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Disease classification: A framework for analysis of contemporary developments in precision medicine

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ABSTRACT

This essay synthesizes key analytical perspectives from the vast social science literature on disease classification spanning various disciplines. The aim is to develop a framework for analyzing changes in Western medicine framed under umbrella terms such as 'precision medicine' and 'personalized medicine.' I argue that understanding these contemporary changes in the conception and enactment of disease requires attention to historical developments in disease classifications. Spinal muscular atrophy is used as an example case to illustrate this argument. To guide further inquiry into the current move in biomedicine towards precision medicine, I outline two analytical dimensions—material and social interactionist aspects of disease classification—and show how these can be fruitfully combined. Possible starting points and questions for analysis are presented and discussed.

1. Introduction

Western medicine is currently witnessing profound transformations in the way that disease is understood, enacted and treated. With the advent of 'precision medicine' during the past four decades, new disease categories are emerging and existing classifications are being redrawn (Green et al., 2022; Navon, 2019). Precision medicine, also called 'personalized medicine' or 'stratified medicine,' refers to attempts to tailor diagnosis and disease treatment to individual characteristics based on genetic variants and other biomarkers (Prainsack, 2017). Rapid advances in computational power and machine learning techniques aid researchers in expanding conventional ways of identifying and delineating ill health by capturing datafied signs of disease (Burton et al., 2022), e.g. through digital phenotyping in fields like computational psychiatry (Semel, 2022). Meanwhile, the blockbuster era of pharmaceutical mass production is giving way to advanced, high-cost products aimed at small patient populations (Dolgin, 2010; McGuire, 2020). Eichler et al. (2021) note that about 40% of the therapies with a new active ingredient approved by EMA in 2018–2019 target a 'rare' disease. These developments raise many questions. What does precision medicine imply for the meaning of 'rareness'? How do molecular markers of biological variation map onto other forms of human difference? Will digital phenotypes precipitate new forms of patient identity and preventive measures? How do novel disease classifications interact with allocative decisions when determining access to high-cost therapies? To answer these questions, it is necessary to critically engage with the process of disease classification.

Classification is the practice of arranging things in groups divided by clear boundaries (Durkheim & Mauss, 1903, cited in Jutel, 2011).[1] This involves both grouping 'similar' components in distinct clusters (*lumping*) and separating 'different' clusters from one another (*splitting*) (Zerubavel, 1996). Accordingly, disease classification refers to practices of delineating different kinds of disease by placing conditions in distinct groups that are separated from one another based on certain criteria of similarity and difference. The delineation of disease is shaped not only by the advancement of medical science but also by social processes (Armstrong, 2011; Aronowitz, 2008; Foucault, 2003 [1989]; Hacking, 1995; Jutel, 2011; Pollock, 2012; Wadmann & Hauge, 2021). Classifying a condition as a disease requires recognition of its undesirability, the technical capacity to identify it, and concerted effort by actors who are willing to include it in the ranks of disease (as opposed to the ranks of the spiritual or the idiosyncratic) (Jutel, 2011).

Classifications are powerful tools; they shape the epistemic space of what is thinkable, conceivable, and targetable (Schramm & Beaudevin, 2019) while also influencing health realities in tangible ways (Bowker & Star, 1999). Disease classifications form the basis of medical specialization and influence under whose jurisdiction a condition's management will fall (Jutel & Nettleton, 2011). They affect patients' access to healthcare, as well as how people understand themselves and are treated by others (Hacking, 1995; Navon & Eyal, 2016). Placement in a disease category can lead to social exclusion due to stigma and limited opportunities for participating in education, work and social life. Hoeyer,

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diagnostic labelling can also provide access to social services and lead to inclusion in new forms of community (Heath et al., 2004; Rabinow, 1996; Rose & Novas, 2005; Whyte, 2009). "Classificatory violence and social entitlement may go hand in hand", note Schramm and Beaudevin: classifications both exclude and include at the same time and have profound implications for people's opportunities (2019:277).

The social science literature on disease classification is comprehensive and spans a variety of disciplines, including medical sociology, medical anthropology, science and technology studies (STS), the history of medicine, and the philosophy of science. However, analytical insights do not travel easily from one field to another, a challenge compounded by the fact that scholarly fields are marked by classificatory practices of its own. The aim of this essay is to synthesize key analytical perspectives on disease classification across these scholarly fields in order to guide analyses of current developments in precision medicine.[2] I argue that attention to the past is needed to grasp contemporary changes in disease classifications because new diagnostic techniques and criteria may layer upon existing ones rather than replace them. Further, I suggest that attention to material and social interactionist aspects of disease classification can fruitfully be combined in analyses of the current move towards precision medicine. Attention to materialist aspects of disease classification can foster insights into the material infrastructure needed to develop and implement new diagnostic and treatment practices and its allocative implications. Social interactionist aspects can generate deeper understanding of the political negotiations, competing concerns and practical work it takes to establish and maintain new delineations of disease and treatment options.

