronowitz, 2009).

Hence, it can be argued that indicator-based diagnosis increases *progression uncertainty* by conflating it with *development uncertainty*. In sum, it increases the temporal uncertainty with respect to whether you would ever have manifest and experienced disease resulting from the identified condition during your lifetime if it were not detected.

Third and more specifically, the relationship between diagnosis and prognosis is changed. While diagnosis may be conceived of as a label of a temporal state of affairs, it now is clear that it is (even) more influenced by potential future events, i.e., by prognosis. Indicators of conditions that can develop to manifest and experienced disease are considered as diagnosis when they can progress into something clinically relevant. Hence, potential prognoses strongly influence diagnoses.

This effect could counterbalance the increasing gap between diagnosis and manifest and experienced disease. However, as we tend to be risk averse, and subject to progress bias (Hofmann, 2020; Hofmann, 2019b), this does not seem to appear. On the contrary, indicators of conditions that have any (weak) connections to manifest disease and illness are prone to become diagnoses. Figure 4 illustrates how the relationship between diagnosis and manifest and experienced disease has changed over time with the introduction of advanced technologies facilitating ever earlier detection of conditions that potentially may develop into disease.

Figure 4 Illustration of how diagnosis has altered its connectedness with manifest and experienced disease (illness) over time as indicators of conditions that may develop into disease are detected ever more early. Lower X-axis is chronological time (from detected indicators to diagnosis and manifest and experienced disease). Right (inverted) Y-axis is historical development over time, where there is an increased (epistemological and temporal) gap between diagnosis and manifest and experienced disease. The latter is illustrated by the upper X-axis indicating the strength of the relationship between diagnosis and experienced disease, i.e., illness.



Discussion

In this article I have argued that science and technology play paradoxical and ambivalent roles: they can both reduce and increase temporal uncertainty. Technologies, such as biomarkers, BigData, AI, ML, and various kinds of precision medicine can come to change the relationship between anamnesis, diagnosis, and prognosis. In particular, diagnoses are less closely connected to manifest and experienced disease resulting in *progression uncertainty*. Additionally, a host of new indicators are even less closely connected to manifest and experienced disease, resulting in increased *development uncertainty*. Together, science and technology have increased *prognostic uncertainty*, which is a crucial type of temporal uncertainty resulting in epistemological and ethical challenges related to phenomena such as overdiagnosis, overtreatment, unnecessary anxiety and fear, useless and even harmful diagnostic odysseys, as well as vast opportunity costs. In doing so, diagnosis has inherited temporal uncertainty from prognosis, i.e., whether what has been diagnosed ever will become manifest and experienced disease (and how).

The claim that science and technology influence the relationship between prognosis and diagnosis may be criticized from at least two points. First, it can be argued that diagnosis has been and is a label of given condition at a specific time. It is categorical and a-temporal (Blaxter, 1978; Sadegh-Zadeh, 2012), and not influenced by prognosis or other temporal matters, such as anamnesis. I think it is hard to justify such a claim as diagnoses have a moral purpose: to help people. The urgency to help depends on the severity, which depends on the prognosis. If the diagnosed condition will not result in something painful or harmful, it will not qualify as a diagnosis.

Second, it can be argued that diagnoses have been influenced by prognosis throughout history, so the relationship between diagnosis and prognosis has not changed (substantially). If a phenomenon, e.g., a physiological or mental condition, was known to progress to disease, it got a diagnosis label. Ductal carcinoma in situ may serve as an example (Esserman et al., 2014), where a condition (cell changes) is labelled after a potential disease (cancer).

However, as has become ever more evident, the influence of prognosis on diagnosis has increased (prognostic) uncertainty as technologies have been able to identify ever more indicators ever less connected to manifest and experienced disease. Medical doctors, researchers, and philosophers therefore discuss non-harmful diseases (Rogers & Walker, 2017). The problem with this is that we remove disease labelling from what matters to people, i.e., pain, dysfunction, and suffering (Hofmann, 2019a; Wendy A Rogers & Mintzker, 2016). Accordingly, we reduce our moral obligations towards persons with diagnoses.

