HOW TRADITIONAL DEFINITIONS OF AUTONOMY IMPAIR DECISION-MAKING IN SPINAL MUSCULAR ATROPHY AND ALZHEIMER DISEASE

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ABSTRACT

Clinical decision making is influenced by available literature, technology, and guidelines, but also by cultural expectations, physician experience, and personal biases. The treatment of various forms of disability is especially vulnerable to these prejudices. Alzheimer Dementia (AD) and Spinal Muscular Atrophy (SMA) represent forms of cognitive and physical disability, respectively. In severe forms of both diseases, patients are often unable to communicate and do not meet traditional definitions of autonomy. However, physicians and consensus guidelines adhere to these very same definitions of autonomy, which subsequently disadvantages patients that cannot verbalize. This bias is reflected in available guidelines for catheter-directed thrombectomy for acute ischemic strokes, which passively discourage physicians from treating patients with baseline AD. Inversely, pediatric definitions of autonomy may expose patients to over-treatment with nusinersen, a medication recently approved for the treatment of SMA. Adapting theories of bodily autonomy will allow physicians to approach the treatment of those who cannot verbalize in a more ethical fashion.

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CHAPTER 1: ON THE QUESTION OF THE VALUE OF LIFE

In 1976, economists Richard Zeckhauser and Donald Shepard posed a now-familiar question: "Which lives should be saved? …What is a life worth?" The question at the time was novel: ten years prior, they note, these questions would have seemed horrific:

> Where should we spend whose money to undertake what programs to save which lives with what probability? Ten years ago, merely asking this question explicitly would have seemed unethical or at least repugnant to many, though its central issues, of course, were addressed implicitly in a whole range of individual and collective decisions… The question of how lives should be valued is now an acceptable one for intellectual discourse, though it is true that for some the answer cannot come through academic discovery processes.[1]

This question is now at the forefront regarding the ethical allocation of a variety of scarce resources, including rare medications, expensive and/or invasive treatments and procedures, transplant organs, and more. It is a topic that will never achieve a universally satisfactory resolution, as the question of the value of life rests largely upon an individual's culture, traditions, and priorities. The natural corollary to, "How do you place a value to life?" is, "Are we equally valuing all lives?" And if not, which lives are we neglecting? Is the neglect intentional? What can we do to address these disparities? And if there is no will to ameliorate the injustice, then why do we pretend to be a just society? And, fundamentally: who, precisely, is the one determining the value of these lives?

The 21st century has placed all these questions in the context of modern technologies, but the fundamental anxieties regarding the ethical and fiscal practice of medicine are not new. What is new is the sheer scale upon which we have this

conversation: we discuss deficits and GDP in terms of hundreds of billions of dollars, if not trillions. And with this increase in scale and scope, there is a renewed sense of urgency in revisiting this question of value for human lives. Are we appropriately matching the cost of interventions with the value of human life? Now that we can better assess the efficacy and cost-effectiveness of various interventions, can we best determine which ones make sense for the population? Who is and who is not receiving these interventions?

Historically, medicine as a whole has not had a respectable track record in addressing these questions in a just and equitable manner. Frequently, these bioethical concerns were perceived as ancillary to the very important matter of saving lives or scientific knowledge, but of course the result of that was gross misconduct and human rights violations as exemplified by the Tuskegee Syphilis experiment, among others. The Holmesburg Prison experiments, in which dermatologist Albert Kligman performed unethical experiments on inmates of a Philadelphia prison, similarly typify historical attitudes of nonchalance regarding people's autonomy—in particular the autonomy of people of color. Of course, these failings are only exaggerated when it comes to the practice of delivering care to those with different bodies or with disabilities. Much of medicine is predicated on the belief that disability is an error or failing of medical science and so it must be fixed or corrected. As such, the presence of disability may in certain cases radically change clinical decision making.

Anecdotally, certain disabilities may dissuade physicians from delivering otherwise recommended interventions. Catheter-directed thrombectomy is a procedure in which a neurosurgeon, an interventional radiologist, or an interventional neuroradiologist

uses a long, thin tube to remove a clot from inside a patient's bloodstream. This has been used in the treatment of acute ischemic strokes since at least 2004, when the FDA first approved a device for this purpose.[2] Yet in a patient with baseline dementia, with varying degrees of other illnesses, the physician may defer, citing uncertainty in the prognosis of a patient who is already so cognitively disabled. If she cannot reverse the dementia, then why bother reversing the stroke? On the other end of the spectrum is pediatric neurodegenerative disease, such as Spinal Muscular Atrophy (SMA). This condition also affects the central nervous system, just as dementia does, but SMA results in primarily a physical disability. Interventions for SMA involve introducing medications to the spinal cord in the hopes that the drug will be able to boost the function of certain genes in order to reverse the disease.

These two conditions are rather different on their face—dementia and stroke are insults to the central nervous system that occur most commonly in elderly patients, and the result is primarily a cognitive decline. SMA is a genetic disorder that also affects the central nervous system, but is most commonly diagnosed in children, although it can manifest to lesser degrees in young adults, and is a physical disability. Indeed, the interventions for them both are also different: one occurs inside blood vessels, the other occurs in the spinal cord. Yet the fascinating and troubling component to both is the data behind the efficacy for these interventions. In the treatment of stroke, it has been well established that most, if not all patients, benefit from catheter-directed thrombectomy. In SMA, it remains to be seen whether or not the interventions help toddlers, adolescents, or young adults at all. This raises the question of why different forms of disability can influence clinical decision-making in opposite ways. Are there ways that society values

or prioritizes physical disability differently than cognitive disability? How do we approach the topic of consent for medical procedures in elderly, non-verbal patients and pediatric, non-verbal patients? Is the cost of certain interventions commensurate with the data behind their efficacy? To echo our initial concerns: are we equally valuing all lives? Who is and who is not receiving which interventions?

An analysis of the available interventions and treatments for different kinds of disability provides a remarkable insight into how we value bodies. What is discernible from available literature is that there are different degrees of cost that we, as a society, are willing to risk in order to intervene and "heal" certain bodies. When it comes to patients with dementia, there is a great deal of hesitation regarding treatments for stroke: available guidelines passively discourage treating those with pre-stroke dementia with novel techniques. However, those with SMA are receiving among the most expensive medications ever created with little more than a hope that it will improve their lives. A recurring question is whether these interventions ultimately save money by improving quality of life and increasing independence for patients, but even that question is framed differently in literature on dementia compared to literature on SMA. In the former, authors caution of the risk of producing more people with disability; in the latter, the hope is to save millions down the road. This arithmetic stems from intertwined concerns regarding healthcare economics and the value of human life, but the calculus itself is rife with bias that stems from antiquated definitions of autonomy. It is a circular trap to place a value on personhood when the definition of personhood depends on the value it produces.

I propose that modern conceptions and formulations of autonomy both thwart the ethical treatment of patients with varying degrees of disability, both cognitive and physical, and explain the discrepancy in how we treat both. It is impossible to honestly and ethically answer the question of whose lives deserve which treatments when the very process of defining whose lives are valuable is fraught with bias. Autonomy traditionally involves discussions of capacity and rationality, but this formulation neglects patients with some degree of cognitive disability; however, more "progressive" theories of autonomy over-correct for this and center too much the concept of "bodily autonomy," in which the body itself asserts its autonomy equally to the mind. The result is various theories of autonomy that do a disservice to those living with some forms of cognitive and/or physical disability. There is a solution, however, that balances modern notions of bodily autonomy as well as traditional beliefs of the role of the mind.