To develop this argument, I first provide a brief, historical brush of changing conditions for diagnostic activity and associated conceptions of disease to illustrate the analytical importance of material infrastructures for disease classification. Then, highlighting the importance of social interaction in precipitating these transformations, I show how disease classification interacts with practices of market formation, patient engagement, regulation and clinical work. Next, I use the example of spinal muscular atrophy to illustrate how historical changes can shape contemporary negotiations of the delineation of disease and how material and social interactionist aspects entangle in this process. I end with a discussion about the kinds of critique social studies of disease classification entails and offer possible starting points for future analysis.

2. Historical transformations of the material infrastructure for diagnostic activity

> "As history shows, it is feasible to introduce completely different classifications of diseases" (Fleck [1935] 1979:21).

In Western medicine, 'the normal' has long been a key organizing concept for the delineation of disease. A declaration of pathology presupposes a given state of normality from which a condition deviates, as Canguilhem (1991 [1966]) observed in his seminal work. Diagnostic activity is key to making such distinctions as symptoms and signs of disease are discerned to infer the presence and nature of a given pathology. Importantly, diagnoses – like other forms of classification, such as the delineation of species or territories – are not merely conceptual frameworks emerging through language. Diagnostic practices rely on and work through material infrastructures. For instance, the notion of 'overweight' could not exist as a category until scales became affordable enough to allow for widespread use and population norms for 'normal' weight were established (Jutel, 2011). In this section, I provide a brief historical overview of major transformations in diagnostic practices and disease conceptions in Western medicine from the 18th century. While necessarily incomplete, my aim is to demonstrate that materiality matters for the conception of disease and that changes in material settings and diagnostic techniques[3] can constitute a tangible starting point for inquiry into disease classification.

Jewson (2009 [1976]) distinguishes between *bedside medicine*, *hospital medicine* and *laboratory medicine* in his influential overview of major shifts in dominant disease conceptions in Western medicine from 1770 to 1870 (see Armstrong, 1995 and Jacyna, 2004 for thorough discussions and critique of this terminology). Bedside medicine refers to the Galenic tradition of humoral medicine that dominated until the late 18th century. According to this framework, disease resulted from an imbalance in bodily fluids – blood, phlegm, yellow and black bile – caused by a complex interplay of social circumstances, along with the history and behavior of individual patients. In this tradition, no distinction was made between the disease and the patient: the person constituted the pathological unit (Tutton, 2012). Conversation was a key diagnostic technique, as the diagnosis depended equally on the patient's account of their physical and emotional state and the doctor's observations. The primary setting of diagnostic activities was (wealthy) patients' homes (Armstrong, 1995; Jewson, 2009).

Around 1800, a new conception of disease emerged. While in the early 18th century disease was synonymous with the symptoms experienced by patients, symptoms came to be understood as indicators of an 'underlying disease' (Armstrong, 1995). In Jewson's terms, bedside medicine gave way to hospital medicine. This transformation hinged on coinciding shifts in diagnostic techniques and the setting of diagnostic activities. The teaching hospital emerged as an important setting for diagnostic activity that nourished a 'clinical gaze' attuned to anatamo-clinical observation, as Foucault famously argued (2003 [1989]). Having patients physically under the same roof enabled doctors to make comparisons of symptoms and clinical signs of disease across patients. After death, clinical signs of disease could be linked with anatomical changes in organ systems to reach a 'final diagnosis' as autopsies were performed in dissection rooms (Tybjerg, 2022).[4] Furthermore, new technological aids, such as the stethoscope, provided opportunities for indirect observations of bodily changes (e.g. through auscultation) (Jutel, 2011). With these changes in material infrastructure, diseases gradually came to be understood as uniform phenomena that could be observed within and across human bodies rather than imbalances unique to each person.

Advancements in diagnostic techniques have enabled medical researchers to locate pathology at even more granular levels of the human body. From the mid-19th century, diseases came to be understood as phenomena that could be observed and manipulated at the cellular level (Jacyna, 2004). The laboratory supplanted the autopsy table as a central site of diagnostic activity (Cunningham & Williams, 1992; Jewson, 2009). Microscopy gained clinical importance as a diagnostic technique by the end of the 19th century and, in the 20th century, biopsies became a mainstay for diagnosing disease (Tybjerg, 2022). For cancer in particular, histopathology (i.e. the investigation of disease in cells and tissue) became key to disease classification. Understood as histological lesions, pathology was increasingly represented through microscopic slides that were less invasive to obtain and less demanding to store than anatomical collections. By comparing slides of stained tissue with clinical information, histopathologists were able to define new subgroups of disease (Löwy, 2013).

