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Regulating diagnosis—Molecular and regulatory sub-stratifications of lung cancer treatment

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Abstract

The sociology of diagnosis has shown that diagnosis not only serves to label the underlying cause of disease but also to provide access to services and resources. Elaborating on this double-affordance of diagnosis, this article examines how precision medicine reconfigures diagnosis as a label and as a process in regulatory and clinical settings. Reporting from an ethnographic case study of the introduction of immunotherapy for lung cancer, the paper unfolds the uncertainties involved in dissecting diagnosis into layers and examines the efforts and negotiations it takes to enable these layers to work both as clinical entities and regulative entities with the purpose of delineating access to treatment. I suggest that the work of subdividing diseases into molecularly defined categories for the purpose of delineating treatment-eligible populations can be labelled 'diagnostic sub-stratification' and argue that it is pertinent to understand the political capacity of this strategy. Diagnostic sub-stratification involves a push of diagnosis from the clinic 'up' into the regulatory system and 'out' into the laboratories, obscuring who is accountable for the diagnostic categories employed to define patients' treatment access.

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access to care, cancer, Denmark, oncology, personalised medicine, regulation, sociology of diagnosis, stratification

INTRODUCTION

With exceedingly high prices and narrow indications, the turn to precision medicine calls attention to classical questions about diagnosis and health-care organisation (Kenny et al., 2021). The use of biomarkers to predict who will benefit from such precision medicines stands at the core of this development (Bourgain et al., 2020). A powerful tool of classification, biomarkers can split known disease categories, implying that patients who suffer from the same disease can be assigned to different diagnostic subgroups with each treatment trajectory. Splitting and lumping disease categories (Zerubavel, 1996) can serve both clinical, regulative, economic and commercial purposes with consequences for individual treatment trajectories, professional collaborations and national budgets (Bergeron et al., 2020; Green et al., 2022; Jutel, 2011; Merrild et al., 2017).

The social implications and negotiations of diagnosis are the locus of the sociology of diagnosis. By bringing attention to the efforts and arrangements it takes to make diagnostic classification appear natural and neutral (Bowker & Star, 1999; Hacking, 2001), as well as to the constitutive outcome of diagnostic classification (e.g. Dewey & Gesbeck, 2015), the sociology of diagnosis demonstrates that the categorisation of disease serves as a roadmap for medical action and resource allocation (Jutel, 2011). The sociology of diagnosis has thoroughly examined the often contested affair of applying diagnostic labels to distinguish between the normal' and the pathological (McGann et al., 2011) and is increasingly exploring the delineation of subcategorisations within existing pathological conditions, as we currently witness with the advent of precision medicine (cf. Joyce & Jeske, 2020; Ross et al., 2021; Wadmann & Hauge, 2021). This study adds to the latter development by examining the uncertainties and politics of slicing disease categories into more narrowly defined layers on the basis of molecular and genetic traits, focusing on the introduction of treatments into standard care and the economic evaluation process that precedes this introduction.

Precision medicine uses information about a patient's genes or proteins to assess which types of patients will benefit from a particular treatment (Prainsack, 2012; Tutton, 2012). It has gained a strong foothold within oncology (Kenny et al., 2021; Polk et al., 2023) and regulatory authorities such as the European Medicines Agency (EMA), where biomarkers are used to stratify the organ-specific categorisation of cancer—for example, breast cancer, lung cancer or kidney cancer—into still more fine-grained subcategories, such as 'HER2-positive breast cancer' or 'non-small cell lung cancer (NSCLC) with programmed death ligand 1 (PD-L1) expression >50%' (Politi & Herbst, 2015). By employing genetics and biomarkers as engines (Conrad, 2005), precision medicine promises to 'finalise' diagnosis by providing a state-of-the-art and personalised 'diagnostic layer' (Ross et al., 2021, p. 3). Associated with advanced technologies and wrapped in technical phrases, the new diagnostic categories can come across as 1:1 representations of biological facts, but a growing body of social science scholarship—particularly from the field of science and technology—has demonstrated how precision medicine comes with new forms of diagnostic uncertainty (Bourgain et al., 2020; Green et al., 2022; Stivers & Timmermans, 2017; Wadmann & Hauge, 2021).

This article studies the introduction of precision medicine into standard care for lung cancer patients in Denmark. Based on an ethnographic study involving both regulatory and clinical

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settings, the paper investigates the question: How does precision medicine shape diagnosis and what are the implications? The analysis (a) unfolds the uncertainties related to the delineation of diagnostic categories that are based on the PD-L1 biomarker and demonstrates how this uncertainty can be utilised in regulatory settings to delineate diagnostic categories and protect national health budgets and (b) discusses the implications of diagnostic authority being pushed from the clinic 'up' into the regulatory system, where recommendations about access to treatment are made and 'out' into the pathology laboratory, where patients are categorised on the basis of molecular tests. Drawing on work on the uncertainties of precision medicine (Green et al., 2022; Kerr et al., 2019; Kuiper et al., 2022; Timmermans and Tietbohl, 2016), the paper's contribution to the sociology of diagnosis (Jutel, 2009, 2011; Ross et al., 2021) is an empirical exploration of the ways in which commercial, national economic and clinical interests intersect as precision medicine passes through national health technology assessment agencies and into standard care in the clinic. Thereby, the study sheds empirical light on issues raised by existing studies on precision medicine in a regulatory context, such as Cambrosio et al. (2021), Green et al. (2022) and Wadmann and Hauge (2021), illuminating the entanglements between molecular, diagnostic categorisation and resource allocation.

