# THE ANTICIPATORY POLITICS OF SICKLE CELL DISEASE:

## An Examination of Policy, Practice, Care, and Innovation in the U.S. and France

Gina Jae

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ABSTRACT

The Anticipatory Politics of Sickle Cell Disease: An Examination of Policy, Practice, Care, and Innovation in the U.S. and France

Sickle cell disease (Fr: *la drépanocytose*) is an inherited blood disorder with over a century of biomedical history in the United States. In turn, with recent decades of migration, it has become the most common genetic disease in France. For those with sickle cell disease who also live in high-income countries, the past fifty years have transformed a fatal disease of childhood into a chronic, but still life-shortening condition. In countries like the U.S. and France, where sickle cell disease also disproportionately affects disadvantaged minorities and immigrants, scientific and clinical knowledge production around sickle cell disease has become entwined with race- and class-based history and politics. This research offers ethnographic understandings of how families and health care providers are negotiating the available options to treat sickle cell disease, including the high-risk undertaking of hematopoietic cell transplantation, in a moment when most children in high-income settings are expected to reach adulthood.

This study builds upon work to understand and redress the durability of health inequalities, as new medical knowledge and innovations in care and prevention become introduced to stratified social systems. To this end, fundamental cause theory (Link and Phelan 1995) has demanded attention to the interplay of social conditions and human agency (Link and Phelan 2002, Lutfey and Freese 2005), in addition to macroeconomic and social policy, to explain the stubborn persistence of gradients in health outcomes. As my research also encountered, this includes contexts where there is universal health care. In fact, national health policies in the U.S. and France have mandated a comparable access to comprehensive care for

children with sickle cell disease, where disease-specific standards are upheld by both governments for the pediatric population. With access to care removed as the ostensible barrier, this project is positioned to discern differences in transplant utilization as attributes of clinical power dynamics and practice differentiation, which I elaborate as *treatment collectives*, that were particular to the health care institutions I observed in both countries.

To this end, I articulate *anticipatory politics* as a novel theoretical framework and analytic lens to distinguish anticipation as a form of care. As an analytical paradigm, anticipatory politics identifies affects and practices as key components in the production of scientific knowledge and clinical work. This approach links anticipation and hopes for the future materially and temporally to the historical contingencies of emergent scientific innovation. As politics, I demonstrate how expectations for the future lives of children become co-produced with structural paradigms that shape who is offered the option to intensify treatment, including the option to undertake high-risk interventions. By reframing anticipation and care as politics at the interface of medical innovation and clinical practice, this project complicates an assumption that universal health care is sufficient to redress disparities in treatment access and health outcomes. This research contributes to science studies and organizational theory by providing a framework to account for the national commitments and personal sentiments that negotiate translational bottlenecks when accessing newer technologies in the clinical setting.

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# Acknowledgments

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# Dedication

For Neko and Sunhi: my inspiration, embodied.

## GLOSSARY OF TERMS

| | |
|---|---|
| Allogeneic transplant | hematopoietic cell transplant performed using stem cells harvested from another person (i.e., donor) |
| Autologous transplant | hematopoietic cell transplant performed using a person's own stem cells |
| Bone marrow transplant | hematopoietic cell transplant performed using stem cells harvested from the bone marrow (often from the hip bones) |
| Cord blood transplant | hematopoietic cell transplant performed using stem cells harvested from umbilical cord blood; because cord blood cells tend to be more naïve to antigens, cord blood transplants are associated with less GVHD, but slower engraftment and higher rejection rates |
| Chimerism | the presence of two different genomes within organs of the same body; after hematopoietic cell transplantation, this is measured by the proportion of donor and recipient blood cell precursors |
| GVHD | graft-versus-host disease; a common complication of hematopoietic cell transplantation, due to lack of tolerance between the donor immune system and the recipient, leading to donor white blood cells attacking the recipient's organ systems |
| Hb[Hemoglobin] SC disease | Hb SC is the second most common genotype for sickle cell disease; Hb $S\beta^+$ thalassemia is a less common genotype that is phenotypically similar to Hb SC, and both genotypes are associated with a longer average life expectancy than Hb SS disease |
| Hb[Hemoglobin] SS disease | Hb SS is the most common genotype for sickle cell disease, also referred to as sickle cell anemia; Hb $S\beta^0$ thalassemia is a less common genotype that is phenotypically similar to Hb SS |
| Hematopoietic cell | blood-forming ("stem") cell |
| Hematopoietic cell transplant | inclusive term for the autologous or allogeneic transplant of blood-forming (stem) cells; stem cells may be harvested from the bone marrow, umbilical cord, and peripheral blood |