As molecular biology and genetics entered the field of medicine in the mid-20th century, medical researchers have increasingly sought for signs of pathology at the molecular level (Navon, 2019). Since blood samples and biochemical testing became mainstream diagnostic techniques during the 20th century, new diagnostic infrastructures have formed. Samples are increasingly stored in large biobanks, turned into digital code, and compared with clinical data from various databases to identify disease at what is now being understood as its 'root' (Tybjerg, 2022, p. 226). The pathological unit is becoming smaller. Genetic variants and other biomarkers are gaining importance as signs of disease. The 'clinical gaze' is giving way to a 'molecular gaze' (Rose, 2007). 'Precision medicine' is gaining traction, even in fields like psychiatry, where narratives have long constituted a main diagnostic technique (Manchia et al., 2020).

During the past four decades, the development of precision medicine has changed the classification of disease in at least four ways. *First*, the current emphasis on biomarkers has led to the emergence of new disease

categories. Some medical conditions are now delineated solely on the basis of genetic mutations with no corresponding phenotype, i.e. without any obvious clinical referent. This is what Navon (2019) calls *genetic designation*. Genetic designation of disease marks an interesting development in the conception of disease as symptoms and clinical signs are not used to infer underlying pathology. Conversely, an 'underlying' abnormality is used to interpret symptoms and signs.[5] *Second*, existing disease categories are being divided into more fine-grained classes (Green et al., 2022). For instance, breast cancer has been divided into multiple subtypes based on genetic markers since the 1970s (Bourret, 2005). Such stratification does not necessarily mean that existing classifications and diagnostic techniques are made redundant. New diagnostic strata may be added to existing ones resulting in multi-layered classifications and expansion of diagnostic tests, as is the case with some types of cancer (Day et al., 2016). *Third*, disease categories are expanded to include risk groups or classes of 'pre-disease' (Green et al., 2022). Extending ambitions of preventive medical intervention that gained traction from the 1950s (Greene, 2007), heritable forms of e.g. heart disease and pre-diabetes have become actionable targets for early disease prevention (Gjødsbøl et al., 2021). Akin to Armstrong's (1995) notion of *surveillance medicine*, pathology is here understood as an abnormality identified in relation to a 'normal' population and distinguished by its degree of variation. Risk classifications based on statistical analysis are used to infer about future illness. Disease turns into a "point of perpetual becoming" rather than a manifest, corporeal entity (Armstrong, 1995, p. 402) while 'patients-in-waiting' vacillate between health and disease (Timmermans & Buchbinder, 2010). *Fourth*, previously distinct disease categories are being grouped into new shared categories based on shared molecular characteristics (Green et al., 2022). For example, rectal and colon cancers have been grouped together based on genomic and epigenetic similarities (Tomczak et al., 2015). Overall, the advent of precision medicine adds complexity to diagnostic activity and – as I will develop – opens possibilities for negotiation about the criteria used to delineate disease.[6]

The emphasis on materiality does not imply that disease conceptions are *determined* by technological change. Akin to Rosenberg's (1989) suggestion that disease can serve as a multidimensional 'sampling device' in historical studies, mapping changing techniques and settings of diagnostic activities can provide researchers with a concrete starting point for inquiry into wider historical transformations that otherwise may appear abstract or obfuscated. Furthermore, attention to material infrastructures invites reflection on the resources needed to enable new conceptions of disease and treatment options. The current move towards high-tech and high-cost precision medicine relies on vast investments that only some healthcare systems can afford. Identifying rare genomic variations requires massive collections of bodily samples, and storing, packaging, cataloguing, processing and analyzing these samples demands considerable resources (Tybjerg, 2022). The current costs of advanced therapies and the specialist infrastructure needed to implement them also raise pressing questions about patient access (Wadmann & Hauge, 2021; Harris, 2022). Analytical attention to the material aspects of disease classification can therefore foster insights into some of the allocative implications of contemporary changes in medicine. Yet to understand how disease and associated treatment options are delineated, attention is also needed to the interaction of social groups involved in classificatory practices. In the following section, I revisit studies of how researchers, clinicians, pharmaceutical companies, regulators, patients and relatives shape disease conceptions and treatment options.

3. The co-constitution of disease classification and pharmaceutical markets, patient engagement, regulatory practices and clinical work

> Classifications "arise from work and from other kinds of organized activity, including the conflicts over meaning that occur when multiple groups fight over the nature of a classification system and its categories" (Bowker & Star, 1999:285).

Classifications emerge from considerable effort to obtain stabilization; that is to establish standards that guide thought and action. While the creation of standards can make life easier for some, it can make life more difficult for those who do not easily fit within the defined categories (Star, 1990). "Conventions are never stable for non-members", Star (1990) contends. To understand the ordering effects of disease classification, it can be helpful to identify instances when they are contested or otherwise subject to negotiation because opportunities for empirical investigation open up when actors are prompted to explicate their views (Bowker and Star 1990; Tavory & Timmermans, 2014). By studying interactions among social groups, social scientists have generated insights into competing ways of delineating disease, the work it takes to stabilize a given classification, and the implications for various actors. In this section, I illustrate how disease classifications can interact with market formation, patient engagement, regulatory practices and everyday clinical work.