The sociology of diagnosis in the era of personalised medicine

A central function of diagnosis is to organise illness. Diagnosis can act as a 'status passage' that connects individuals to group identities (Glaser & Strauss, 1971; McGann, 2011) and serve as a roadmap through health-care systems (Jutel, 2011). It can offer a gateway to the legitimacy of a condition (Jutel, 2009) but can also be a source of stigma (McGann, 2011). While diagnoses can create clarity and guide clinical decision-making, establishing the boundaries of a disease is rarely a straightforward affair (Joyce & Jeske, 2020; Ross et al., 2021; Swallow, 2020). Both the delineation of a new diagnosis at the aggregated level and the provision of a diagnosis at the individual level often involve contestation and negotiation. Sociologists of diagnosis have, for example, elucidated the complexity of constructing the boundaries around different types of cognitive deterioration diagnoses in a memory clinic (Swallow, 2020) or of classifying pre-risk states of disease (Aronowitz, 2015) and have followed patients whose symptoms do not fit existing categories (Nettleton, 2006), which pushes some to pursue lay paths to diagnosis (Jutel, 2011; Madden & Sim, 2015). Central to negotiations and contestations of diagnosis is the uncertainty found around the borders of many if not most disease categories (Kuiper et al., 2022).

Precision medicine involves new forms of diagnostic uncertainty (Bourgain et al., 2020; Bourret et al., 2011; Green et al., 2022). While precision medicine speaks to the naturalisation of disease by employing 'advanced' technologies to match therapies to patients at the most granular levels of the body (Kerr et al., 2019; Ross et al., 2021; Stivers & Timmermans, 2017), medicine or diagnosis has not been reduced to a question of biology (Bourret et al., 2011; Keating & Cambrosio, 2004). There are several examples of the uncertainty that can be imbued in 'precision' diagnoses. (1) Diagnosis does not always result from biological symptoms. For example, Navon and Eyal (2016) show how the geneticisation of autism did not only generate a biological explanation of autism but came to transform and expand the autism population. (2) There can be discordance between phenotypes and genotypes (Rabeharisoa & Bourret, 2009; Timmermans, 2017). (3) The technologies to analyse potential treatment benefits are not perfect (Bourgain et al., 2020) and (4) The capacity to interpret the 'precision' information can be lacking (Ross et al., 2019). While uncertainty adds complexity to clinical decision-making (Joyce & Jeske, 2020; Ross et al., 2021), studies show that it can also be productive (Kuiper et al., 2022; Latimer, 2013) and serve to resist

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the standardisation of clinical decision-making and return the decision-making power to the clinic (Swallow, 2020).

Scholarship from sociology and science and technology studies (STS) has addressed the handling of the uncertainties associated with precision medicine in multiple settings, including tumour boards, the clinical encounter (e.g., Cambrosio et al., 2021; Timmermans & Buchbinder, 2012), and regulatory settings (Bourret et al., 2011, 2021; Cambrosio et al., 2017; Holloway & Miller, 2022). As an increasing number of precision treatments pass through regulatory agencies and into standard care, the significance of comprehending the interconnections between 'precision diagnosis' and regulation with the purpose of prioritising access, as well as its ramifications, becomes more pronounced (cf. Hughes & Doheny, 2019). 'Regulation' connotes different associations in different disciplines (Drahos, 2017; Green et al., 2022). Here, I use it to refer to practices of developing and enacting allocative decisions both within and outside clinical practice. Central to this approach is an understanding of the regulation as a co-producer of the entities that are regulated, which implies that entities such as indications and populations do not necessarily precede rules and regulations (Cambrosio et al., 2017). The combination of rising costs and narrow diagnostic categories makes the regulated implementation of precision medicine a pertinent sociological focus (Kenny et al., 2021, p. 4). For this study, I therefore seek to combine key elements of the sociology of diagnosis, namely the focus on diagnosis as a social and regulatory category that provides access to resources, with studies of diagnostic uncertainty related to precision medicine. This approach provides an analytical lens attuned to the study of the introduction of precision medicine—an introduction that involves negotiations of disease categories with both diagnostic and regulative purposes.

BACKGROUND FOR THE STUDY

Multiplying treatment options and costs

Lung cancer is one of the most common cancer types and the leading cause of cancer death worldwide (1.76 million deaths annually) (Ferlay et al., 2015). The prognoses are poor; most patients are diagnosed with advanced disease implying a 5-year survival prognosis of 2%–6% (cancer.net 2019). Within the last 5–10 years, lung cancer treatment has experienced a paradigm shift or even a revolution (Politi & Herbst, 2015; Rusch et al., 2018), resulting in a rapid innovation of new 'precision' treatments and an accompanying rise in treatment costs. The new treatments constitute a significant rise in treatment costs per patient, as many are extremely expensive compared to traditional chemotherapies (Barnes et al., 2017; Vergnenègre & Chouaïd, 2018; Wiersma et al., 2019). At the core of the changing treatment paradigm is immunotherapy and its related biomarkers. While the actual prices are not publicly known, experts assessed that the introduction in 2017 of the immunotherapy, Keytruda (pembrolizumab), as first-line treatment for certain types of NSCLC would result in a population specific increase of approximately 500 million DKK (67.2 million Euros) or 450.000 DKK (60.000 Euros) per patient (Danish Council of Ethics, 2018; Nice, 2018).