| | |
|---|---|
| Myeloablative transplant | a hematopoietic cell transplant, where the conditioning regimen is intended fully destroy the blood-forming cells that populate the bone marrow; without a rescue of transplanted hematopoietic cells, the dose of chemotherapy and/or radiation used is often fatal |
| Non-myeloablative transplant | also called “reduced intensity” hematopoietic cell transplant, where the conditioning regimen is intended to make space for the graft without fully destroying the blood-forming cells that populate the bone marrow; acquired tolerance (i.e., mixed chimerism) enables non-myeloablative transplants to use lower doses of chemotherapy and/or radiation and/or immunomodulating drugs (e.g., monoclonal antibodies), broadening the pool of transplant candidates, but at the expense of increasing graft rejection or GVHD |
| Sickle cell anemia | alternate term for Hb SS disease |
| Sickle cell disease | denotes the disease category of sickling hemoglobinopathies, including Hb SS, Hb SC, Hb $S\beta^0$ and $S\beta^+$ thalassemia genotypes, as well as less common variants |
| VOC | vaso-occlusive crisis, also referred to as vaso-occlusive disease and sickle pain crisis in common parlance; VOC also describes broader sickling phenomena, where symptoms due to red blood cell distortion, adhesion to blood vessels, cell rupture, and inflammation can be provoked in virtually all organs |

## Introduction

> [T]he language of medicine is hardly a simple mirror of the empirical world. It is a rich cultural language, linked to a highly specialized version of reality and system of social relations, and when employed in medical care, it joins deep moral concerns with its more obvious technical functions.
>
> Byron Good (2003[1994]:3)

Sickle cell disease remains prevalent across the historic malaria belt that includes Sub-Saharan Africa, the Mediterranean and Southern Europe, the Arabic peninsula, and the Indian subcontinent. The present distribution of sickle cell disease worldwide also reflects more recent centuries of geopolitical movement. This includes the repercussions of the trans-Atlantic slave trade and European colonialism to the contemporary global migration flows that continue to bring trait carriers to the Western hemisphere and Northern Europe. In high income countries from regions, sickle cell disease predominates among populations who are also marked as racial and ethnic minorities. In the U.S., for example, the majority of sickle cell patients are also identified as Black and Latinx. The particularities of an individual's ancestry, however, can render the apparent markers of race and ethnicity as imprecise signifiers, at best, of an increased likelihood to inherit the recessive allele.[1] That sickle cell disease continues to be dubbed a "black disease"—a still-common assumption today across lay publics—is sometimes met with a mixture of derision and frustration among many advocates for the disease. And yet, the nuance that apprehends the diversity of affected populations bumps against the demographic reality that

roughly 90 percent of constituents with sickle cell disease in countries like the U.S. and France are also Black and/or of African descent.