CHAPTER 2: THE PRINCE OF ALL MALADIES

The early 2000s represented a radical change in how we approach cerebrovascular disease. Currently, the leading cause of morbidity and mortality for both women and men in the general American population is cardiovascular disease, accounting for nearly 25% of all deaths every year.[3] Close by is cancer, a heterogeneous group of diseases that claims nearly 600,000 lives every single year.[4] But if cancer is the emperor of all maladies, then cerebrovascular disease is surely the prince. Strokes kill 140,000 Americans every year—about 5% of all deaths—and is one of the leading causes of mortality and morbidity in the world.[5] In the US, more than 795,000 people have a stroke every year. Strokes are the leading cause of serious long-term disability; per the CDC, they reduce mobility in more than half of stroke survivors age 65 or older.[6]

The definition of a stroke is rather vague and is typically described as a sudden-onset, focal neurological deficit. This definition makes no mention of reversibility; nor does it include causes of the stroke. Generally speaking, strokes are divided into two categories: hemorrhagic or ischemic. Hemorrhagic strokes occur when a blood vessel in the brain ruptures, spilling blood into the cranium. This can be quickly devastating for the individual, as numerous processes occur simultaneously: portions of the brain are deprived of blood due to the rupture; concurrently, the blood fills the skull and can compress the brain and herniate its contents through different holes in the skull, compromising basic vital functions of the brain; and, the blood itself irritates the brain and cause seizures. Hemorrhagic strokes represent only a little over 10% of all strokes.[7] The remaining 90% or so are ischemic strokes; these occur when something—typically a clot or a ruptured plaque of cholesterol—travels down a blood vessel and occludes it,

preventing blood flow from flowing past it. The brain tissue past the blockage becomes deprived of blood, and with it oxygen and nutrients. Brain matter has a very poor capacity to store nutrients, so within minutes the brain begins to die. Another form of stroke is sometimes colloquially known as a "mini stroke," and is a Transient Ischemic Attack (TIA). This occurs with a clot forms in the blood vessels, causing some form of neurological changes in speech, behavior, mentation, or strength, but the clot is broken down and the symptoms reverse within 24 hours. TIAs are known as heralds for a larger, impending stroke, and must be acted upon immediately before irreversible harm comes to the individual.

When it is clots that cause the ischemic stroke, the treatment has been the intravenous delivery of a medication to break down the clot. If delivered within 4 hours of the onset of symptoms, there is a wealth of data that suggests that patients regain functional capacities similar to how they were before the stroke, although it bears mentioning that this data has come under more scrutiny as of late. Other than the "clot-busting" medications, there are other methods of improving outcomes for patients who have just experienced a stroke: secondary prevention of future strokes include controlling blood pressure, cholesterol, any abnormal heart rhythms, and preventing the formation of future clots. Generally, this is the same rationale behind treating those who are at high risk for heart attacks, because fundamentally, a heart attack and a stroke is the exact same disease, simply in different locations. Untreated, the natural history for strokes is very poor.[8]

In the early 2000s, a development occurred that changed the way modern medicine approaches the problem of ischemic strokes.[9] It involved introducing a long,

narrow tube called a catheter into a patient's arterial system and navigating it up to the brain where the clot was causing the occlusion. Once there, physicians had various options, such as either delivering the clot-busting medication directly, or delivering suction to remove the clot, or even mechanically breaking up the clot. The result is the same: restoration of blood flow to the areas of the brain that were previously starved of it. The advent of this technique was heralded as a new era in the treatment of one of the most common and otherwise intractable diseases that afflict humans. Because this technique occurs entirely within the blood vessels of the body, it is known as endovascular catheter-directed thrombectomy, or simply catheter-directed thrombectomy.

With the development of any new technique or medication, the requisite questions that arise are those that dictate its judicious use. In which patient population is this technique best tolerated? What are indications or contraindications for using this technique? Who stands to benefit the most from this intervention? How soon must it be initiated in order to have a benefit? While these questions are challenging in and of themselves, they become even more complex when considering a population of patients who may lack the ability to consent for these interventions: those with advanced dementia. Current guidelines are sparse when it comes to the matter of deciding how best to approach patient selection for these interventions. Goyal et al. posed a question of who should not receive thrombectomy, hoping to better elucidate which patients should not be treated with endovascular thrombectomy. It is a challenging question, as the authors note:

> In stroke, key prognostic factors are age, stroke severity, comorbid illness, imaging-defined stroke severity…and the location of occlusion; all may act in concert to define prognosis. We recognize, without substantial evidence from

> RCTs [randomized clinical trials], the concept of biological vs. chronological age (conventional accelerators of biological aging are smoking, hypertension, diabetes, sedentary lifestyle, and comorbid conditions [heart disease, previous strokes, cognitive impairment, cancer, chronic renal disease, etc.]). Often these factors are combined into the concept of frailty. Together, the prognosis may be so poor that treatment will be ineffectual, and this defines the futility of treatment.[10]

Said another way, there are no clear guideposts to be found here. It is a frustrating example of so many guidelines in medicine, a mixture of objective criteria and subjective recommendations on how best to interpret them, with very little guidance on how best to approach the biases that all physicians carry with them. It is a startling abdication of responsibility to gloss over the concept of chronological vs. biological age precisely because so many physicians rely on this gestalt to develop their sense of when or when not to intervene. Intriguingly, we begin to see the authors' thoughts regarding the role of pre-stroke disability with respect to deciding to treat with thrombectomy. "The current 'art' of decision-making here means estimating prognosis. Quick questions about independence may not be sufficient as this may be answered affirmatively by family members when the patient requires help with most of the daily activity."[11] The authors suggest that if families were to accurately (or, less charitably, honestly) report that the patient required assistance for most daily activities then that would be reason enough to not intervene, despite an otherwise low complication rate. The implication is that it is futile to intervene on a patient who already has baseline disability. The authors also discuss post-stroke disability, and describe a "bad stroke," in which the physician must make urgent decisions without all possible information, and they suggest that the decision to proceed with thrombectomy may result in good outcomes, but "at that time we have

already invested resources, and it is possible that we have already committed the patient to an extended and undesirable state of disability."[i,12] This concern regarding invested resources and long-term disability is explicitly vocalized in the authors' ultimate discussion of healthcare economics. "It is possible that widespread use of thrombectomy may increase the number of severely disabled patients who will require constant care and result in increased expense not only for the procedure but for subsequent follow-up." The authors follow this with a tepid counterpoint, "Similarly, there will be a dramatic health care savings when patients who would otherwise have been disabled are independent because of thrombectomy." Yet the repeated concerns regarding the negative consequences of disability make it clear that the primary focus is healthcare costs, rather than savings. This conjecture echoes the initial concerns of the economists Zeckhauser and Shepard regarding how best to place a price on life, but the emphasis on economics and arithmetic can distract from what we truly discussing: human beings. It is clear from multiple references to both pre- and post-stroke disability that the problem is disability itself, rather than its temporal relationship to the cerebrovascular insult. Said another way, these authors are asking, "Is a life disabled a life worth living?" without reflecting on if—much less why—that question is dehumanizing to the patients for whom they are trying to care.

The authors only briefly mention what they consider disability or comorbidities that would dissuade from intervening on acute strokes. They cite "cognitive impairment" as one such example without expanding on how they define it, despite the fact that this

[i] Of note, the authors describe a "bad stroke," not a "patient with a bad stroke," an example of how often and easily physicians and medical literature center the pathology rather than the patient.

umbrella-term encapsulates so many of their patients who are older in age or who have had prior strokes. Within this group would be patients who have dementia, which adds a troubling layer of complexity because the presence of this "cognitive impairment" would subsequently become among the most important factor to consider when assessing prognosis and reasons for intervention. At the risk of preaching to the choir, this is precisely where the field of bioethics can accomplish its most necessary and important work: in clinical scenarios that—despite or even because of the inclusion of objective measurements, images, and data—does not lend itself to easy decision-making. As we will see, the discussion of cognitive impairment, dementia, and other forms of disability is not simply an academic conversation, but one with very real clinical consequence, as the most commonly used scales to assess the severity of strokes is based on the severity of perceived disability.