Immunotherapy refers to numerous methods and treatments (Oiseth & Aziz, 2017) that seek to improve the immune system's ability to attack cancer cells (Dobosz & Dzieciątkowski, 2019). This study focuses on so-called PD-1 checkpoint inhibitors, which—in short—support the immune system's ability to attack cancer cells. The first checkpoint inhibitor for first-line treatment of lung cancer (pembrolizumab) was approved for marketing for a subpopulation by EMA in 2015. This type of immunotherapy works by preventing the cancer cells from 'tricking' the

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immune system. Some cancers produce a protein (PD-L1) that combines with a receptor of the body's T-cells (PD-1) (part of the immune system), which inhibits the immune system from recognising and thus attacking the cancer cells. By blocking the PD-1 receptors, the combination is prevented, and the immune system's ability to recognise and attack cancer cells improved (EMA, 2022). These immunotherapies are relevant for tumours that produce the 'tricking' protein PD-L1.

Cancer tumours express PD-L1 on a spectrum of 0%–100% of cells analysed for diagnosis. Randomised controlled trials conducted by the pharmaceutical companies have shown that PDL1 expression—although not perfect (cf. Muller et al., 2017)—is able to predict which tumours will benefit from immunotherapy on the population level (Bylicki et al., 2019; Garon et al., 2015). In applying for marketing approval with EMA, the companies have, therefore, used PD-L1 scores to define the subpopulations for whom they market their product. Yet, the association between PD-L1 expression and treatment benefit is a contested affair, as the analysis in this article demonstrates.

Responses to multiplying costs

Reflecting the general cost increase of medicines, HTA agencies have been established in many countries to evaluate new pharmaceuticals and create guidelines to regulate their use. When companies have obtained an EMA marketing approval and wish to market a new drug in Denmark, they submit an application to the Danish Medicines Council, which was established in 2017 as the first institution in Denmark with a political mandate to include treatment costs in their evaluations (a parallel to the UK's National Institute for Health and Care Excellence [NICE]).

Denmark is a welfare state with universal access to treatment, making the question of differentiated access to treatment particularly pertinent. The five regional government administrations of Denmark operate the public hospitals and are responsible for the organisation and payment of health service delivery, including medicines. The Danish Medicines Council consists of three units: (a) the Board, which has the overall responsibility for making recommendations about access to treatment based on both clinical benefit assessments and cost assessments; (b) the secretariat, which manages the evaluation process; and (c) a number of expert committees on different therapeutic areas (Wadmann & Kjellberg, 2019). Each committee consists of medical specialists, one clinical pharmacologist, one pharmacist and at least one patient representative. As part of this study, I followed the work of the expert committee on lung cancer.

At the time of the study, the process of assessing new treatments and indications followed the process illustrated below.[1]

The expert committee's primary task is to undertake clinical benefit assessment (pillar 4 of Figure 1), that is, define the assessment protocol (e.g., specify the patient population, the comparator and the outcome measures) and critically appraise the data received from the pharmaceutical company applicant (Wadmann & Kjellberg, 2019). The economic evaluation is made by Amgros, and the final decision based on the clinical and the economic assessment is made by the Council.

DATA COLLECTION

This ethnographic study is based on fieldwork conducted in relation to a wider research project on health-care priority setting (2018–2022). For this study, I draw on data relating to lung cancer,

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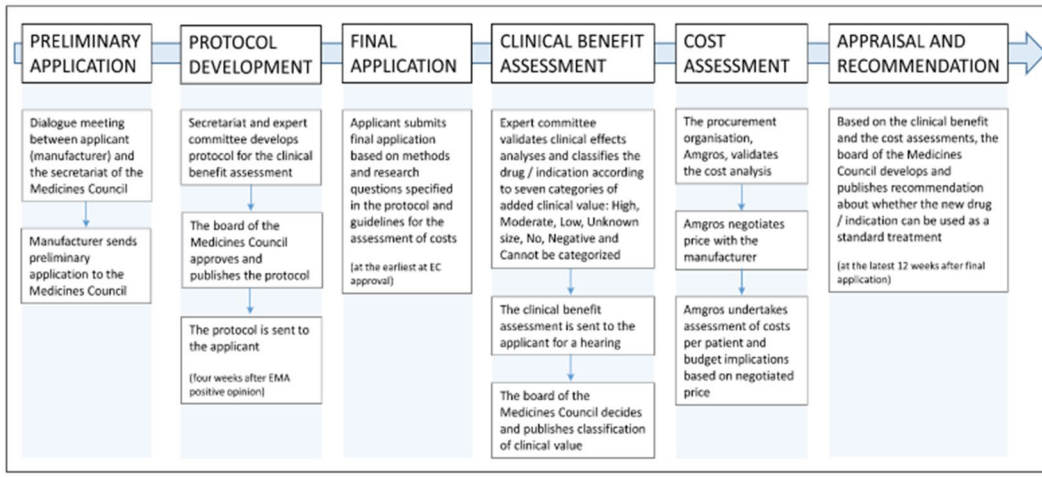


FIGURE 1 Illustration by Wadmann & Kjellber (2019).

which were obtained by attending monthly meetings of the Danish Medicines Council's expert committee on lung cancer (7 meetings, 3–5 h), conducting interviews with committee members (5) and employees (4) and by being included on e-mails about meeting drafts and discussion of documents. During the same period, I conducted observations in a lung cancer clinic at a hospital in Denmark (including 156 patient consultations, 28 subunit conferences and 22 meetings) (see also Hauge, 2020). At the core of the discussions in the expert committee was the question of how to delineate access to immunotherapy; a question which hinged on the diagnostic uncertainty related to the PD-L1 biomarker. The engagement with diagnostic categorisation in both clinical and regulative settings made diagnosis a highly relevant analytical focus for this study. It should be noted that the expert committee is not tasked with performing economic evaluations but function within a regulatory infrastructure (the Medicines Council), where such evaluations are conducted. Rather than explicit economic discussions, therefore, data from the expert committee meetings provide insights into the experts' efforts of navigating within this infrastructure while remaining within their mandate (see Figure 1). Further, by focusing the fieldwork on the Danish regulatory setting, I am not able to include the politics of diagnostic substratification as it may play out within the industry or internationally with EMA, although this would have been relevant.