With the burden of sickle cell disease disproportionately shouldered by groups who also contend with race and class-based inequalities, the repercussions of unequal treatment are also borne out in the stratified health care arena. As summarized in the report from the U.S.-based Institute of Medicine, differences in access to recommended health interventions consistently have been reproduced across racial and ethnic lines. This discrepancy has been found to occur in both public and private institutions, even after correcting for upstream factors such as health insurance coverage, patient preference, and disease severity (e.g., IOM 2003). Historically disadvantaged minorities continue to experience the burden of unmet standards of care, from recommended cancer screening and treatment (e.g., DeLancey, *et al.* 2008) to chronic pain management (e.g., Meghani, Byun, and Gallagher 2012). To explain the persistence of observed racial and ethnic inequalities in cardiovascular morbidity and mortality (e.g., KFF and ACCF 2002), complications of chronic diseases like diabetes (e.g., Willi *et al.* 2015), the distribution of solid organ transplants (e.g., Malek *et al.* 2011), and maternal mortality (e.g., ACOG 2015), the IOM report acknowledges that health services research and policy interventions need to redouble attention to the granular impact of implicit bias within health systems and provider interactions with patients. In recent years, explaining inequality has increasingly employed the analytic lens of intersectionality, where social disadvantages associated with race, class, gender, and sexuality become compounded across hierarchies and through existing power dynamics.

I first learned about sickle cell disease in secondary school science class, where it continues to be taught an example of an autosomal recessive condition inherited via mendelian genetics.[2] Undergraduate pre-med classes added the more granular detail that a survival

advantage explains the persistence of the sickling mutation in malaria-endemic regions. Whereas those who inherit both copies of the recessive gene experience anemia and life-threatening illness, heterozygote trait carriers are not only healthy[3] but also protected from cerebral malaria, an oft-fatal complication of an already destructive parasitic infection. But I only began to knowingly meet individuals who were living with sickle cell disease with medical training.

Both the medical school I attended and my residency program were located in urban centers, where the complications of sickle cell disease were common indications for emergency room visits and hospital admissions. Much of my initial exposure to the medical management of sickle cell disease was stitched from the patchwork of generalist training experiences that took part in this care. These included clinical encounters with patients and their families in the pediatric and adult emergency departments, during their hospitalizations, and as a provider of outpatient follow-up that took place in primary care clinics. Cases that still readily come to mind often coincided with the acuity of patients' conditions at the time, for example when severe illness necessitated their transfer to an intensive care unit or the escalation of complex pain management.

Perhaps unsurprising, then, is that among those training experiences that stand apart in my memory is a case of unequivocal rupture between a patient and her health care providers. During the internship year of my residency,[4] I rotated for several weeks in the respective adult and pediatric Emergency Departments. While working an overnight shift, I was assigned to an adult patient presenting with a sickle cell pain crisis. I met her as she lay on one of the stretchers that crowded one of the walls of the emergency room. Flimsy curtains provided the perfunctory septations between the gurneys. She had walked to the hospital alone from a nearby apartment

complex; we were both still on the younger side of adulthood. She grimaced during my interview, but answered my questions and allowed me to perform an abbreviated physical exam.

I presented the case to the supervising physician. Upon mentioning that the patient had asked for Demerol for her pain crisis, the attending shook her head, no: "They ask for Demerol, because it gives them a rush." This was not the last time that I would hear a version of this explanation during my residency. Meperidine, the trade name for Demerol, is an intravenously administered medication used to treat severe pain in hospital-based settings. At the time, meperidine was falling out of favor, in part, due to its association with an increased risk of seizure; however, there was a parallel perception among certain physicians that meperidine was "too addictive." At the time, alternate intravenous opioids were still readily available. The aggressive marketing of prescription pain medications that fuels the current opioid epidemic was beginning to take hold, though the impact of this shift in clinical practice would intensify by the time I completed residency. But even in 2002, patients with sickle cell disease who had come to expect access to meperidine during a pain crisis began to encounter restrictions to this medication from health care providers, and this produced clashes during the clinical encounter. I returned to the patient's bedside, offered morphine instead of Demerol, and told her I would need to order blood tests as part of her work-up.