How we talk about disability is how we talk about stroke, and we talk about disability in dizzying layers, like clinical Matryoshka dolls—prior definitions of disability reside within newer categorizations of disability, which reside in newer definitions still. The modified Rankin scale (mRS) is currently the most commonly used metric to assess the severity of stroke; as Hong et al. describe, the mRS "assigns stroke survivors among 7 levels, including the extremes of normal and dead and 5 intermediate degrees of disability." [13] At 0, the patient is asymptomatic; a 1 involves having no significant disability despite symptoms; a 3 involves requiring help, but the patient retains the ability to walk; a 5 denotes severe disability, including incontinence and requiring nursing care. The scale ends at 6, in which the patient is dead. It is a remarkably bland admission that disability is considered to be on the same spectrum of death, the

implication being that one who is disabled is less alive than those who are not. The authors do not scrutinize this scale, and instead move on to describing their method of using disability weights (DWs) in order to confirm the validity of the mRS by comparing it to the World Health Organization's previously established disability classes (DC). DWs are numerical scores assigned to different levels of disability, as judged by a group of neurologists and emergency physicians. A value of zero describes "normal health without disability" and a value of 1.0 indicates "dead or as bad as being dead," raising the question of what precisely is "as bad" as being dead.[14] These physicians were asked to assign values based off the prompt of assuming they were allocating health system resources and "had to decide what number would make them indifferent between the choices of extending the lives of 1000 healthy persons for 1 year versus extending the lives of N persons with the mRS health state for 1 year."[15] It is yet again, another banal admission that the lives of 1000 abled individuals are equivalent to larger numbers of disabled folks. The physicians used the WHO classification of 7 disability classes as a rubric to design their own disability weights. The WHO classes use a patient trade-off (PTO) method to rank how useful people are with different degrees of disability: they rank erectile dysfunction equal to angina (chest pain indicative of heart disease); blindness was equivalent to paraplegia (paralysis of the legs); a radius fracture in a stiff cast, which this author has sustained, was equivalent to infertility.[16]Said another way: this group of physicians designed Disability Weights to test the validity of Disability Classes as compared to the modified Rankin Scale. It is no wonder that at each step of the way, they echoed what prior groups had said.

What does it mean that we approach these patients as if they are already partly dead? The Rankin scale codifies "ability" into our definition of normal and suggests that the only people worth saving are those who were previously abled and who have the potential to be returned to that productive state. It is the notion of reversibility that is key for using the mRS to guide treatments of stroke: those who have an entirely reversible disability who can be restored to near "normal" functionality should be treated, but those who have baseline disability, to whom an intervention would "only" restore to their prior limited abilities, may not merit such intervention. Sacks et al. touch upon this tension in their consensus guidelines for endovascular interventions for ischemic strokes. In 2018, various societies, including the American Association of Neurological Surgeons, American Society of Neuroradiology, and others, wrote:

> It is important to note that, although achieving an mRS score of 0–2 is an important goal, it is not the only marker of a favorable outcome after endovascular therapy. Some patients may have important clinical benefit with an mRS score shift from 4/5 down to 3…This suggested threshold should not dissuade centers from treating individual patients if they believe there is a potential benefit from the procedure. Given the multiple factors that influence outcomes, centers are encouraged to benchmark their outcomes against those from a similar patient population.[17]

A frustrating aspect to this consensus guideline is that lack of clear definition on what constitutes a "good clinical outcome." Nor do the guidelines describe other examples of clinical benefit. Given the heterogeneity of available resources at hospitals as well as the patient populations themselves, these guidelines ultimately encourage the hospitals to come to their own definitions of success. Yet another aggravating aspect to this messaging is its superficiality. The guidelines here have an opportunity to strongly

encourage physicians to consider the benefit of any reduction in mRS, but the authors come up short by only suggesting that "some" patients may have clinical benefit in any reduction of mRS score. The reason that this inconsistent messaging is so important is because a significant portion of patients who have strokes also have baseline dementia, and the mRS does not make any consideration for these patients.

Very simply, dementia describes pathological aging. As humans age, there are a variety of expected changes that are considered normal. For example, we accumulate more pigmented fats in our skin and organs, which can give those characteristic "liver spots" on the skin. We develop cataracts in our eyes. We have a degree of cognitive slowing, in which case higher executive functions may take longer than before, for example filing taxes or organizing bills. However, this aging process is considered unhealthy and pathological when it results in decreased independence for the patient and their family. For example, a hallmark of dementia is becoming lost in one's own neighborhood—this is frequently what brings a patient into the office of their primary care doctor. One common misconception regarding dementia is that it is a typical end-process when someone becomes old enough—that dementia is simply part of growing old. This is not the case. As the disease progresses, patients will lose the ability to care for themselves, including performing Activities of Daily Living (ADLs), such as rising from bed, transferring from bed to standing or to chairs, showering, toileting, and feeding themselves. Eventually, patients will become incontinent, and may require assistance in eating. Complications can arise from lack of mobility, lack of nutrition, and aspiration of food into the lungs due to abnormal mouth and throat function as they forget how to coordinate a swallow. All the while, the patients may experience difficulty in accessing

long-term and short-term memories; their personalities may change. It can be a devastating process to witness, as a loved one slowly loses their independence, their memories, and their personality. There are a variety of causes of dementia, but the most common cause is Alzheimer's disease. The precise cause of Alzheimer dementia is not entirely known, although it has been well-established that an abnormal protein appears in large quantities in the brain. These proteins, known as amyloid beta and tau, result in the death of neurons and the gradual pruning of neuronal connection in the brain. The result is globally depressed brain function, resulting in functional impairment, and the other processes as described above.

The presence of baseline dementia in patients with stroke has serious consequences for how physicians decide when to intervene with catheter-directed thrombectomy. Busl et al. found in an analysis of patients with and without dementia had very different courses following their strokes: those with baseline pre-stroke dementia had over 3-times the risk of death than those without; furthermore, dementia was an independent predictor of less likely favorable discharge from the hospital.[18] Yet available evidence is that endovascular therapy appears to benefit most patients.[ii,19] Venema et al. decided, in their paper regarding the selection of patients for endovascular treatment of strokes, that "treatment should not be withheld based on one characteristic. Some patients belonging to one of the subgroups that are considered as having no benefit of intra-arterial treatment…may still benefit from intra-arterial treatment substantially if other characteristics are [favorable]."[20] It is easy to see the challenge that confronts

[ii] Busl et al. found CDT increased risk of mortality in their cohort, although this significance was lost in multivariate analysis.

patients when deciding whom to treat. But if physicians continue to rely on the modified Rankin Scale, then they will assuredly undertreat those who may otherwise benefit from this treatment. The result of all this is that the most commonly utilized tool for assessing the severity for one of the most common illnesses in the United States has a serious methodology flaw that complicates and may worsen the care for those with dementia.

Several confounders may partly explain physicians' reticence to treat those with pre-stroke dementia, including a bias against the elderly as well as assumptions regarding comorbidities in the elderly. Ageism refers to a prejudice against people on the basis of their age, and is frequently wielded against the elderly. Common assumptions are that of cognitive slowing, less productivity as compared to younger individuals, and assumptions of generational differences. It is nearly impossible to separate dementia from age: only select populations are susceptible to early-onset dementia, such as those with Down Syndrome; otherwise, only 3% of patients with dementia are under the age of 75.[21] This is certainly a concerning possibility, as the largest payer for medical services in the United States is Medicare, suggesting that physicians would have a bias against the vast majority of their patients. Another possible confounder is a perceived relationship between dementia with physical disability. As dementia progresses, patients become increasingly confined to bed, require help toileting and feeding, and may develop pressure ulcers on the back of their heads and their lower backs. The same analysis of Busl et al. that found worse outcomes for patients with dementia also found that comorbidities and physical disability were not significantly different between those with dementia and those without. Said another way, for mild-to-moderate dementia, physical illness or disability is no different than age-matched individuals without dementia, and as

such should not demand any particular consideration in the physician's decision-making process.

It is true that clinicians require a means to evaluate and define every disease and disability as well as a means of determining which patients would experience a benefit from which intervention. A neurologist may rightly ask, "So what if we use disability as a reason to intervene? Is that not what we are supposed to do as physicians?" The primary problem with this mentality is that it defines disability itself as pathology, as opposed to a state associated with pathology. In re-framing how we look at disability, we can be more precise in our language: we are treating the new symptoms that are limiting the quality of life of the patient, as opposed to targeting disability itself. This is not simply a superficial change in labeling. This permits disability to be part of the life and identity of a patient, as opposed to the traditional, reductive view of disability as an abnormal, negative quality that limits the patient. Furthermore, it would actively invite the consideration of the patient's baseline independence and disability rather than centering the absence of disability as "normal." This, in turn, would not permit physicians to project their own notions of what they perceive as appropriate or desirable degrees of mobility and independence as they consider whether or not to intervene. Anecdotally, it is all too common for physicians to evaluate patients and ask themselves, while tutting, "What kind of life is this? What quality of life am I returning this patient to?" Physicians are not the arbiters of what is or is not a desirable life—the patient is, and absent the consent of the patient then it falls to their family. If family is not present, then it should not fall to the prejudices of the physician: they must balance the available data, assess the risk of harm, and decide that restoring any degree to independence may be beneficial in a

disease process whose natural course is otherwise so atrocious. It may behoove the medical community to develop a new means to evaluate the severity of stroke by making the values relative to the patient's baseline, such that a "-1" score may mean something different for this author than for a patient with dementia. This would remind the clinician that the goal is to restore functionality and independence to a patient according to their prior state, as opposed to what "normal" is. One limitation of this approach is in the case of the unknown patient who presents with neurological deficits consistent with acute ischemic stroke but without family to describe their baseline function. In this situation, the mRS still has its use, and can help evaluate the patient and their response to therapy. The scenario of the undifferentiated patient brings us back to the conclusion that Goyal et al. reached:

> In summary, given the broad efficacy and safety of thrombectomy, one has to carefully think about which patients with proximal occlusion should not be offered treatment. Further work is required to better understand how various prognostic factors (age, time from onset, imaging parameters) act collectively to predict outcomes. However, these tools will be imperfect as many factors (speed and quality of reperfusion) after decision-making substantively affect patient outcome… In the meantime, given the poor natural history of disease in patients with proximal occlusion, proven efficacy and low complication rate of thrombectomy, it is probably better to err toward treatment rather than no treatment. (Goyal et al.)[22]

These recommendations reiterate the importance of re-framing how we talk about disability. Traditional interpretations of disability center the pathology, portray disability as simply a progression along the path to death, and neglect the patient at the heart of the matter; in the setting of acute ischemic stroke, this may unintentionally preclude patients from receiving treatments that may benefit them. The presence of cognitive disability

further exacerbates these problems. The challenge of Alzheimer dementia is that, historically, it is exceedingly easy to disregard the patient because conventional definitions of personhood rely exclusively on verbalization, patient-expressed desires, and rationality, which are all concepts held under the umbrella of "autonomy." While it is critically important to update and re-frame how guidelines and physicians discuss and describe disability, there is added required work of updating how medical professionals think about autonomy. Until physicians and other healthcare providers embrace a new definition of autonomy, patients with dementia will continue to experience different levels of care in many more domains than simply ischemic stroke.

These discussions of dementia, age, and stroke are at odds with a different disease process in a different patient population: Spinal Muscular Atrophy (SMA) primarily affects young children, sometimes shortly after birth. Historically, treatment involved physical therapy, the insertion of breathing tubes, and support as needed. However, the advent of a new medication revolutionized the treatment of SMA in a fashion very similar to how endovascular treatments changed our approach to ischemic strokes. Yet, physicians may hesitate to treat elderly patients with dementia who subsequently suffer a stroke, treatment is nearly always recommended for young patients with SMA despite less data being available for this medication. Evaluating the extent of our enthusiasm for treating SMA reveals a significant amount regarding our attitudes toward a different kind of disability: one that predominately affects the body and spares the mind.

CHAPTER 3: TREATING THE PHYSICIAN OR TREATING THE PATIENT

Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disease, characterized by the loss of motor neurons and subsequent degeneration of skeletal muscles. It is the most common genetic cause of infantile mortality, with an incidence of 1 in 11,000 live births.[23] It is caused by a genetic mutation of the *SMN1* gene, appropriately named Survival of Motor Neuron 1 (*SMN1*) due to its central role in the survival of motor neurons in the anterior horns of the spinal cord. Most humans have two functioning versions of this gene, named *SMN1* and *SMN2*. The two genes are nearly identical, although the functionality of *SMN2* is significantly reduced in all humans: over 90% of the translated protein from *SMN2* is shortened and nonfunctional due to aberrant splicing.[24] In people with a mutated *SMN1* gene—such as those with SMA—they must rely entirely on the contributions of the relatively diminutive *SMN2* gene. The result can be catastrophic, depending on how many copies of *SMN2* the individual has to compensate for the dysfunctional *SMN1*: more copies of *SMN2* result in a less severe manifestation of disease, as quantity substitutes quality in this case.

The literature currently describes five variants of SMA, with Type 0 (sometimes considered a subset of Type 1) being the most severe: it presents in newborns, often within six months, who perish within the first weeks or months of life due to respiratory failure, regardless of respiratory support. It manifests with weakness and hypotonia: the so-called "floppy baby syndrome," characterized by neonates who struggle to raise their head or hold their limbs against gravity. Early studies found 68% of patients with SMA Type 1 do not live to their 2nd birthday, although modern interventions have reduced this number to "only" 30%.[25] Those with Type 4 have "adult-onset" SMA, and have life

expectancies no different than any other healthy individual in the general population. As the mutated gene only codes for proteins important in the survival of motor neurons, unrelated organs and processes are spared: "Although patients are ultimately profoundly disabled, intellectual development and function are not affected."[26]

On December 23rd, 2016, the U.S. Food and Drug Administration approved Spinraza® (Nusinersen) for the treatment of SMA in adults and children. It was hailed as a victory by community activists, such as Cure SMA. "We are thrilled to see our community's efforts culminate in the approval of nusinersen: not only the first-ever approved treatment for this disease, but also one that addresses the underlying genetic cause of SMA," the group wrote in a press-release soon after the FDA announced its approval of the drug. "This has been a story of all groups—families, researchers, companies, and the FDA—working together as one community to reach this amazing milestone."[27] Biogen, both the manufacturer of nusinersen as well as the sponsor of its clinical trials, received fast-track designation as well as priority review for nusinersen, "leading to a rapid transition from research study to approved medication."[28] Nusinersen is administered directly into the thecal sac, a membrane that surrounds the spinal cord and which contains the cerebrospinal fluid. In that way, it is much like a lumbar puncture or "spinal tap," only instead of removing a small volume of liquid, a small amount is injected in. Once administered, nusinersen modifies the alternate splicing of *SMN2*, allowing for the production of the full-length SMN protein that was otherwise impossible without a functioning *SMN1*.

Since its advent, nusinersen has raised hopes for patients and their families as much as it has raised eyebrows of those watching its development, approval, and sale.

The reasons for this scrutiny are plentiful: first, there are questions regarding its remarkable price. At $125,000 per injection, nusinersen is among the most expensive medications in the world. Second, there is a paucity of data behind its supposed efficacy: the FDA approved it primarily based on one clinical trial and subsequently extrapolated from the results and generalized its approval for both adult and pediatric patients. Third, there remain questions regarding the role of informed consent and autonomy in a patient population (namely, infants) that can neither be informed nor consent, and their caretakers that quite literally have only one option for pharmacological intervention.

While these are compelling bioethical issues in their own rights, nusinersen is also illuminating and troubling for what it reveals about our cultural thoughts and questions regarding physical disability in vulnerable bodies. Are we holding ourselves to the same standard of questioning the quality of life for these patients as we do in discussions of other diseases? How does our interpretation of non-verbal consent in pediatrics cases inform our discussion of non-verbal consent in other cases? What does it mean about our priorities as a society that we are willing to spend so much money with such tenuous data in order to treat this a rare disease—is this a reflection of capitalism finding a way to generate profit from orphan diseases; or, a symbol of our compassion and ingenuity and capacity to help those in need? Are we behaving differently with this form of disability than other forms of disability?

The first and most shocking aspect of nusinersen is its price: at $125,000 per injection, it is among the most expensive medications in the world. Patients are expected to receive six injections in their first year of treatment ($750,000) as an initial treatment, with three injections per year for the rest of their lives thereafter ($375,000) for

maintenance, not including administrative costs. This amounts to $1.5 million in the first three years alone. While these prices are stunning, this is the United States of America, where overpriced life-saving medications are as American as the insulin one takes before eating apple pie. Nusinersen finds itself in good company, as cerliponase alfa costs $702,000 per year; and, eteplirsen, for Duchenne Muscular Dystrophy, is a paltry $300,000 per year for a patient of 25 kg.[29] The list of expensive medications continues, with dozens of drugs approved for cancer treatments in the past decade, each nearly $100,000 per year.[30] Expensive medications are not the exception in the US—they are very much the norm, and they should elicit several bioethical considerations, chief among them: is this an appropriate use of healthcare dollars? Who is bearing the brunt of these cost: families, or other payers? And, in so many words: is it worth it?