Data collection was done in accordance with Danish rules and guidelines, which included approval by the board of research ethics at VIVE—the Danish Center for Social Science Research, approval by the hospital and approval and signed collaboration agreement with the Danish Medicines Council. Informants have been offered the opportunity to review citations in context, resulting in some—mostly technical—modifications.

ANALYSIS 1: NEGOTIATING DIAGNOSTIC SUB-STRATIFICATION ON UNCERTAIN GROUNDS

The following analysis unfolds the uncertainties related to the use of the PD-L1 biomarker to delineate diagnostic categories and demonstrates how this uncertainty can be used in negotiations about indication size, affecting public expenses for treatment. I begin by presenting the formal treatment algorithm.

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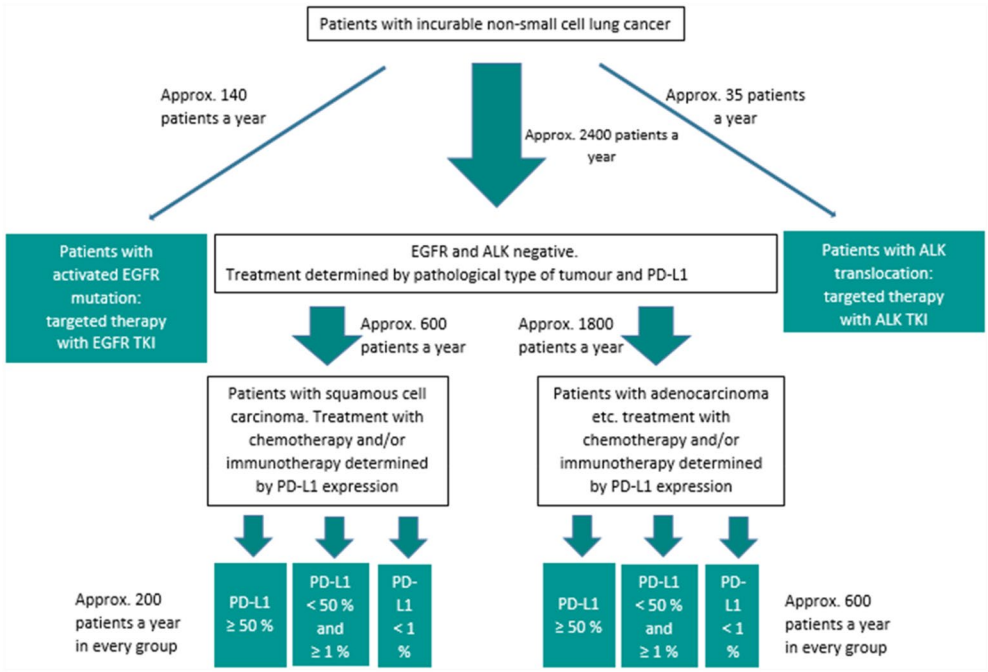


FIGURE 2 Treatment algorithm for lung cancer, illustrated by the Danish Medicines Council, translated by the paper's author.

During the period of observations, the expert committee for lung cancer drew up the treatment algorithm for NSCLC[2] (Figure 2), drawing on the indications defined by EMA; the standardised way of grouping patients with NSCLC in Denmark at the time of this study.

The treatment algorithm divides the NSCLC population into multiple subcategories, reclassifying lung cancer into rarer subtypes by incorporating biochemical and molecular information, as has happened with many diseases during the last decades (Bourgain et al., 2020; Keating et al., 2016; Löwy, 2010). The figure shows that the selection of first-line treatment depends on the presence of genetic aberrations qualifying for targeted (precision) treatments (epidermal growth factor receptor and anaplastic lymphoma kinase). The majority of patients with NSCLC do not have these aberrations (Reck et al., 2016), but are divided into two groups: squamous cell carcinoma and adenocarcinoma. Both of those groups are then stratified into three subgroups depending on their tumour's expression of PD-L1 (<1%, 1%–50% and >50%) (Danish Medicines Council, 2019).

Diagnostic sub-stratification as regulation through categorisation

The use of biomarkers introduces *potentiality* as a parameter of diagnostic categorisation, which comes with distinct contestations and foci (Brown et al., 2011). During several meetings observed in this study, the Danish Medicines Council's expert committee on lung cancer debated the use of PD-L1 to stratify patient populations in relation to several immunotherapies. A traversing

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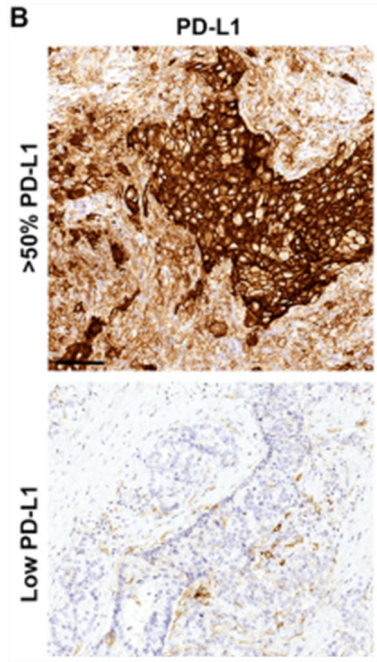


FIGURE 3 Silva et al. (2018): PD-L1 immunostaining scoring for NSCLC with high and low expression of PD-L1. NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1.

concern was the validity of PD-L1 assessments (cf. Bourgain et al., 2020). In this field note, a pathologist explains the practical process of assessing PD-L1:

> You receive the tiny bit of tissue and fix it in formalin and embed it in paraffin, giving it a gel-like structure. Then the lab technician produce sections that make the tumour cells visible. Then you can tell if it is adeno or squamous cell carcinoma. Then you make the PD-L1 test: A fine cut tissue slide that you colour: – it's an overnight process in a machine. Then they [laboratory workers] send it to us – the pathologists – and we look at it in a microscope. We want at least 100 cells. The membrane on the cells must be brown; this is what we look for when we determine how many are positive.
>
> (Expert committee meeting)

Three factors make PD-L1 an imperfect biomarker (Bourgain et al., 2020), according to interviewed informants and clinical research (i.e., Grigg & Rizvi, 2016).