Exploring the co-constitution of disease classification and pharmaceutical markets, studies have shown how existing treatments can be used to define new classes of disease. Kramer (1993) refers to this dynamic as 'diagnostic bracket creep', i.e. shifts in diagnosis to reflect the potentials of new technology. Others describe this dynamic as part of a wider process of 'pharmaceuticalization' (Biehl, 2007; Ferguson, 1981; Williams et al., 2011). In an illustrative example, Fishman (2004) traces the emergence of 'androgen deficiency syndrome in women' by outlining how collaboration between medical researchers and pharmaceutical companies served to assemble a variety of symptoms into a 'marketable diagnosis' that matched the properties of existing drugs, like Viagra (sildenafil). This not only provided new market opportunities for companies, but also promoted certain ideas about 'normal sexuality' for women to grapple with (Fishman, 2004; Jutel, 2010; Moynihan, 2003). Other examples include the changing classification of 'attention deficit disorder' in connection with the marketing of Ritalin (methylphenidate) (Conrad & Potter, 2000; Lakoff, 2000), the emergence of 'premenstrual dysphoric disorder' in conjunction with the rebranding of Prozac (fluoxetine) (Greenslit, 2005), the renaming of social phobia to 'social anxiety disorder' to boost sales of Paxil (paroxetine) (Healy, 2001), and the launch of awareness campaigns about 'restless legs syndrome' and subsequent promotion of Requip (ropinirole), previously approved for Parkinsons disease, as a possible solution (Woloshin & Schwartz, 2006). Yet difficulties of delineating given disorders can also hamper commercial attempts at value-creation because diagnostic standards remain in flux. As Lakoff (2005) demonstrates, biotech companies' ambitions to create market value can be challenged by failed attempts to establish 'diagnostic liquidity', i.e. diagnostic entities that are standardized enough to enable circulation of diagnostic information and support claims of universality. Hence, attention to the interplay of medical knowledge production and marketing activities is important to understand how new disease classes appear and become stabilized (Moynihan et al., 2002; Sismondo, 2009; Wadmann, 2014).

Disease classification also interacts with the identity and engagement of patients (Charmaz, 1983; Jutel & Nettleton, 2011; Whyte, 2009). Some people can experience diagnoses as liberating, as it can help them make sense of their situation – but others can experience this as subjugating or stigmatizing (Wahlberg & Bauer, 2016 [2009]). Identities can alter or even rupture as people experience 'biographical disruption' (Bury, 1982) or engage in 'narrative reconstruction' (Williams, 1984). However, the very act of labelling may also set in motion processes that gradually change the content of the label itself, what Hacking (1995) calls 'the looping effects of human kinds'. Extending Hacking's argument, Navon and Eyal (2016) eloquently show how the category of autism expanded and grew more heterogeneous over time through several 'looping' processes. Parents of autistic children first promoted the idea that autism is a genetic disease in order to combat the stigma associated

with the dominant understanding that autism originated from poor emotional attachment between parents and children. As alliances formed between families, genetic researchers, and research funders, a new understanding emerged: autism was a continuum of impairment that reflected inherited traits. Subsequently, the adjustment of diagnostic criteria (to better capture phenotypic variability) came to change the genetic makeup of the population (as more people were included), which provided new opportunities for seeing similarities with previously unrelated mutations – and thus the content of 'autism' as a diagnostic category changed. Other examples include the attempts of social movements to debunk diagnoses, like hysteria or homosexuality (Rosenberg, 2006); recognize conditions, like Miner's lung or Lyme Disease, as (new) diseases (Aronowitz, 1991; Bloor, 2000); or shape the direction of medical knowledge production (e.g. Callon & Rabeharisoa, 2008; Epstein, 1995; Moreira, 2015) through 'evidence-based activism' (Rabeharisoa et al., 2014). To understand how ideas about disease and treatment come to change, attention should therefore be given to the mutual shaping of disease classifications and patient engagement.