An immediate question is just how "appropriate" this price is for nusinersen, and a useful way to evaluate the cost-effectiveness of a medication is to look at the incremental cost-effectiveness ratio (ICER). The ICER compares the price of a medication regimen as compared to its incremental cost: that is, "the price of the new therapy minus the present cost of treatment."[31] It is an especially useful metric when looking at chronic, high-intensity illnesses such as SMA when there are multiple costly interventions required to maintain any degree of quality of life: procedures and equipment such as tracheostomies, gastrostomy tubes, inpatient hospitalizations for exacerbations, outpatient nursing, physical therapy, and more, as well as the maintenance of this equipment. The reaction to the price of the medication shifts from, "Why is it so expensive to order and administer this medication?" to "How expensive is it to live with SMA without this medication?" Lee et al. conducted a retrospective cohort analysis of

inpatient admissions of children diagnosed with severe SMA. 229 children met criteria for analysis, and the group found the average inpatient (not outpatient) cost was $104,197 per child per year over an eight-year span. Only 32% of patients had tracheostomies, which are tubes inserted into the throat in order to facilitate breathing, but they represented 60% of admissions and 63% of total costs. When looking at mean 3-year cumulative costs for those with tracheostomies, the cost increased significantly: up to $250,000 as compared to $111,000 in those without. Another group, Armstrong et al., looked at a similar cohort of 239 children within the Department of Defense (DOD) Military Healthcare System (MHS) and compared the economic costs incurred through treatment and specialist consultations, as compared to a randomized group of children without a diagnosis of SMA. As opposed to Lee et al., the Armstrong study assessed both inpatient and outpatient costs. Children with SMA had a median of 197 days of non-urgent outpatient visits as compared to 21 days in the comparison group. 85% of children with SMA had a visit with pulmonologists and/or neurologists, compared to 7% in the control group. Inpatient costs accounted for only 27% of the total health care costs in children with SMA.[32] Said another way: inpatient admissions are expensive, but they are only a quarter as expensive as the daily outpatient expenses incurred in the management of a chronic illness. Lee et al. took this analysis and applied it to their own work with children with tracheostomies, and estimated that the true total costs for children with SMA were likely four times the inpatient spending—that is, over $950,000 in children with tracheostomies and $410,000 in those without over three years.[33] Interestingly, Lee et al. frames the $1.5 million three-year cost of nusinersen as a bargain: “If, as early clinical trials suggest, nusinersen is able to improve the clinical course of children with

SMA, it may be able to substantially reduce these expenses. If so, its incremental price—the relevant economic consideration—may be considerably below its listed price of $1.5 million over three years, particularly when families select a course of tracheostomy and technology dependence."[34] The crux of this argument rests on the optimistic hope that nusinersen will so substantially and significantly improve the clinical course of patients that a large investment up front and early in the course of a patient's life will dramatically reduce the need for a lifetime of specialist consultations and interventions down the road. The tone of this analysis is remarkably different from that used by Goyal et al. in their analysis of patients who undergo catheter-directed thrombectomy as discussed previously. Then, the authors cautioned of the possibility of producing thousands of people with lifelong disability—here, there is no such trepidation, but a sanguine outlook on the possibility of this exceedingly expensive medication saving some dollars down the road. As of now, there is little data currently available to support this optimism only because so little time has passed since nusinersen's approval. Thus, it is difficult to say whether the price of nusinersen per se represents a challenge to the bioethical principle regarding the allocation of scarce resources because it is impossible to assess the long term impact of a new medication when it has only been in use for two years. Indeed, it may very well be that nusinersen, despite its staggeringly high price, may be the more economic and just option than pursuing supportive care. Then again, we may also realize that nusinersen does not provide the benefit we hoped, that it is exorbitantly priced, and that it perfectly encapsulates the adage from Dr. Ian Malcolm: "Your scientists were so preoccupied with whether or not they could, they didn't stop to think if they should." However, what is known is that families must confront the reality of its costs here and

now, which means participating in the complex web that is insurance companies, human resources, and the modern American approach to the delivery of healthcare. Thus, the price of nusinersen is in and of itself a bioethical quandary largely because it is a logistical quandary: by definition, erecting administrative obstacles between patients and their care will create disparities in care between those who have the resources to navigate that complex system and those who do not.

So, how do patients approach the task of paying for nusinersen? A pamphlet entitled "Navigating Insurance and Support Programs for Spinraza® (nusinersen)" explains the intricacies of acquiring a Family Access Manager (FAM) who will help with logistics of treatment; in addition, a Lead Case Manager (LCM) will help with financial assistance. The detailed explanations contained therein about prior authorization, what to do if an insurer denies the request, and definitions of deductibles are simultaneously admirable and unimpressive: important and critical to inform patients, but absolutely disheartening to see how difficult it is to acquire appropriate medical care. At one point, the pamphlet helpfully suggests, "If you are insured through an employer, ask your employer's human resources department to advocate on your behalf. Your employer may have contacts at the insurance company." It is difficult to imagine an employer so willing to vouch for their employees, but perhaps the makers of Spinraza® know something that others do not. Given the history of expensive medications in the US, there are plenty of examples of the hardships that confront families when they embark on this journey: in 2013, a panel of over 100 experts in Chronic Myeloid Leukemia (CML) signed an editorial lambasting the high prices of tyrosine kinase inhibitors for CML—drugs that "only" cost up to $138,000 annually for treatment:

> In Europe and many developed countries, universal health coverage shields patients from the direct economic anxieties of illness. Not so in the United States where patients may pay an average of 20% of drug prices out of pocket…and where medical illnesses and drug prices are the single most frequent cause of personal bankruptcy. High drug prices may be the single most common reason for poor compliance and drug discontinuation, and the reason behind different treatment recommendations in different countries. (Experts in Chronic Myeloid Leukemia)[35]

The reasoning behind such high prices is opaque at best. The authors observe a wide spectrum of pricing for the same drugs depending on the country, reflecting the fact that "drug prices reflect geopolitical and socioeconomic dynamics unrelated to the cost of drug development."[36] This fact is inconsistent with the assertion that the high prices of medications reflect the high cost of bringing a successful drug to market, often cited at $1 billion. As another example, the authors discuss imatinib. Imatinib, marketed under the name Gleevec®, was originally developed as a "goodwill gesture," in that very few people expected the drug to be efficacious, much less lucrative. Daniel Vasella, Chairman and CEO of Novartis, discussed in a book the struggle of balancing the moral imperative of making an affordable medication for patients and their doctors, and the need for healthy profit margins for investors; ultimately, imatinib was priced at $30,000 per year in the United States, a price described as "high but fair" as it would allow developers to recoup their investment within two years.[37] However, when it was found to be wildly efficacious, increasing the estimated 10-year survival from under 20% to over 80%, the price was changed: from $30,000 in the US in 2001, to $92,000 per year in 2012, and up to $146,000 just before its patent expired, without clear reasoning behind this increase.[38,39] Shortly after its patent expired in February of 2016, imatinib was available

in the US a generic, but at $140,000, just barely cheaper than the brand formulation. Interestingly, the price in Canada was only $8,800 for the generic, and $38,000 per year for the brand.[40] Thus, not only are families embarking on an arduous journey of attempting to secure financial security in paying for this medication, they are doing so for what appears to be an arbitrarily high price. For this reason, nusinersen represents a large bioethical challenge which contributes to the larger conversation of why drug prices are so high in the United States. In the US, the prices often reflect a cultural and often misplaced expectation that the free market economy will control drug prices and that, truly, how can one place a monetary value on human life? Europe seems to have no such moral qualms, as the UK's National Institute for Health and Clinical Excellence (NICE) has decided that a year of human life is worth approximately $50,000.[41] The World Health Organization suggests that interventions that avoid one disability-adjusted life-year (DALY) and which cost less than three times a nation's per capita Gross Domestic Product (GDP) are cost effective: in the United States, this calculation places the average American's life-year at $178,594.[42,iii] By these metrics, nusinersen must surely be an efficacious drug if it costs so much—it must offer decades of DALY that would otherwise be denied patients; after all, the US "tolerated" a wildly expensive medication such as Gleevec® (imatinib) precisely because it worked so well. But this question is what prompts the necessary conversation regarding the data behind the advent of nusinersen.

[iii] With GDP derived from the World Bank, which estimates the 2017 US per capita GDP at $59,531.66. The calculation offered by the WHO is intriguing, in that it almost entirely ignores centuries of imperialism and colonialism, as if the conditions and economies in nations in Central America, the Caribbean, Africa, or Southeast Asia (to name a few) simply developed in a vacuum—or as if the success of developed nations such as the United States deserves no further scrutiny or context.