1) Tumour contingency: A tumour may have varying expressions of PD-L1, for example, a high expression on one side and a low on the other. The tumour's expression can also change over time. Figure 3 illustrates what high and low expressions of PD-L1 look like (Silva et al., 2018).
2) Human contingency: Histochemistry relies on the extraction of tumour tissue. However, sometimes it is not possible or safe to reach the tumour due to its position in the body, or too little tissue is extracted. Further, the analysis of PD-L1 expression relies on a manual count of brown cells using a microscope. For some treatments, the indication involves a cut-off of 1% positive cells, which can be difficult to assess in small samples. A pathologist explains to the

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lung cancer expert how such cases are handled: *"Sometimes we don't mind that there are fewer cells. It's easy if it's very positive. I take a quick look: Is it above or below 50%? Others are very careful and count all the cells. It's difficult when the line is 1%..." The member of the secretariat adds: "If you have 101 cells and one is brown, it's under 1%. If you have 98 cells and one is brown, it's above...".* (Observation, expert committee)

3) Machine contingency: Pharmaceutical companies market their products with their own assays, implying that multiple assays are present on the market. Different technologies provide different levels of colouring, which means that test results can differ, as a pathologist explained to the expert committee (observation). This risk has been eliminated in Denmark after quality appraisal, according to an expert pathologist (interview, external pathologist), but knowledge about the possible variance still circulates.

Together, these uncertainties made the members of the committee question the value of the PD-L1 biomarker. Particularly the pathologist, who represented the profession responsible for the PD-L1 testing, was critical. During a meeting in the committee, he firmly expressed his concerns:

> "PD-L1 is a redundant idea! Very exaggerated!" [...] "we are doing histochemistry; is it brown or not? And you know how small the biopsies are? Tiny!" [...] The leading oncologist asks "do you find that we place too much value on PD-L1?" The pathologist confirms and says his peers agree.
>
> (Observations, expert committee)

In an interview, an oncologist takes a similar point of view:

> Well, the problem with the splitting [into subpopulations]... Everybody likes it when you can say clear-cut "if you have this expression, then this happens, and if not, then this happens". But this is not the case with PD-L1 [...] a tumour can be positive in a top corner and completely negative on the bottom. [...] We have to take this biological fact seriously. [...] PD-L1 is fluffy.
>
> (Interview, oncologist from expert committee)

From this argumentation, some clinicians conclude that all lung cancer patients should be offered immunotherapy:

> Pathologist in the expert committee: "as oncologists, you're able to look at the patients and see if it works, aren't you?" [...] [in the future] all patients will be given immunotherapy, and those that respond are probably positive and those that don't, are not.
>
> (Observations, expert committee)

> You have no earthly chance of knowing the truth [about the benefit of PD-L1]. If [...] the chemo is no longer working. And the patient is doomed to die... [...] Then you could say "what about immunotherapy?", "Well, that was negative", "Yes, but what about giving the patient a chance?" Because after all, it could be that there had been a metastasis that would reveal something else.
>
> (Interview, external pathologist)

In spite of some oncologists and pathologists being inclined to pursue a strategy where the patient's clinical response to immunotherapy—rather than a PD-L1 assessment—determines

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whether they should (continue to) be offered immunotherapy, the expert committee keeps working with PD-L1, partly because they feel a pressure from the Board of the Medicines Council.

The expert committee has been frustrated by the Board's reliance on PD-L1, as is seen in the following field note. Here, two members of the committee have attended a meeting with the Board, where an external pathology expert gave a presentation on PD-L1. One of the committee members reports to his colleagues about the pathologist's presentation:

> [The pathologist] finished with a slide that showed a big tumour, where everything had been coloured [i.e., subject to PD-L1 testing]: One side was entirely brown, and the other one wasn't. If you'd taken a biopsy from the one side, it would have given a different result than from the other. The image was shown throughout the discussion, and I think that was good!
>
> (Observations, expert committee)

The quote above shows the oncologists' attempt to debunk the reliance on PD-L1, which they have come to question on the basis of existing studies and on their own experience with immunotherapy. Both committee members who attend the Board meeting found that the presentation made the Board more aware of the imperfection of PD-L1 assessments.

At their next meeting, the committee discusses how to define the subpopulations in the protocol for another type of immunotherapy (durvalumab):

> The member of the secretariat sums up the next step of the process: "You [members of expert committee] can choose to divide at 25% and call it high and low. Or to consider the full population above 1%". An influential oncologist interrupts and says "we will get it thrown right back at us by [by the Board, if we do not divide the population]". The group pauses. Another oncologist then suggests dividing the population into three subgroups: all above 1%, 1%–25% and above 25%. [...] An oncologist critically remarks "there is nothing to support that a cut-off of 25% is worse than 33% or 47% or any other percentage in that area".
>
> (Observations, expert committee)

Notably, the comment, 'we will get it thrown right back at us', shows that the committee members are concerned about whether the Board will accept the subpopulations they propose in the protocol. If the Board requests that the committee adjusts the subpopulations, the process of getting the new immunotherapy into the clinic will be delayed, which is a big concern for many oncologists in and outside the committee. In the end, they settled on below 1%, between 1% and 50%, and above 50%, which was accepted by the Board.