Disease classification can also influence and be influenced by regulatory practices (Abraham & Davis, 2007; Cambrosio et al., 2006, 2017; Davis & Abraham, 2011; Faulkner & Poort, 2017; Rosenberg, 2006). The standard-making processes of regulatory agencies, such as the European Medicines Agency (EMA) and the American Food and Drug Administration (FDA), can consolidate certain perceptions of disease as borders are demarcated between 'symptoms' and 'disease' (Fishman, 2004) and 'medical' and 'lifestyle' problems (Lievevrouw et al., 2021; Lucivero & Prainsack, 2015). For example, the FDA's approval of Lyrica (pregabalin) as a therapy for fibromyalgia recognized this contested condition as a biological entity (a neurochemical aberration) rather than a psychogenic disorder (Barker, 2011). Yet when new 'objects of government' (Lezaun, 2006) are defined, regulatory agencies may themselves get reconfigured. Lievevrouw et al. (2021) show how the FDA's efforts to standardize the regulation of digital health technologies also altered the regulatory role of the FDA itself; emphasis shifted from being a 'safety watchdog' to being an 'innovation enabler'. Furthermore, diagnostic codes not only serve clinical purposes but also form the basis of managerial practices, such as quality assurance, performance management, institutional reimbursement, and legal functions related to liability issues and social service entitlements (Jutel & Nettleton, 2011; Wadmann & Hoeyer, 2018). However, such institutional embedding may not only expand the impact of disease classifications but also loop back on the coding practices of healthcare workers and possibly shape medical knowledge production (Hoeyer *forthcoming*; Wadmann et al., 2013).[7] Hence, to understand the formation and implications of disease classification, the co-production of technological innovation and regulatory practices is of analytical importance (Cambrosio et al., 2006, 2017; Jasanoff, 2005).

Finally, for disease classifications to make a practical difference in clinical settings, they must be embedded in daily work practices and organizational routines, which are also influenced by other considerations (Green et al., 2022; Timmermans & Haas, 2008). Biological parameters and social concerns can interact when decisions about life-prolonging treatment are made and patients vacillate between 'critically ill' and 'dying' (Hauge, 2020; Timmermans, 1999). Navne and Svendsen (2019), for instance, show how vital values and social considerations about family life with a very prematurely born child interact in treatment decisions in neonatal clinics (see also Svendsen, 2022). Furthermore, different ways of knowing disease (Pickstone, 2010) interact in clinical practice and clinicians of various specialties may enact disease in different ways (Mol, 2002). Diagnostic processes can therefore be marked by frictions between different types of expertise and the outcomes of such processes depend on how these ambiguities are dealt with in practice (Gross, 2008).

Taken together, the aforementioned examples illustrate that the delineation of disease and associated treatments does not occur in a social vacuum. Attention to the social interactions that shape disease classifications can generate insights into the political negotiations, competing concerns and practical work it takes to establish and maintain boundaries between normality and pathology, 'lifestyle' and 'medical' conditions, treatment eligibility and ineligibility, active treatment and end-of-life care, etc. In relation to the current development of precision medicine, social interactionist aspects of disease classification invite analysis of how the turn to high-cost, high-tech therapies interact with transformations in the business models of life science companies (Bourgeron & Geiger, 2022), formation of patient identities and communities (Callon & Rabeharisoa, 2008; Navon, 2019), new divisions of labor and expertise (Day et al., 2016), and establishment and change of regulatory standards, for instance related to 'orphan disease', 'real world evidence' and 'innovative medicines' (Burton et al., 2022; Eichler et al., 2021). Furthermore, attention to social interactions can prompt insights into the practical work and negotiations it takes to interpret molecular signs of disease and make them actionable in clinical practice and everyday life. Even if current initiatives to promote precision medicine may create the impression that the scale and speed of genetic testing is key to greater diagnostic precision, "diagnoses do not 'jump out' of the genomic code" (Gjødsbøl et al., 2021, p. 332). Epistemic uncertainties often prevail as genotypic and phenotypic signs of disease do not always map easily onto each other (Timmermans, 2017). Hence, it requires a lot of work for genetic data to become actionable. To understand the actual implications of disease classifications, analytical attention should be paid to the work it takes for clinicians, lab technicians, patients and relatives to deal with ambiguities, reconcile various ways of knowing disease and turn these into practice. Finally, disease classifications can take on new meaning as they travel from research settings and clinical practice into administrative decision-making. In the following section, I develop this point through examining the case of spinal muscular atrophy, illustrating how past debates can shape contemporary negotiations of the delineation of disease and how material infrastructures and social interactions both play a role in this process.

4. The classification and reclassification of spinal muscular atrophy

For a long time depicted as monsters or errors of nature, patients with severe muscular dystrophy were largely excluded from common humanity. Parents were, for instance, advised not to become too attached to their children (Callon & Rabeharisoa, 2008). During the past four decades, however, social perception of people with such conditions has changed radically, and presently, spinal muscular atrophy takes center stage in cutting-edge developments of precision medicine. To understand what enabled this transformation, it is instructive to trace the material infrastructure and social relationships that shaped the classification of spinal muscular atrophy.