One of the most concerning aspects of nusinersen's approval revolves around the amount of data behind it as well as the speed with which it was approved. Per the FDA, the approval of nusinersen for the treatment of SMA for both adults and children begins and ends "primarily on one controlled trial of 121 infants with SMA."[43] The study was published in the New England Journal of Medicine in a 2017 publication of the journal, and was entitled, "Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy."[44] Patients ranged in age, from 1-3 month of age (7%), 3-6 months old (47%), and 6 months to about 9 months (46%). It was double-blinded, such that neither the prescribing physicians nor the parents knew whether the patient which intervention the patient was receiving.[iv] Researchers assessed whether or not there was a benefit by evaluating the improvement of motor milestones, such as "head control, sitting, ability to kick in a supine [lying down] position, rolling, crawling, standing, and walking."[45] This is important, as one of the principal ways parents and physicians develop a suspicion of the disease is by noting a loss of milestones during development. Furthermore, it was a 13-month, "international, randomized, multicenter, sham-controlled, phase 3 trial that assessed the clinical efficacy and safety of nusinersen in infants who had received a genetic diagnosis of spinal muscular atrophy, had two copies of *SMN2* (which is subject to copy-number variation), and had had onset of symptoms at 6 months of age or younger."[46] Of the cohort studied, 81 of the original 121 patients were in the study long enough to be included in the assessment of the drug's effects. The study was designed

[iv] Of note, the study was sponsored by Biogen and Ionis Pharmaceuticals, the developers of the drug; they also designed the trial in collaboration with the lead investigators. The authors write, "The first draft of the manuscript was written by the first author and the senior industry author (penultimate author); medical-writing assistance was paid for by Biogen. The sponsors reviewed the manuscript and provided feedback to the authors, who had full editorial control." That said, there is no reason to believe there is any degree of impropriety in the design of this study.

such that one group was randomly assigned to receive nusinersen via intrathecal administration (into the sac that contains the spinal cord) or undergo a sham procedure with only a skin prick (i.e., placebo). The study had two primary efficacy end points: the first was motor milestone response, and the second was event-free survival defined by time to death or the use of permanent assisted ventilation (i.e., tracheostomy or ventilator support). Researchers evaluated the first end point by using the Hammersmith Infant Neurological Examination (HINE), a quantifiable method of assessing overall neurological function in infants; the second, by parental diaries and hospital records. The HINE includes eight motor-milestone categories: voluntary grasp, kicking, head control, rolling, sitting, crawling, standing, and walking. Patients were screened for a baseline score in these categories, and again were assessed at days 183, 302, and 394. Patients were considered to have a response if they two criteria: 1) improvement in at least one category; and, 2) more categories with improvement than categories with worsening. The results were certainly remarkable for the cohort that received nusinersen. Interim analysis revealed 41 patients in the nusinersen group achieved a motor-milestone response while zero patients in the control group did ($p<0.001$). This held true in the final analysis, which included 51 patients in the nusinersen group. Fewer infants in the nusinersen group died by the end of the trial than in the control group: 16% vs. 29%; and, the risk of death in the nusinersen group was 63% lower than the control (HR = 0.37, 95% CI, 0.18 to 0.77, $p = 0.004$).[47] Remarkably, adverse events were similar between the two groups, although the nusinersen cohort actually experienced fewer severe and serious adverse events.[v] The study was appropriately ended early, and one assumes the control group was

[v] Serious adverse events were defined as events that cause severe discomfort, incapacitation, or substantial

subsequently given access to nusinersen although the authors never specifically address that in the text. However, the authors rightfully note: "Several of the infants who received nusinersen died, none achieved normal motor development, and some needed continued feeding and ventilatory support; these findings indicate that nusinersen is not a cure in symptomatic patients." More research is needed, as it is still a very early stage for this medication.

To be clear: there is no doubting the remarkable effect this medication had on the nusinersen test group. However, the data truly is only applicable to that specific cohort; the FDA subsequently approved nusinersen for use in pediatrics (ages 0-18 years) and adult patients (18 years and older). The physiology of a growing and neuroplastic infant is monumentally different from an adult patient. A recent study at Temple University Hospital looked at the intrathecal administration of nusinersen in 17 adult patients with ages ranging from 19 to 64; this in and of itself is a remarkable range of ages for a chronic illness and makes conclusions exceedingly difficult to draw, and the primary end point was "only" respiratory, a relatively easy system to quantify when compared to neurological development and motor milestone achievement.[48] These patients were at different stages of physical therapy, respiratory therapy, and stage of disease—it is difficult to overstate just how irresponsible it would be to extrapolate one patient's response to another if the two patients are at entirely different ages and stages of disease. So the notion of approving nusinersen for use in populations not yet studied is itself a

effect on daily life, although one wonders how to go about asking a 6-month old infant how uncomfortable they feel. Serious adverse events were defined as any "untoward medical occurrence that resulted in death or a risk of death, hospitalization or prolonged hospitalization, persistent or substantial disability or incapacity, or a congenital anomaly or birth defect," raising the question of how a medication administered after birth can cause a birth defect.

remarkable turn of events. It is unclear what the long term effects of this medication is in children and young adults; it is unclear if the patients suffered from any side effects that are typically verbalized by patients (e.g., back pain or headache following lumbar puncture); and, it is unclear what the efficacy is in patients who are already neurologically developed (i.e., adults). Is it safe to continue administration of this medication during unrelated infections? What is the incidence of allergic reactions? Indeed, there is much about the proper administration and patient selection that is currently unknown. This is not to say that nusinersen should not be approved; simply that a study in children should likely lead to the approval of a medication for the population of children studied. It represents a remarkable challenge in that there is clearly a bioethical imperative to do good (the principle of beneficence), but there is a great of potential harm that remains unknown. Lumbar punctures are not benign procedures: in patients with severe scoliosis and contractions, they can be exceedingly difficult, often requiring direct administration at the cervical and thoracic vertebral levels as opposed to the more commonly accessed lumbar regions (despite the common name of "lumbar" puncture). The risk of damage to the spinal cord increases in the cervical and thoracic spaces, as there is less relative cerebrospinal fluid separating the cord from the edge of the sac. It is difficult to quantify just how much harm we are avoiding when we cannot even assess the potential risks we may encounter.

The question, then, of whether or not nusinersen is "worth it" depends largely on how we as a society value vulnerable bodies. Is it worth its value in dollars? We shall see with further data whether it makes sense to invest further in this medication; as of now, it is impossible to say. Is it worth intervening on the vulnerable in order to provide them a

better quality of life? Most assuredly—but that is not what we are doing with nusinersen. We are assuming consent in order to intervene on vulnerable bodies without sufficient data but at great economic cost for families. A more difficult question to answer is why we are so concerned with these specific bodies that we are willing to use a relatively unknown and expensive medication in order to help them. Physicians and nurses in Pediatric Intensive Care Units (PICUs) grapple with this question every day, as they daily perform a large number of procedures on very small patients while assuming their consent. Appropriately for our discussion, bioethicist Wim Dekkers draws a comparison between patients with severe dementia and neonates—both populations that cannot communicate their wishes to healthcare providers:

> In this regard, another comparison forces itself upon us; namely, that between the person with severe dementia, for whom death is not far away, and the severely handicapped newborn, who fights for life. When caregivers in neonatal intensive care units have to decide whether or not to continue medical treatment, it appears that the newborn infant's energy and vigor contributes to the clinician's judgement about life expectancy and the continuation or termination of treatment. In ethical decision making in a neonatal intensive care unit, the phenomenon of vitality appears to have moral… These newborns tried, so to speak, to express their will and to execute their autonomy in *statu nascendi* just by demonstrating their vitality.[49]