Additionally, it may be argued that diagnoses are not necessarily categorical concepts or processes but can be hypotheses of conditions persons may have (conjectural diagnosis) (Sadegh-Zadeh, 2012). That is correct, but the hypotheses are temporal and will (by differential diagnoses, by testing treatments, or “test of time”) be corrected or reach a conclusion. In particular, in the “test of time”, where the diagnostic strategy is to test and retest a patient over time to reduce uncertainty in populations of low prevalence (Almond & Summerton, 2009; Irving & Holden, 2013) the uncertainties are as described above (Table 1).

Besides, diagnostics is used in a wide range of settings, such as for confirmation/exclusion, triage, monitoring, prognosis, screening (Bolboacă, 2019), and check-ups and it can be argued that the temporal uncertainty is not the same for all of these. As I have acknowledged, development and progression uncertainty are most prevalent in screening, but are also highly relevant in other diagnostic settings.

Furthermore, I have applied a broad and implicit definition of temporal uncertainty, as this study has been explorative. Nonetheless, three conceptions of timing have appeared throughout the study. Firstly, I have identified uncertainty with respect to the past (recollection, anamnesis). Second, there is uncertainty in the various steps of the diagnostic process in time (present, diagnosis). Third, I have identified two types of uncertainty with respect to the future (progression, development).

Moreover, as pointed out by many scholars, diagnoses are malleable and pragmatically organized (Töpfer & Wiesing, 2005; Wieland, 2013) and influenced by a wide range of drivers. I fully agree with this. My point here is that the moral appeal to help people stems from the negative experience of manifest and experienced disease in terms of pain, dysfunction, or suffering (Mayerfeld, 1999).

Clearly, diagnosis always seems to have been influenced by prognosis (Bolboacă, 2019), as there has been a “dia-prognostic” connection, and there is a whole new are of “theranostics.” Acknowledging this, the point here is to provide a more conceptual analysis of the relationship between diagnosis and prognosis, especially related the vast advances in science and technology. In particular, I have tried to show how the temporal uncertainties of prognostic has added temporal uncertainties to diagnostics.

Relatedly, it may be argued that this study is both about anamnesis and prognosis, and that these concepts should be part of the title. However, the reason these concepts are part of the study is because of their relation to (the temporal uncertainty of) diagnosis. Thorough analyses of the uncertainty of anamnesis and prognoses warrant more in-depth work than can be fitted in one article.

It may also be maintained that this study does not contain any extensive elaboration of science and technologies or any sophisticated conception of disruption (Topol, 2012). I fully agree with this as it has not been the purpose to provide this, but rather to use recent advances in science and technology as examples.

The concepts “development uncertainty” and “progression uncertainty” are not new (Hofmann, 2019a). However, in this article they are set in the context of temporal uncertainty in diagnostics and in relation to temporal uncertainty in prognosis. Moreover, much more can be said about the various aspects of temporal uncertainty. The same goes for ignorance (Whooley & Barker, 2021). However, this article is limited to temporal uncertainty related to emerging diagnostic technologies in general.

Correspondingly, very much more can be said about the concept of “manifest and experienced disease” than is possible in this article. While manifest disease is the “gold standard” of disease diagnosis, experienced disease (illness) is arguably the “diamond standard” (Hofmann, 2019a), i.e., what matters most to people. The shift from these standards to indicators (“aluminum standard”) represents “an epistemic ignorance toward the lived experience of illness” (Whooley & Barker, 2021) and a breach with the ethos of medicine (Hofmann, 2019c). Correspondingly, much more could be said about the relationship between disease and diagnosis, but this has been well covered elsewhere (Aronowitz, 2009; Copeland, 1977; Copp et al., 2017; Engelhardt Jr, 1985; Jutel, 2011; Moynihan, 2011, 2013; Nickel, Barratt, Copp, Moynihan, & McCaffery, 2017; Risør, 2016; Stempsey, 1999; Tresker, 2020; Vitor Pordeus & Rosenberg, 2017).