The first clinical description of spinal muscular atrophy is usually attributed to a case report published by Guido Werdnig at the department of Pathological Anatomy at the University of Graz in 1891. The report described two brothers who developed a progressive muscle weakness around the age of 10 months and died three and six years old (Werdnig, 1891 cited in Dubowitz, 2009, p. 69). The technique of autopsy enabled Werdnig to connect the symptoms of early onset muscular weakness with observations of degeneration of the anterior horn cells of the spinal cord (Dubowitz, 2009). In the subsequent decade, this link between clinical symptoms and underlying signs of disease was strengthened. Notably Johan Hoffmann, who was to become a prominent figure at the Heidelberg School of Neurology, refined the descriptions of spinal cord changes and used these pathological signs to distinguish the condition – that eventually became known as Werdnig-Hoffmann's disease – from the family of muscular dystrophies (Kuhn, 2001). Throughout the 20th century, a number of clinical case series confirmed this pathological finding and when the technique of electromyography gained traction in neurology in the 1950s, spinal muscular atrophy could be distinguished from muscular dystrophy in a non-invasive manner. However, new questions were raised due to significant variability in patients' clinical

symptoms. In the 1950s, researchers who identified patients with milder symptoms speculated that these probably represented a "genetically independent" condition even if the possibility of a "benign variant of Werdnig-Hoffmann's" disease could not be excluded (Wohlfart et al., 1955 cited in Dubowitz, 2009, p. 72). These milder cases were eventually lumped under the eponymous name of Kugelberg–Welander disease. The naming of various conditions provided a temporary stabilization of spinal muscular atrophy. However, the stage was set for prolonged debate about the delineation of this disease.

While spinal muscular atrophy had been described and named by the 1950s, "there was no cure, no care, no research, no constituted facts, and no causal relationships on which to draw to find solutions" for patients with inherited muscular diseases (Callon & Rabeharisoa, 2008, p. 234). The conditions were prone to stigma, social exclusion, and deep uncertainties. However, patients and relatives also formed relationships around these conditions. They articulated concerns, built organizations, and formulated questions to create interest among medical specialists (Callon & Rabeharisoa, 2008; Jeppesen, 2017b). Importantly, the patient community did not leave research production to medical experts. In particular, the Association Francaise contre les Myopathies took a risky decision in the late 1980s. Placing themselves on a public stage, family members active in the association arranged a broadly televised TV show, the Telethon, with the aim of collecting enough funds to launch large-scale research. Pitting part of the research community against them, they decided to invest profoundly in developing a technology platform for genetic research, the Généthon (Callon & Rabeharisoa, 2008). In 1992, the Généthon produced the first mapping of the human genome and has pioneered research in gene therapy from 1997 (Genethon, 2022). Hence, the community of patients and family members actively shaped knowledge production in ways that came to redefine not only their own conditions but also the professional trajectories of medical researchers (Bucchi & Neresini, 2008; Callon & Rabeharisoa, 2008).

The locating of a particular gene for spinal muscular atrophy in 1990 and the development of a genetic test in 1995 constituted important milestones in the development of the diagnostic category (Dubowitz, 2009). Conditions previously separated by distinct names were now lumped together in a new disease category named after the location of the shared genetic mutation, 5q spinal muscular atrophy. Based on this molecular sign of disease, geneticists also identified cases that were not previously recognized as spinal muscular atrophy (Dubowitz, 2009). Hence, the identification of genotypic similarity led to a broader phenotype. However, this did not put an end to the quandaries of classification. To make sense of the clinical variation, neurologists applied a variety of criteria to subdivide the patient population. Characterizing the situation as a "chaos in classification", the editor of the journal *Neuromuscular Disorders*, Victor Dubowitz, noted: "Against this background of an infinite range of clinical permutations it is not surprising that there has been heated debate on classification and both the lumpers and the splitters have had a field day" (1991:77). In 2007, consensus was reached about a classification of 5q SMA that divided the disease into five subtypes based on phenotypic characteristics (Wang et al., 2007). Even if the degree of severity varies within each subtype, and as many as 25% of patients elude precise classification, the classification has nonetheless been considered useful by neurologists in communication with patients about disease prognosis (Gusset et al., 2021; Kolb & Kissel, 2001).

This stabilization of the disease classification has been challenged yet again as the high hopes of patient and research communities have recently materialized in novel therapies targeting the genetic mechanisms of 5q spinal muscular atrophy. The high pricing of these therapies has fueled debate about the value of these therapeutic innovations (Rabeharisoa & Doganova, 2021) and in some jurisdictions, access has been restricted by payers due to cost concerns (Wadmann & Hauge, 2021). In this process, the disease classification has turned into a contested rationing device and the old debate about how to delineate the condition is revived once more. Some parties emphasize the genetic similarity of patients with spinal muscular atrophy when arguing for broad treatment access, while others highlight the clinical variability when justifying cut-offs that restrict treatment access (Wadmann & Hauge, 2021).