Public criticism of the Medicine Council's decision

When the Medicine Council's recommendation for the immunotherapy Keytruda (pembrolizumab), was published, it was subject to critical comments in the Danish health media. One oncologist criticised the scientific assessments:

> The available data show that there is a significant survival benefit in the PD-L1-negative patients. I don't understand how you can afford to throw away a

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> survival benefit like that, almost regardless of what the treatment costs. The consequence is that there are some patients, who do not receive the best treatment [...] I think it is hopeless that the Medicines Council is once again making decisions as they see fit, concluding things across studies and making decisions with incomprehensible arguments that are not properly scientifically based.
>
> (citation from Danish online article by Kraft (2019), translated by the author)

The oncologist's argument is that there is no solid *scientific* reason for the decision about excluding patient categories on the basis of their PD-L1 status, implying that the real reason is the *cost* of the treatment. Another influential oncologist similarly challenges the Medicine Council's role in utilising scientific arguments to frame economic decisions:

> As a clinician, I find it difficult to see the thread of consistency in the Council's decisions. ...When the Medicines Council says no to the introduction of new treatments and medicines, in the end, we [the clinicians] are the ones facing the patients; the ones, who have to explain why they cannot get the treatment or medicine they expect. I often feel squeezed between politicians' promises of a world-class healthcare system, and the reality, which is that there is something we cannot or must not do.
>
> (oncologist cited by Andersen (2019), translated by the author)

From this oncologist's perspective, the Medicines Council prevents the oncological community from providing the best treatment to lung cancer patients and leaves the clinicians with the task of having to justify this to the patients.

In sum, this analysis has shown that diagnostic classifications based on the PD-L1 biomarker are not set in stone, but involve a number of uncertainties and negotiations. As noted by Swallow (2020), such negotiations are not only about how to handle uncertainty, they also involve commercial and regulatory interests. In addition to demonstrating the practical uncertainties related to the PD-L1 (cf. Bourret, 2005), the analysis has attempted also to analyse how the decision-makers respond to and use them (cf. Green et al., 2022). The uncertainties imbued in the PD-L1 disease categories create grounds for negotiability; it is possible to use PD-L1 categories to delimit access as a means to restrict costs for treatment or to debunk the categorisation's validity and argue in favour of inclusive access to immunotherapy. Although slightly out of this article's empirical scope, it may also be possible for pharmaceutical companies to use the categories strategically, when presenting their trial results in applications for marketing approval; at least this was discussed during committee meetings (see also Goldstein et al., 2017).

ANALYSIS 2: DISPERSING DIAGNOSTIC AUTHORITY

In the clinic, the porous PD-L1 categories become solidified through their inscription in the work processes and collaborative infrastructures of the professionals quickly after the Medicines Council's recommendation. Through this process, the authority to diagnose—a cornerstone of the medical profession (Heritage, 2005; Jutel, 2009, 2011)—becomes dispersed.

Diagnostic categorisation involves the arrangement of things in groups divided from one another by clear boundaries (Jutel, 2011, p. 18). With the turn to precision medicine, the 'things' categorised and grouped, such as PD-L1 scores, are only visible to professionals working in laboratories and other technical departments of the hospital. The move of diagnostic authority from clinicians to pathologists is not new, but the increasing reliance on molecular and genetic

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biomarkers amplifies this shift (cf. Bourgain et al., 2020). In the following, a pathologist leading a national quality test programme explains how laboratory testing can overwrite existing diagnoses:

> In the early days of immunohistochemistry, we could see that the results were often very different [depending on the hospitals' equipment]. [...] For example, when a patient at a small hospital got a lung cancer diagnosis based on an immunohistochemical analysis of a metastatic lesion, then we got the preparation, you know the glasses and the blocks etc. And then we could see "well, these staining reactions are completely wrong". And then we perform some new ones and obtain a different result, for example, that the patient had a kidney cancer...
>
> (Interview, external pathologist)

The reliance on the pathologists' expertise in combination with the lack of trust in the validity of PD-L1 makes it unclear who accounts for the diagnostic categories. A paraclinical specialty, the pathologists consider it their task (only) to assess if the tissue samples contain PD-L1 expression on more than 50%. Even though pathologists regard the PD-L1 biomarker to be a dubious source of information, as shown above, they provide the information on request from their colleagues in oncology. Oncologists, however, are equally sceptical towards the PD-L1 scores. Here, a senior oncologist explains his position:

> ***Interviewer*:** What is your own experience and is there a connection between the PD-L1 expression and the patient's benefit from immunotherapy?
> ***Oncologist*:** No. No. Well, there is a tendency that those with a high PD-L1 expression, they have good responses. But then again, we also have high-expression patients who progress after four treatments. And then we have some squamous cell patients who are negative, who can have nivolumab [a type of immunotherapy for patients with squamous cell lung cancer] who go 30 cycles. It just works. And you think to yourself "then why not the rest?", so I wouldn't say that my clinical estimation is that we... are in fact using immunotherapy in the most optimal manner. I hope that we will expand at some point'.
>
> (Interview, oncologist)

Why, then, do they follow this categorisation and the accompanying treatment recommendations? Formally, clinicians in Denmark have the discretion to make treatment decisions that contravene the recommendations of the Danish Medicines Council. This is inscribed in the statutes of the Medicines Council as the seventh principle:

> 7. Based on a medical assessment of individual cases, it should be possible to prescribe medicines that are not recommended as standard treatment; for instance, to be able to provide high-quality treatment for patients with rare diseases or to avoid functional impairment.
>
> (Ministry of Health, 2016)

Yet, in reality, the clinicians' possibilities for using this discretion are limited. The economic reimbursement system implies that hospital departments must use their existing budgets to cover expenses for treatments prescribed outside of the recommendations (Wadmann & Kjellberg, 2019). This setup provides a strong incentive to follow the guidelines, and the guidelines are rarely contravened.