She became upset. Amid her words of frustration, she protested that it would have been better for her mother had she not been born, than to have endured the suffering of her disease. By the time I returned to the physicians' work station at other side of the Emergency Department, I did not have to report the patient's displeasure with the proposed plan. Her unhappiness was already broadcast across the row of beds that also signified the distance between us. The attending held firm: labs and no Demerol. When I returned to the bedside with the same news,

the patient threatened to leave. After another round of circular argument, I made a last, empty-handed, request for the patient to stay.

"I'll be all right" she replied, removing the nasal canula from her face and dispatching the loop of plastic tubing over her head. As she stood up from the stretcher, I saw that beneath the hospital gown, she was dressed in pajamas. She repeated her recitation to the mostly empty stretchers as an audience—that it would have been better never to have been born—before showing herself out. I returned to the work station with the unsigned AMA ("Against Medical Advice") discharge paperwork and a defeated look. The attending remarked that perhaps the oxygen had helped her feel better enough to go home.

In the scheme of sickle cell disease medicine in the U.S., this type of breakdown in patient care has been customary, particularly for the adult patients of color who have had to engage the health care system to access restricted medications from physicians who became gatekeepers in managing their pain. Compared to non-Hispanic Whites, people of color have received inferior pain management writ large, including for non-surgical, cancer-related, and chronic pain syndromes, and this race and ethnicity-based disparity has been documented as a health safety and quality of care concern in the U.S. (Meghani, Byun, and Gallagher 2012). An undesired but also anticipated consequence of the current effort to rein in excess prescribing of narcotic medications has been the inappropriate restriction of pain management, compounding stigma for patients with sickle cell disease, who have historically been refused adequate treatment for pain crises (NHLBI 2017).[5] Ultimately, the scene was remarkable for being unexceptional and an all-too-familiar rejoinder that even my still modest training had partially anticipated. Despite having heard stories of similar rifts between patients and providers, in the moment, I felt powerless to alter its course.

Hence, as consequential direction for this project was a more structured introduction to sickle cell medicine as a subject of social study and historical significance. After residency, I began a clinical research fellowship, while expecting my first child. Three credits short of completing my public health masters, I grasped the extent of my indifference towards becoming an epidemiologist. In the fall of 2006, I took an elective course housed in the anthropology department, where The Troubled Dream of Genetic Medicine (Wailoo and Pemberton 2006) was on the syllabus. Wailoo and Pemberton's book described the "perilous lottery" of offering bone marrow transplantation to children with sickle cell disease on an experimental basis. They cited transplant physician E. Donnall Thomas' reasons that families might accept a significant procedure-related mortality rate in an attempt to cure their children: "'We heard an argument that a 10% mortality with transplantation may not be acceptable… On the other hand, we have heard that the quality of the life for sickle cell disease patients in many instances is perhaps worse than death'" (Wailoo and Pemberton 2006:136). In a perverse turn, Thomas' ethical justification for families to consider this risky and highly morbid procedure in hopes of averting a quality of life "perhaps worse than death" summoned the words of my own patient from the Emergency Department, who had decried having ever been born.

Shortly after taking this course, a semester where I became reacquainted with the language of social theory and ethnographic research, I attended a grand rounds lecture led by a pediatric transplant physician, Gustavo del Toro. Grand rounds provide continuing medical education to the wider community of physicians and trainees within a given specialty. Dr. del Toro made an impassioned argument to increase the availability of hematopoietic (or "blood-forming") cell transplantations—also referred to in lay parlance as "stem cell transplants," including their most common iteration, the bone marrow transplant—in the treatment of sickle

cell disease. When successful, he argued, transplants delivered what appeared to be a lasting resolution to the symptoms and long-term sequelae for children with sickle cell anemia.