While the history of spinal muscular atrophy is long and complex, it demonstrates the importance of understanding past quandaries of classification because these shape contemporary medical and social debates. Transformations in diagnostic techniques (observation of symptoms, autopsy, electro myography, genetic testing) provided for new ways of identifying pathology and delineating the disease. These transformations were not only a result of technological progress. Social innovation (crowdsourced research funding) also paved the way for medical innovation (gene testing and gene therapy). However, the development of a specific genetic test did not provide a clear-cut answer to how patients with 5q spinal muscular atrophy were to be 'lumped' together or 'split' into subtypes. Taking a historical view reminds us that disease classifications are temporary stabilizations. Diagnostic categories can be challenged by patients who do not 'fit in', transformed through a combination of technological innovation and social agency, and renegotiated as they move to new spheres of practice (Wahlberg & Bauer, 2016 [2009]). Yet classifications are also 'stubborn' in the sense that their embeddedness in routines and material infrastructures tends to make changes gradual and layered, rather than disruptive.

5. Discussion: towards an analytical framework for inquiry into precision medicine

The delineation of disease is not merely an epistemic activity. It relies on practical work, social negotiations, and material infrastructures that can be studied through empirical analysis. Social scientific analyses of disease classification have sometimes been criticized as attempts to debunk scientific truths or claim that disease is merely a social construct, yet this narrow view undermines their affordances (see Hacking, 1995 for a discussion). Rather than assuming that disease is 'given' by nature or resorting to social abstractions, a more nuanced understanding of the emergence, change, and treatment of disease may be obtained by empirical investigation of how biological, technological, and social elements interact at given points of time and in specific locations (Timmermans & Haas, 2008). Why is this important? First, debates about medical innovation have long been polarized between 'triumphalist' and 'muckraker' accounts (Greene & Sismondo, 2015). Some celebrate medical progress without taking into account the social dynamics that shape diagnostic and treatment practices. Others critique medicalization, i.e. attempts to turn social problems into medical ones, without attending to the biological aspects of disease (Timmermans & Haas, 2008). It is important to bridge these accounts to move beyond polarized debate. Second, awareness about the conditions that shape diagnostic classifications can make it possible to question existing conceptions of disease and associated treatment regimes. As Fleck (1979 [1935]) suggested, communities of thinkers (*thought-collectives*) tend to rehearse similar ideas about disease phenomena, rarely questioning assumptions as they develop a shared language and joint methods to acquire knowledge (see Harwood, 1986 for a discussion). Thinking of disease classifications as temporary stabilizations can invite new types of knowledge production and support medical innovation. Third, by creating awareness about the dynamics that contribute to delineating disease in certain ways, researchers can create a foundation for debate about issues that may easily be silenced as 'technical' questions. Social scientific critique of shifting or contested boundary-drawing will not in itself provide a basis for determining if disease classifications are fair or legitimate. However, such inquiry can shed light on the social implications of particular ways of delineating disease and treatment options. The emergence and change of disease classifications have different implications for those involved: new treatment and market opportunities may arise, research agendas may prosper or dwindle, healthcare budgets may come under pressure, patient identities and health prospects may change. Societal debate about these issues is often limited by the inability of most people to understand

the technical aspects of and gain insights into these processes. In the absence of empirically grounded knowledge, conspiracies about 'greed', 'self-interest' or other motives tend to thrive, contributing to further polarization. Researchers can provide for more nuanced debate and inform polices related to research and market regulation by explicating the dynamics that contribute to medical innovation, along with their implications. "The critic is not the one who lifts the rugs from under the feet of the naïve believers, but the one who offers the participants arenas in which to gather", wrote Latour (2004:246).

To inform inquiry into current developments in precision medicine, much can be gained from the rich and ongoing debate in social science about disease classification. Based on a synthesis of existing literature, this essay suggests that contemporary changes in disease conceptions and treatment options continue to be formed by legacies of the past. To guide inquiry into changing conceptions of disease and the possible implications, analytical attention is warranted to both material infrastructures and social interactions. As researchers, we can encounter challenges when seeking to identify the conceptual and material fabric of disease classifications because we tend to be members of the same social practices in which these very systems work (Bowker & Star, 1999). Therefore, we may treat conventional, emic divides as natural (Zerubavel, 1996). Temporal distance can be one useful strategy when seeking to identify otherwise taken for granted assumptions. Another is to shift locations and engage with various groups to avoid 'actors blindness' and explore the implications of particular classifications for different actors (Bowker and Star 2000; Schramm & Beaudevin, 2019).

Where to begin? There are many possible starting points for analysis. Changes in diagnostic techniques and settings can be tracked. 'Spatial zones' may be identified, i.e. physical boundaries that organize activity (Zerubavel, 1996). Changes in market dynamics can be traced (e.g. number and types of patents used to protect medical innovations and wider transformations in business models). 'Boundary cases' that do not fit readily in diagnostic categories may be explored. 'Rites of separation' can be identified, i.e. symbols and practices used to demarcate a difference between phenomena that may otherwise be difficult to separate (Zerubavel, 1996). Furthermore, categories that conflate cultural and biological markers of difference may be questioned and explored (Pollock, 2012), such as the use of sampling strategies in population genomics that operate on assumed correlations among territory, language, culture, and body that link back to racial typologies (Schramm & Beaudevin, 2019). Table 1 summarizes these and other possible starting points for analysis along with research questions that can guide inquiry into current developments in precision medicine.