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Additionally, the organisation of the diagnostic process implies that the assessment of PD-L1 expression is 'black-boxed' for the oncologists in the clinic, if they do not have a specific interest in biomarkers, as this interview with a younger oncologist shows:

> ***Interviewer***: What about the discussions about the uncertainties of using PD-L1 as a criterion... Do you block those out or..?
> ***Oncologist***: Yes. Personally I do. I have to say... And perhaps this is because I'm still early in my career... I still have to prioritise how I spend my time, and to develop my knowledge and skillset. So... I haven't fully reached the level where I've become critical to the specifications about PD-L1. No, I don't question them.
>
> (Interview, oncologist)

The assessment of PD-L1 is the pathologists' responsibility and as such not within the professional realm of the oncologists. This is also acknowledged by the pathologists:

> ***Interviewer***: The exact PD-L1 score is not something you usually provide to the oncologists, right?
> ***Informant***: Yes, yes, but well, that is true. You partially push the uncertainty away by saying that it is 'above 50%', and the oncologists can't do anything other than say, 'well, you decide'. And that's that. Then we just have to expect that the pathologists live up to that, even though we know how difficult it can be...
>
> (Interview, external expert pathologist)

As Hayes et al. (2021) have shown in the case of autism, an individual can only be inside or outside a diagnostic category. In the case of the sub-stratification of lung cancer patients, this binary is made possible through the dispersion of tasks and responsibilities between the professionals involved in settling on a diagnosis and treatment plan.

In sum, the introduction of immunotherapy into standard lung cancer care amplifies the ongoing move of diagnosis away from the clinician's turf. The definition of diagnostic categories has been pushed *up* to the regulatory level into an infrastructure of priority setting and rationing. While neither the Danish Medicines Council nor the expert committee consider the PD-L1 score a highly reliable diagnostic parameter, the resulting categories nonetheless structure treatment selection. Further, the diagnostic process is moved *out* to the laboratories, and while neither the pathologists who produce the PD-L1 scores, nor the oncologists who formally request the PD-L1 scores, consider them particularly reliable, the scores retain their function as providers of diagnostic categories.

DISCUSSION

This article has demonstrated how the introduction of precision medicine into standard care is formative for the diagnostic labels and processes that organise lung cancer treatment. The paper unfolds the emic process of stratifying diagnosis in a regulatory and clinical setting. On this basis, it suggests that diagnostic sub-stratification—in addition to being an emic process that can come across as technical and neutral—is also a useful sociological concept that can be used ethically to make intelligible the interests and negotiations involved in the delineation of indications for expensive, personalised treatments. In the following paragraphs, I discuss three key areas where this study adds to the existing sociological scholarship on diagnosis by providing empirical insights into the impact of precision medicine. Firstly, it illuminates how precision medicine has

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reconfigured the politics of diagnosis and classification. Secondly, it demonstrates the redistribution of diagnostic authority from the clinic to the laboratory and regulatory settings. Finally, it shows that the dispersion of accountability for diagnosis in a regulobioclinical collective enables the porous diagnostic categories to endure.

1) Classificatory politics of precision diagnosis

The study shows how HTA agencies and the infrastructure that surrounds them mediate—in the Latourian sense (Cambrosio et al., 2021; Latour, 2007)—precision treatments and the sub-diagnoses they are co-constituted with, as they are introduced into standard care. Sociological scholarship on diagnosis has demonstrated what may be termed the political capacity (Marres, 2013) of a diagnosis (Jutel, 2011), which involves both identity politics and resource allocation. While it is well known that disease categories determine access to health-care resources, for example, through systems such as the Oregon Health Plan (cf. Wadmann & Hauge, 2021), precision medicine takes these dynamics to a new level. The diagnostic process is now based on even more granular levels of the body, and disease categories are defined through even more specific biomarkers. This leads to diagnostic categories that not only serve to identify diseases but also—and often primarily—to guide therapy selection (cf. Cambrosio et al., 2021). This study sheds light on how these classificatory politics are playing out in the regulatory infrastructure of precision medicine, often through seemingly technical decisions.

In line with recent studies (Green et al., 2022; Ross et al., 2021; Wadmann & Hauge, 2021), the study shows that with precision medicine, stratification often unfolds *within* the boundaries of existing disease categories (hence the 'sub') which are split up via molecular strata, as we see with the PD-L1 biomarker. The politics of sub-stratification are about drawing lines or defining layers (Ross et al., 2021) that divide a disease into more fine-grained categories (Zerubavel, 1996). Typically, the subcategories reflect an expected response to a particular type of treatment (Ross et al., 2021; Wadmann & Hauge, 2021). Therefore, the categories loop with the development of new therapies, in the sense that the treatments often come to define the categories used to label patients' disease, rather than the other way around (Cambrosio et al., 2021), which is different for diagnostic categories of precision medicine in comparison to classical diagnoses. Advancing this observation, this study illuminates how the introduction of precision medicine into standard care can result in further reconfigurations of diagnostic layers: A treatment indication suggested by a pharmaceutical company can be adjusted by regulatory bodies with the purpose of delineating access and protecting national budgets, resulting in situations where populations that used to be one come to have different publicly available treatment options and—potentially—very different prognoses and life courses (Wadmann & Hauge, 2021).