Summarizing the available clinical trials to date (e.g., Vermylen *et al.* 1998, Bernaudin, *et al.* 2007, Mischlitch and Walters 2008), del Toro noted that 85 to 95 percent of the children who underwent a myeloablative transplant using a matched sibling as their donor maintained sufficient quantities of unaffected red blood cells to halt the progression of sickle cell disease.[6] Over time, mortality had been limited to five percent, or roughly one treatment-related death for every 20 patients who undergo this particular iteration of transplant. By comparison, transplants for most other conditions, including many cancers, produce much lower rates of remission and more of the complications that regularly confer a 30 percent treatment-related mortality.[7] Despite the relative success of hematopoietic cell transplantation in the treatment of sickle cell anemia, however, they continue to be performed infrequently.

Among the multiple caveats for undertaking transplant for sickle cell disease is that the versions of this procedure that have produced the best outcomes, with greater than 90 percent rates of engraftment without relapse and the fewest deaths, have used a myeloablative conditioning regimen. Myeloablation is a transplant method that utilizes an aggressive cocktail of toxic drugs and/or radiation intended to completely destroy the host's own bone marrow. A myeloablative transplant regimen exposes the body to potentially lethal doses of chemotherapy and other immunosuppressive or radioactive agents, such that sufficiently healthy organs are needed to withstand the short-term toxicities of the conditioning regimen itself. This requirement alone—for patients to undergo transplant with their kidneys, liver, heart, and lungs largely spared of the damage routinely incurred by longstanding sickle cell disease—has historically excluded

most adult patients as candidates for myeloablative protocols. Hence, the transplants for sickle cell disease that use the more toxic conditioning regimens have largely been limited to children.

Another limitation that has prevented transplant from being performed more widely, even among the younger children with sickle cell disease, is that the most favorable outcomes are observed with matched siblings as donors. Not only do siblings need to have been born healthy to donate, they also need to have inherited the same genes for the human leukocyte antigens (HLA) that underwrite the immune system's recognition of self. On the one hand, even trait carriers of the sickle gene mutation may potentially donate for stem cell transplant. By mendelian probabilities alone, however, the likelihood of being unaffected by sickle cell disease while inheriting the same HLA alleles from each parent is three in 16 (18.75 percent).[8]

To date, myeloablative transplants using matched sibling donors have produced the most consistent results in terms of maintaining stable engraftment. In other words, the most toxic transplant regimens have also produced a greater likelihood that the host with sickle cell disease does not reject the donor cells. In addition, myeloablative transplants using matched sibling donors have produced fewer of the severe complications, such as a high grade and/or chronic graft-versus-host disease (or GVHD), a result of donor immune cells attacking the organs of the host, which can result in a fatal outcome. With both stable engraftment and relatively low GVHD, myeloablative transplants with matched sibling donors have produced survival rates of 95 percent or better. By contrast, transplants using unrelated donors identified through bone marrow registries have demonstrated high rates of graft rejection with relapse to sickle cell disease, severe graft-versus-host disease, and procedure-related deaths. I also discuss this further in Chapter 4.

The solution that Dr. del Toro proposed to redress a dearth of viable transplant donors sounded radical enough, though it had been conducted for other conditions: to perform embryo selection using in vitro fertilization (IVF) and pre-implantation genetic diagnosis (PGD) in an effort to ensure an ensuing pregnancy is unaffected by sickle cell disease and HLA-matched to an existing sibling. National policies that dictate the legality and availability of PGD, including the extent of the embryo selection that can be performed, vary across countries. In the U.S., PGD is both legal and federally unregulated and thus, readily available through the private sector.[9] The French government has formally sanctioned the use of IVF and PGD for the purpose of HLA-typing embryos in order to conceive an unaffected child who can potentially donate stem cells for transplant (Fagniez, Loriau, and Tayar 2005). In fact, when PGD is used with the therapeutic intent to treat an affected older sibling, the French health care system also covers the cost of these technologies. With a successful pregnancy, the umbilical cord blood harvested at birth can be cryopreserved for future use, when the hematopoietic cells are extracted and processed for donation.