Given the vast attention to health informatics, one can ask whether artificial intelligence (AI), machine learning (ML), together with BigData will solve the problems with (prognostic) uncertainty. Given the massive hype of such technologies (Bossuyt, 2011; Fox & Do, 2013; Frohlich et al., 2018; Goldfield, 2014; Labrique, Vasudevan, Chang, & Mehl, 2013; Mazzanti, Shirka, Gjergo, & Hasimi, 2018; Mohanty et al., 2021), this is a highly relevant question. For example, it has been argued that AI can re-humanize medicine (Topol, 2019). However, problems with data quality, validation, explainability, replicability, and transferability indicates that the solutions are yet not at hand. It is not clear how the technology that generates the problem has the resources to solve it.

Despite extensive efforts to reduce (diagnostic) uncertainty, uncertainty appears to prevail (Whooley & Barker, 2021) and temporal uncertainty is increasing. The saying that “the more we know, the more we know that we do not know” persists. “Absolute certainty in diagnosis is unattainable, no matter how much information we gather, how many observations we make, or how many tests we perform.” (Kassirer, 1989) There may of course be many ways to conceptualize the ambiguous role of science and technology in medical evidence production. One way to address the problem that science and technology at the same time can reduce and increase uncertainty is to differentiate between data, information, knowledge, evidence, and wisdom (Car, Sheikh, Wicks, & Williams, 2019). While we may get vast amounts of data and information, they do not necessarily provide knowledge and evidence to reduce uncertainty. Even more, they do not increase our wisdom. As long as we do not know what the information items mean for people’s experienced life (pain, dysfunction, suffering), they are of little value.

Another implication of this study is that while the concept of *kairos* has mostly been discussed in therapy, e.g., in terms of finding the right time to treat the patient, the temporal uncertainty of

diagnosis indicates that there is also a *kairos of diagnosis*. Both with respect to finding the right time of taking a diagnostic test and of making a diagnosis.

As already alluded to, this may also have implications for our moral duties with respect to people with diagnoses and for medical taxonomy and nosology. Classifying conditions based on indicators with great temporal (prognostic) uncertainty may not make much sense, as getting diagnoses may be more harmful than helpful.

Conclusion

This study has identified temporal uncertainties in disease diagnosis and related this to uncertainties in the diagnostic process from anamnesis to prognosis. First, there is uncertainty with respect to the recollection and relevance in the anamnesis. Second, there are uncertainties in each specific step of the diagnostic process. Thirdly, there is uncertainty with respect to prognosis, i.e., whether findings will develop into manifest and experienced disease. Over time diagnosis has become more subject to prognostic uncertainty. This is because diagnosis has become (more connected to indicators that are) less closely connected to manifest and experienced disease.

While science and technology have increased our knowledge of disease mechanisms and progression, they have also enlarged our uncertainty about whether (and how) the diagnosed conditions progress to manifest and experienced disease, i.e., *progression uncertainty*. Moreover, the vast increase in the number of indicators have come together with the tendency to connect them to diagnoses, generating *development uncertainty*. We have many more indicators of disease, but we are ever more uncertain whether what they indicate develops to something that is relevant to people's health. Hence, together advances in science and technology have (over time) increased our *prognostic uncertainty* for a wide range of diagnosed conditions, weakening the epistemological standing of diagnoses. This increase in temporal uncertainty poses basic epistemological and ethical challenges as it can result in overdiagnosis, overtreatment, unnecessary anxiety and fear, useless and even harmful diagnostic odysseys, as well as vast opportunity costs. The point is certainly not to stop our quest for knowledge about disease, including knowledge on diagnosis (anamnesis and prognosis). We need such knowledge to improve diagnostic classification and to be able to help more people in ever better manner as early as possible. However, in order to obtain this, we need to pay careful attention to temporal uncertainty in the dynamics of anamnesis, diagnosis, prognosis, and disease.

Statements and Declarations

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