In this case, the physical movements of the patient are interpreted as vitality, as an invitation to continue the medical treatment in order to prolong and ensure life. Dekkers extends this interpretation to the elderly who may pull at lines and tubes that have been inserted into their bodies in order to support them or deliver medications. The implication here, of course, is that it is morally justifiable to assume consent from a neonate because there is the *potential* of decades of life that remain to be lived, while in a

patient with dementia there is no such future. This returns us to the troubling consideration of the role that age has in decision-making. In the case of neonates and of patients who have severe dementia, the caretaker and family must assume a degree of consent in both. And in both cases, the caretakers project interpretations on the patients' non-verbal actions, asking themselves, "What does this patient want? What do their movements mean? Would I want this in their position?" It is inconsistent to assume only a neonate would want an intervention of questionable efficacy that may improve their circumstance but that an elderly patient would not unless, of course, we are simply projecting our own anxieties about disability and mortality onto the patient. One can hardly imagine a family investing $125,000 per injection in order to possibly return some as-of-yet unknown degree of independence and memories to an elderly loved one with severe dementia who can no longer verbalize but who pulls at lines, catheters, and tubes. In the case of both the non-verbal patients with dementia and with newborns, the problem of traditional definitions of autonomy lie at the heart of the matter because these definitions are predicated on communication and rationality. The result is inconsistent reasoning behind the interventions for both patients: if one assumes bodily movements are a form of assent and reflect the autonomy of the patient in neonates, then every conceivable intervention and medication is justified, no matter the cost; if, however, we assume that lack of verbalization means a lack of personhood and autonomy, then it is possible to justify fewer interventions, such as in the case of the elderly with dementia. Very clearly, an updated definition of autonomy is needed in order to resolve the dissonance between the two scenarios, one that recognizes the role of bodily movements

in nonverbal patients but also includes makes room for traditional notions of verbalization and rationality.

CHAPTER 4: A NEW PARADIGM OF AUTONOMY

Treating patients with acute ischemic stroke and those with SMA is exceedingly challenging. As in many arenas of medicine, physicians must delicately balance the availability of evidence, the possibility of the benefits to the patients, the dangers of foreseen and unforeseen side effects, and the respect for patient's wishes. Initially, I introduced the topic of catheter-directed thrombectomy with a story of an elderly woman with severe dementia who was confined to her bed, and who was not verbal. The physician who was available had only minutes to assess the situation, examine the patient, analyze the imaging, calculate the likely prognosis, weigh the risks of likely complications, and determine whether or not an intervention was indicated. Ultimately, he decided not to act. "I can't improve her past her baseline," he commented, "so what quality of life am I returning her to?" As evidence, he cited the fact that she could not communicate and could not independently move. In his eyes, these were critical characteristics to have for a fully-realized life and, by extension, a fully-realized human being. It goes without saying that this perspective seemed principally informed by his own opinions on autonomy and what "quality-of-life" meant to him.

Part of the problem that many physicians and physician-groups bring to the treatment of those with severe disability is one of cultivating a definition of autonomy that exists outside classic paradigms of able-bodied and neurotypical individuals. Traditional definitions of autonomy revolve around the notion that competent beings are those that "free, self-sufficient, rational, independent, and autonomous subjects."[50] This notion is inextricably intertwined with decision-making capacity; for this reason, children and adolescents are infrequently thought of as capable of consenting because their ability

to make decisions have yet to be realized. For this same reason, individuals under the influence of drugs, or those that are suffering from dementia are also not generally considered to have competence or autonomy in the same sense as other adults. Generally, with this sense of autonomy comes a sense of personhood itself—an autonomous human being is a fully-independent, fully-realized, self-determining person with internal goals, personal rules, and meaningful choice. If the aim of medicine is to restore functionality to "normal," then how do you approach a patient who was never "normal" to begin with? Or one who, due to various circumstances, can no longer return to "normal?" The result of not recognizing the autonomy and personhood of a patient is that it becomes exceedingly difficult to find reasons to intervene and help those patients. After all, what is the point of helping a person who is not a person? Many folks with chronic illnesses have spoken of the endless frustration of exasperated physicians, flummoxed at disease states that resist easy solutions, who become increasingly disheartened at the prospect of "dealing" with a patient whose health will never improve. The questions we are asking here are not new, but they remained unsatisfactorily answered.

Coming to a new definition of autonomy, one that incorporates more bodily elements and that elevates the role of the non-verbal communication, can help address this cultural error. Wim Dekkers, MD, PhD is a professor of Ethics at the University Medical Centre Nijmegen, in the Netherlands, and frequently writes on the topic of patient autonomy in medical care. One of the principal challenges and failings that physicians confront in the care of those with dementia is the common reflex to dehumanize the patient. Dekkers, in his explanation of severe dementia, says:

> Generally, dementia—for example, Alzheimer disease—is a long-lasting and gradual process. While the body of the person with dementia often remains strong for a number of years, mental capacities as well as accumulated competencies and memories of a lifetime gradually slip away. People with advanced dementia generally do still have fears and longings, even if these are limited to the immediate present, but in cases of severe dementia, the self (or call it the mind, the soul, the will) that constitutes the central locus of humanity is severely affected or may even be lost. The self is, so to speak, increasingly fragmented and scattered.[51]

The focus, Dekkers emphasizes, is frequently on what is "gone" with dementia—memories, autonomy, decision-making, and verbalizations. Instead, it may be useful to reframe our focus on what remains in dementia: the body and its movements. It is possible to interpret defensive movements from patients as expressions of vitality as well, just as we do for pediatric patients. Dekkers emphasizes the living body, in which we understand and view the body as not simply a vessel for the mind but as a being as autonomous and free as the mind itself. In this regard, Dekkers diverges quite significantly from traditional Cartesian perspectives on the body and the mind. René Descartes advocated that the mind and body were separate substances, such that what happened to the body has no bearing on the mind. This is a rather glorified view of the body, and imagines a body that is simply a conduit for sensations and is under complete control of the mind. Dekkers sides with French philosopher Merleau-Ponty, who posited that the lived body is a person's only access to the outside world, and as such the body itself is instrumental to the development, consolidation, and continued life of the mind. "All structures and functions of the lived body," Dekkers writes, "are modes of being to the person."[52] This radically changes how a clinician can approach a patient with severe dementia, or a pediatric patient who cannot verbalize.

Julia Lawton, a medical sociologist and ethnographer, discusses the concept of "bodily autonomy," in which the ability of an individual to control the physical boundaries of their body is a necessary, although not sufficient, criterion by which we can understand autonomy. Such that as one loses control over the boundaries of their body, they increasingly lose their personhood and autonomy. However, an immediate problem of this conception of bodily autonomy is the sheer number of devices and tools we use in the hospital on a daily basis to facilitate bodily functions and which themselves violate the physical boundaries of the body. For example, in patients that have respiratory failure, physicians often place a tube inside the patient's throat in order to mechanically ventilate the patient. In those that cannot tolerate food by mouth, physicians can place tubes directly into the stomach or intestines in order to deliver food and medications, bypassing the mouth. In patients that have chronic diarrhea and cannot walk to the bathroom, or are sedated or in a coma, rectal tubes can provide relief for caregivers and ensure that the patient is not constantly soiling themselves. Some patients cannot feel when their bladders are distended due to spinal cord injuries—in these cases, urinary catheters can drain the bladder, and the patient can manage the disposal of the urine themselves. All of these examples are tools that allow patients to regain more control over their bodies, even though their presence necessarily violates physical boundaries in the body. Even mechanical ventilation, in which the patient is not breathing by themselves at all, gives the body time to heal and allows the patient to grow stronger to later reclaim autonomy of the body. Lawton has a very strong point that physicians and bioethics must think of the body as a living, autonomous entity that is informed by and connected to the self or mind, but the notion that control over physical boundaries is in and of itself a necessary

criterion to develop bodily and self-autonomy is not consistent with a modern era in which various tools and devices permit patients to control their bodies and lives. One wonders what Lawton would think of prosthetic devices such as artificial joints, which also require violation of physical boundaries but which restore functionality and independence to patients.

All this to say, the concept of bodily autonomy reasserts the importance of a body to its mind, which can be critical to more ethical and compassionate treatment of those with dementia, when it can be challenging to find or recognize a traditional sense of personhood or autonomy. Dekkers lands on a formulation of his own form of bodily autonomy: "a combination of the biomedical notion of bodily automatisms and the phenomenological idea of the lived body."[53] The human body has its own life, both dependent on the patient's higher cognitive faculties yet largely independent as well, as evidenced by the sheer number of functions the body performs without input from voluntary nervous system (e.g., micturition, defecation, perspiration, digestion, heart rate, breathing, and more). The result, Dekkers claims, is that one must communicate with Alzheimer patients via their bodies, and one must recognize that the body itself has a lived autonomy. Dekkers agrees with Stephen Post, who wrote in *The Moral Challenge of Alzheimer Disease*, "The key to an adequate ethics of dementia is full attention to the many ways of enhancing the non-cognitive aspects of human well-being while not underestimating remaining capacities."[54] This formulation of autonomy, balancing verbal and non-verbal and cognitive and physical aspects, is equally appropriate for neonatal patients who similarly cannot express their wishes and who may frequently act in ways that can be *interpreted* as refusing care.