Dr. del Toro already had identified families from his urban hospital-based practice who were prepared to undergo all three procedures—PGD, IVF, and transplant—in hopes of eventually curing their children's sickle cell disease. As the out-of-pocket expense of assisted reproductive technologies is significant, and usually not covered by private and state-sponsored insurers in the U.S., many families do not have means to pay for them. In 2007, Dr. del Toro petitioned the Department of Health of New York State, making the case that Medicaid, the state-sponsored health insurance, cover the cost of IVF and PGD. Del Toro had argued that the usual prohibitions against the state funding of infertility treatments could not be inveighed in the case of "IVF with therapeutic intent," which enlists these technologies on the medical grounds

for treating an existing child.[10] Ultimately, the Department of Health declined, fearing the downstream economic and legal burdens of setting a precedent of offering assisted reproductive technologies as an obligation of the state.

New York State's Task Force on Life and the Law[11] also weighed in on the ethics of the proposal. The Task Force is a multidisciplinary body formed in 1985 and charged with developing public policy reports on the bioethical implications of end of life care, genetic testing, assisted reproductive technologies, physician assisted suicide, and organ and tissue transplantation. In fact, the Task Force did not object to the overall premise of using PGD for purposes of HLA-selection. Though it did not consider the concept of "savior siblings" as inherently unethical, the Task Force questioned whether the communities affected by sickle cell disease (i.e., the populations who experienced higher prevalence of the disease in the region) would accept IVF and PGD as instruments to treat an affected child. At that time, no published reports had documented the views of families affected by sickle cell disease on this use of IVF with therapeutic intent.

And so began my foray into the biopolitics of sickle cell disease and technologized medical interventions, initially with attention to the ethics of assisted reproduction in conjunction with transplant. I am indebted to Gustavo del Toro for including me as a researcher on his study of IVF with therapeutic intent, a project to which he devoted time, resources, and mentorship beyond his professional allotment. Dr. del Toro ensured administrative support and recruited medical students to work with me as research staff, and he never interfered with the process of data collection, analysis, and manuscript writing. We conducted a pilot study using semi-structured interviews to elicit the views of 13 adult patients with sickle cell disease and 10 parents of affected children toward a hypothetical use of IVF, PGD, and transplant with the

objective to treat an existing child. All members of the research team were given the opportunity to present findings from this study at regional meetings and scientific conferences. These venues included research and advocacy meetings which covered a range disciplines, including hematology, pediatrics, transplant medicine, public health, and social sciences and addressed audiences in the U.S. and abroad. Ultimately, we summarized our work in a peer-reviewed publication (Jae *et al.* 2011).

This predissertation experience lay the groundwork for the eventual evolution of this project. While still a clinical fellow, I began to appreciate the complex science and clinical challenge of transplant medicine. During this period, Dr. del Toro recruited two families who underwent PGD and IVF (provided pro bono by a local fertility clinic, also through his advocacy) that eventually led to HLA-typed pregnancies. The stem cells harvested from the umbilical cord blood and bone marrow of both children were eventually transplanted to their older siblings.

During this period of pre-doctoral research, I had the opportunity to observe consultations with parents who were considering transplant for their children. In the process of undergoing a transplant work-up, families travelled to myriad appointments to undergo the necessary diagnostic testing and consultations with specialists. I also became more familiar with the everyday rhythms of transplant rounds, including the precipitous complications that could punctuate and extend an already lengthy and arduous hospitalization. I began to grasp the intricate home and clinic-based regimens that were required of families after discharge, and how these might extend for months, sometimes years, when recovery became disrupted by difficult infections associated with immune suppression, potentially life-threatening graft-versus-host disease (GVHD), or a delayed recovery of donor-derived blood cell lines.