Disease classification is a ubiquitous part of contemporary developments in precision medicine. This nuanced and historied process has profound implications for patients, relatives, clinicians, researchers, regulators and life science companies. Social scientific analyses that take into account not only the epistemic aspects of disease classification but also the material and social dimensions are vital to understand how new disease conceptions emerge, along with anticipating their possible implications. Further, awareness of the historical conditions of disease classifications equips social scientists to understand diagnostic categories as temporary stabilizations and anticipate future shifts.

Table 1
Analytical framework for inquiry into current developments in precision medicine.

	Analytical dimensions	
	Material infrastructures	Social interactions
Possible starting points for inquiry	Changing of diagnostic techniques	Changing dynamics in markets for diagnostic devices and treatments
	New settings of diagnostic activity and other forms of 'spatial zoning'	Shifts in patient identities and communities and possible 'looping effects'
	Distribution of resources needed to develop and enact new diagnostic categories (e.g. funds, equipment, lab capacity, samples)	Negotiation of boundary cases that elude precise diagnostic classification and 'rites of separation'
	Embedding of diagnostic categories in administrative systems (e.g. billing) and authoritative documents (e.g. manuals, guidelines, contracts)	Categories that combine cultural and biological markers of difference Controversy over delineation of treatment options
Strategies to avoid 'naturalization' of emic categories	Temporal distance	Shift of location and/or social groups
Examples of questions to guide analyses of precision medicine	How do new diagnostic techniques and molecular signs of disease add to existing ones? Which ambiguities arise from multilayered classifications? How are such ambiguities dealt with in clinical and administrative practices? What are the implications for patients who do not readily belong in a given category? What does the development of more fine-grained disease taxonomies mean for conceptions of rareness? Does the notion of 'orphan disease' lose traction as a marker of patient identity and as a regulatory category. Or will new subdivisions of 'rareness' evolve (e.g. 'ultra rare' diseases)? What are the possible consequences for patient communities? For market regulation? How is knowledge about genetic markers of disease shaped by cultural conceptions of human similarities and differences when patients are recruited and samples gathered for genetic databases? How may this affect the possibilities for identifying and treating genetic disease among minority groups? How do economic concerns interact with classifications of disease when novel gene therapies are evaluated and what are the implications for patient access? Which forms of social innovation arise in response to conventional innovation models to enable the development and spread of new treatment options?	

6. Notes

1. The notions of categorization and classification are often used interchangeably. Following Hacking (1995), I use the notion of category to refer to an overarching concept that can be divided into classes.
2. I include work mainly from the sociology of diagnosis, STS, history of medicine and medical anthropology. Anthropological studies have compared indigenous disease cosmologies to western forms of medical knowledge (van der Geest et al., 1996) and used cultural comparisons to challenge western understanding of e.g. placebo effects (Comaroff, 1976). However, this essay focuses mainly on research conducted in the Global North.
3. In English, the notion of technology has a modernist connotation associated with engineering while the French notion of technique tends to be broader defined and encompass also non-technical elements (Bruun & Wahlberg, 2022). Marcel Mauss' influential definition, which I lean on in this essay, emphasizes that techniques are an 'ensemble of movements or actions' that are 'organized' and 'work together towards the achievement of a goal' (Mauss, 2006 [1941/1948], cited in Bruun & Wahlberg, 2022, p. 4).
4. Dissection-based anatomical mapping was also undertaken before the 19th century, but the focus was on general anatomy or individual curiosities rather than pathology. In the 19th century, organs and body parts – displayed as separate entities – came to take center stage in anatomical collections more frequently than whole bodies (Tybjerg, 2022).
5. The opposite situation also occurs: some patients struggle with symptom-based dysfunctions that are clearly experienced as disease – but without any discernible pathological signs (often labelled 'functional disorders').
6. The fine-graining of disease classifications is reflected in the history of the International Classification of Disease (ICD). The earliest

predecessor to this manual, The Bertillon Classification of Causes of Death, listed 161 categories in 1893. The latest version of the manual (ICD-11) includes 55,000 codes; a fourfold increase in the number of codes compared to the previous version (ICD-10) (Moriyama et al., 2011).

7. Disease codes may be influenced by a variety of strategic and practical concerns. For example, strategic coding is a well-known, unintended effect of performance management schemes.

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Ethical statement

The research protocol that forms the basis of this work has been reviewed and approved by the Institutional Review Board of The Danish Center for Social Science Research – VIVE.

Declaration of competing interest

The author declares that she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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