Dekkers' arguments are not without fault, and he himself is frequently guilty of a profoundly ableist bias. "In persons with dementia," he writes, "not only the mind but also the body gradually deteriorates. The person with severe dementia is extremely damaged in his mental and bodily existence. The body of such a person is in a sense a less human body than the body of a person who is not so diseased."[55] Unfortunately, this perfectly parallels the modified Rankin Scale (mRS) as previously discussed, which describes a spectrum from "normal" to death or "as bad as being dead," with intermediate degrees of disability, as if disability is simply a stepping stone into the ultimate disability: death. He similarly remarks, "People with severe dementia cannot entirely be denied a (rudimentary) form of selfhood or personhood. They definitively are not persons in the strict sense of moral agents who are self-conscious and rational and demonstrate a minimal moral sense, but at least they can be called persons in a (weaker) social sense." In theory, this is meant as a charitable recognition of the tenuous but still real relationship people with dementia have with their memories and humanity. In reality, it reads as a dismissive simplification of a complex relationship with selfhood, time, and the body. By opening his section with these comments, Dekkers' undermines and weakens his later defense of the humanity of patients as autonomous beings.

Ultimately, I remain unimpressed with theories of autonomy that rely too heavily on the ability of the body to regulate its borders because these theories largely ignore the reality of many patients that live with varying degrees of disability and different abilities. It is perfectly reasonable to go home with an in-dwelling urinary catheter, or a colostomy, or a large wound with a vacuum seal on it with the expectation of closing the wound at a later date. It is the height of ableist arrogance to assume that bodies that cannot regulate

their boundaries somehow reflect a dehumanization or loss of autonomy of the person or are somehow "less than" others. There is very little special about being able to hold urine—it is a skill nobody is born with, one that is easily erased by numerous medications, a skill that many lose with age, and one that has absolutely no bearing on the wholeness of a person. Similarly, this applies to many patients with a range of different bodies. Cartesian dualism is limited in its theory that the body barely matters for the formation of a person, but Lawton's notion of bodily autonomy reveres too highly the role of the body in the development of personhood. Dekkers comes closer to touching upon a more realistic appraisal of the relationship between bodies of matter and bodies of mind, yet his arguments are limited by demeaning attitudes toward disability. Balancing these three theories reveals a definition of autonomy that may help physicians approach their patients in a more humanistic, ethical manner: autonomy is a spectrum of both physical and cognitive independence found in human beings and which is expressed by varying degrees of bodily movements and verbal communication which ultimately convey the wishes and goals of the person in question.

The interpretation of the goals and wishes of a patient is no less challenging with this definition, but it allows space for both the evaluation and valuation of the body in assessing the autonomy of a patient. This definition also does not diminish the role of cognition or rationality in autonomy, permitting traditional definitions to still have a place in the appraisal of autonomy. Perhaps most importantly, in a patient who lacks one or both of these aspects of autonomy, this new definition demands the physician reflect on whether or not they are projecting their own definitions of personhood or autonomy on the patient. No longer would a physician be able to assess an elderly patient with

dementia and decide that due to their nonverbal status, they have no autonomy and thus no personhood—it would require the physician to assess other forms of communication and autonomy. This definition permits physicians to continue treating patients with SMA as before, but it more explicitly emphasizes the fact that the physician is only relying on a part of the whole definition of autonomy and would certainly call for continued interrogation of the patient's autonomy as the patient ages and develops more cognitive faculties. This definition similarly endorses the continued treatment of those with advanced Alzheimer dementia regardless of their baseline disability, which would go considerably to correcting the flaws of the mRS. That said, the mRS would still be useful in allowing physicians to communicate and evaluate the unknown, undifferentiated patient with neurological deficits. Ultimately, an updated definition of autonomy that integrates cognitive and bodily elements does not detract from current practices, but does expand the possibility of treating patients in a more humane and ethical fashion. This definition simply asks physicians to be more deliberate and mindful in their language and in their assessment of their fellow human beings.

A limitation of my own discussion in this paper is that I do not critically analyze the relationship between medicine, bioethics, and capitalism. Traditional notions of a person's functionality or autonomy may frequently be intertwined with an assumption of that person's productivity in a financial sense. Disability and welfare are entwined in the United States, and it is nearly impossible to have a discussion of one without the other—certainly on a policy level. Indeed, this point may significantly contribute to the relative moral ease with which we perform procedures and interventions on neonates—if a physician can "fix" an otherwise sick baby, then that baby can go onto to grow and

become a “contributing” member of the workforce. No such possibility is available to an elderly patient with severe dementia, and the specter of capitalism most certainly has a significant impact on how we value certain bodies. In a similar vein, I only briefly touched upon the larger relationship between insurance companies, pharmaceutical companies, and hospitals—a topic that would surely dwarf the scope of this thesis. It may well be that the ethical practice of medicine and the economic system of capitalism are incompatible. Another limitation of this paper is, perhaps, its sheer provincial nature: in many ways, nusinersen represents a quintessentially and uniquely North American approach to medicine and healthcare. It is a remarkable drug that represents decades of rigorous investigation and research and which addresses a dire need in a desperate community, but which is so exorbitantly priced that patients must navigate a complex, labyrinthine bureaucracy of insurance companies and employers in order to pay for it such that only the best insured and wealthiest and most resourceful of patients are able to access it, and whose efficacy is as of now unknown and poorly understood. Regarding the practice of catheter-directed thrombectomy for ischemic strokes, it does not appear that the North American approach to deciding whom to treat differs significantly from our international counterparts, so that aspect may be more generalizable.

Another, more obvious limitation of my analysis is the fact that I am not disabled and I have relied heavily on the writings of other abled authors. This risks infusing ableism into my own writing and furthermore exacerbates the historical silencing of disabled voices. Disability is more than a pathology or disease—it is an identity and a culture a million different lived experiences, and there are innumerable voices in the community that bring a needed face to an otherwise forgotten or neglected identity. These

authors have found a large presence on social media, in particular Twitter. Among these voices are writers and activists such as Alice Wong (@sfdirewolf), TheDisabilityEnthusiast (@twitchyspoonie), Vilissa Thompson (@VilissaThompson), Matthew Corland (@mattbc), Crutches&Spice (@Imani_Barbarin), Emily Ladau (@emily_ladau), and many more. These writers have different experiences with different forms of disability, and rightfully speak out against various injustices levied against the disabled community, from interpersonal ableist aggressions to structural inequalities to erasure. In order to highlight the education, work, and activism of disability advocates and disabled folks, Matthew Corland recently wrote a Twitter thread detailing precisely how ableist the concept of QALYs are. "The very core of QALYs—the foundation upon which they are built is simply this assertion: a year of non-disabled life is worth more than a year of disabled life."[56] He went on to describe various problematic and discriminatory aspects of the concept of QALYs. This is emblematic of the work and effort that befalls many disabled folks, and to which hopefully I may draw a degree of attention.

Integrating discussions of bodily autonomy into our analysis of how physicians may care for patients with SMA and those with ischemic stroke, it is easy to appreciate the nuance and delicacy required for these cases. In both scenarios, there are interventions available with unclear benefit for patients in great need. Yet it also presents an opportunity to correct a medical injustice, in which limited paradigms of personhood and autonomy may themselves represent limited options for patients in need. By recognizing new theories of autonomy, it becomes easier to intervene in order to help a patient achieve what they desire regarding the quality of life. However, for those who

reject or otherwise do not adopt suggestions to update definitions of autonomy, it is necessary to justify why not. This becomes acutely important in the setting of the patients with acute stroke. If the physician decides not to intervene because they do not see value in the patient's baseline level of disability, then it is important to be honest and admit that rather than pretend the decision is coming from a place of concern for the patient's autonomy. Only in identifying this thinking can we subsequently work on expanding this narrow definition of personhood and begin the work necessary to reverse the harms that traditional definitions of autonomy inflict on those with SMA and AD as well as other disabled persons.

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