2) Redistributing the diagnostic authority

Precision medicine is thoroughly embedded in a transformation of the process of introducing treatments into standard care that offers a more central role to HTA agencies in defining disease (sub)categories. The increasing influence of HTA agencies as mediators of indications and thus sub-diagnoses is not formally limited to precision medicine, yet, the vast majority of cancer treatments—and all treatments for NSCLC—evaluated by the Danish Medicines Council since its establishment in 2017—can be categorised as precision or 'targeted' treatments. This study has offered insights into one central strategy though which HTAs and economic-regulatory concerns become involved in disease categorisation: diagnostic sub-stratification. For clinical purposes, sub-stratification can be used to predict risk or treatment response, yet when employed in a

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regulatory setting—clinical and economic-regulatory concerns fold into each other, sometimes leading to different treatment algorithms and recommendations than strictly clinical reasoning would have. While economic arguments far from determine the resulting diagnostic categories, the regulative process nonetheless involves driving, defining and solidifying the sub-stratification of patients, as guidelines travel into clinical practice. As the HTA agencies solidify their role as experts in determining the value of new treatments for specific populations, the origin of the practiced diagnostic categories, moves 'up' towards the regulatory system.

Sub-stratification also moves the diagnostic process further *out* of the clinic and into the laboratories. Only few years ago, lung cancer only had a few subcategories, but the increasing reliance on parameters such as proteins and genes has changed the terms of disease categorisation and treatment selection. While the oncologists—among many other things—continue to assess whether patients are well enough to be offered a treatment, the selection of which treatment the patient (potentially) receives is based on work the oncologists are not involved in; patients are referred 'treatment ready', as the oncologists call it; that is, with complete laboratory work that makes it possible to place them in the treatment algorithm. In continuation of STS studies that have unfolded the uncertainties and interpretations molecular and genetic analyses require (Kerr et al., 2019; Timmermans & Tietbohl, 2016), this study has shown how the introduction of immunotherapy into standard care hinges on an arrangement, where diagnostic uncertainty is contained within the laboratory and separated from the clinical encounter.

3) Shifting diagnostic accountabilities—towards regulobioclinical collectives?

Attending to the accountability of diagnosis, the study addresses the concerns raised by Beaudevin et al. (2019) about the impacts of precision medicine (in their case genomics) on clinical practices, when authority is delegated to regulatory levels. In the case of using PD-L1 to stratify populations, the study has shown how the diagnostic process continues inspite of clear frictions. Oncologists in the clinic do not express responsibility for the way the diagnostic sub-stratification is done: Some are critical and others do not consider it their responsibility to know or understand the details of the biomarker, but they all make their decisions on the basis of the PD-L1 scores. While the pathologists provide the PD-L1 scores, they do not consider themselves accountable for the diagnostic classification either. The Danish Medicines Council has no legal authority and only issues recommendations, and, therefore, they cannot be held accountable for the way the Danish regions and hospitals grant access to treatment. Accordingly, none of the involved parties feel fully responsible for the use of the PD-L1 stratification, but nonetheless it ends up structuring treatment choice. Extending the observations by Beaudevin et al. (2019), this study shows how precision medicine hinges on what may be termed a 'regulobioclinical collective', highlighting the importance of regulation in shaping the development and implementation of precision diagnostics in intersection with biological and clinical practices. Through the regulobioclinical collective, diagnostic responsibility is distributed through sub-tasks taking place both in the clinic, the laboratory and in national HTA agencies, making the categories durable in spite of their evident porosity.

CONCLUSION

The introduction of precision medicine into standard care in national health systems involves changes of diagnostic labels and processes, which calls for sociological attention. Precision

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medicine is characterised by narrow indications and rising prices. The narrow indications imply that existing disease categories are split into subcategories or layers based on genetic or molecular strata predictive of how well the subgroups will respond to a treatment. While precision medicine comes with promises of a more accurate basis for diagnosis and treatment, the delineation of which patients constitute eligible subgroups is subject to new forms of uncertainty.

The paper contributes to existing studies of diagnosis in the era of precision medicine by illustrating how precision medicine alters diagnostic decision-making, and in doing so, creates new intersections between diagnostic categorisation, uncertainty and economic regulation. The paper illustrates this transformation by attending to the strategy of diagnostic sub-stratification, which has three important aspects. Firstly, it can involve strategic delineation of patient populations with the purpose of budget control. Secondly, it can reconfigure diagnostic expertise, pulling diagnostic authority *up* to the regulatory level, where treatment value is assessed and indications defined, and *out* to the laboratories, where patients are categorised. Thirdly, it can dilute accountability for diagnosis in the collective made of regulatory, clinical and pathology actors, enabling diagnostic categories to endure in spite of the collective knowledge of their uncertainty. Overall, the paper aims to demonstrate the political capacity of diagnostic uncertainty in the context of precision medicine, as well as the sometimes complicated intersections between clinical and regulatory concerns as they unfold in negotiations over diagnostic categorisations.

AUTHOR CONTRIBUTIONS

Amalie Martinus Hauge: Conceptualization; data curation; formal analysis; methodology; writing – original draft; writing – review & editing.

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DATA AVAILABILITY STATEMENT

The documents analysed in this article are openly available, and access information is provided in the reference list. The interview transcripts and field notes are confidential due to ethical concerns and GDPR concerns. More information about the data is available on request from the corresponding author.

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ENDNOTES

[1] Amgros, mentioned in the figure, is a Danish, cross-regional organisation that works to secure supplies of medicines for public hospitals through procurement and tendering procedures.

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[2] Lung cancer is categorized as small celled lung cancer (SCLC) or NSCLC, which is the most widespread form.

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