By the time I matriculated into the doctoral program in Sociomedical Sciences, I was immersed in a heady mix of themes ripe for anthropological examination: the ethics of reproductive, genetic, and transplant technologies; their scientific knowledge production in sickle cell disease; and the sociopolitical intersections of these with race and class. As I became more familiar with the medical literature, however, new questions began to emerge. Why did so much of the published research on transplantation for sickle cell disease, including the studies with the largest patient cohorts, originate in Europe? This included a seminal study from Belgium (Vermylen *et al.* 1998), which reported on their first 50 patients transplanted for sickle cell disease, using myeloablative conditioning regimens and matched sibling donors. Within a decade, a study from France reported on their own twenty-year experience with myeloablative transplants for children with sickle cell disease, publishing long-term results for 87 patients (Bernaudin *et al*. 2007). Given the effort and resources required from families and the health care system to implement PGD, only to incrementally increase the donor pool of matched siblings at best, how had these centers achieved their transplants numbers, if mendelian genetics has been the ostensible barrier?

In 2009, I had the opportunity to present a poster at an international symposium on sickle cell disease in Brazil.[12] By then, I was starting the second year of my doctorate, pregnant with my younger child, and investigating possible field sites for my dissertation. There, I noticed a shift in the representation among the presenters and attendees, compared to the other sickle cell meetings I had attended. While the usual suspects from North America were there to present their respective clinical, research, and advocacy projects, a decidedly global distribution of participants and invited speakers was reflected across the entire program, which was simultaneously translated in Portuguese, English, and French. I made certain to attend the

plenary from one of the authors of the French transplant study. Her talk ended with a slide that mentioned PGD as a means for bridging the need for a matched sibling donor. Was this the reason why so many transplants had been performed in France? I hurried to speak with her afterwards.

To my surprise, the presenter's reply mirrored my own question about the French experience with this technology. She asked, "Has your center had a pregnancy [using PGD]?" Thus far, attempts to conceive a HLA-matched donor had not yet produced a successful pregnancy in France.[13] Her query served as a reminder that carrying out PGD had pragmatic consequences beyond its conceptual fodder for ethical debate or political controversy. In practice, PGD was time-consuming and technically difficult, with a low likelihood of producing its desired outcome. Notwithstanding the painstaking process of undergoing IVF and meeting the financial cost to access these technologies, reaching a term pregnancy was hardly a guarantee, in spite of the best efforts of patients and their specialists in the field. Though the French government provided financial support for families to access IVF and PGD performed under the medical grounds of conceiving a potential transplant donor, these attempts had not yet resulted in a HLA-typed pregnancy. This exchange became a turning point for this project, as I realized that the puzzle of differential transplant utilization across sickle cell disease centers could not be explained by the availability of advanced reproductive technologies. Clearly something else was happening that enabled certain institutions to maximize the practice of myeloablative transplants for children with sickle cell disease, with their siblings as donors.

## Methods

Link and Phelan's (1995) theory of "fundamental causes" demonstrates how inequalities in health outcomes persist over time, when those with greater social capital are the preferential beneficiaries of life-prolonging interventions. When antecedent social gradients stratify access to new knowledge and efficacious treatments options, the earliest adopters of these interventions also tend toward those of higher socioeconomic standing and other forms of health-relevant capital, including education, power, and prestige. Hence, should new knowledge facilitate actionable preventive strategies, and if breakthrough interventions prove efficacious, health outcomes diverge further along existent social gradients. Thus, *fundamental cause theory* dismantles the misrecognition of an instrumental driver of health inequalities: namely, that "disparities in health status have increased… *in significant part because of* remarkable advances in our ability to prevent, diagnose, and treat disease" (Freese and Lutfey 2010:68).

Differential access to transplant highlights the challenge of introducing new knowledge and innovative therapeutics without exacerbating existing inequities in health outcomes. A central contribution of the theory of fundamental causes links the persistence and reproduction of gradients in health outcomes to social conditions that intersect with, race, ethnicity, class, and other markers of socioeconomic status over time. Fundamental cause theory not only implicates ill health as a risk disproportionately shouldered with social disadvantage, but also articulates how social capital affords its prevention and alleviation. Hence, among the challenges of remedying disparities in health outcomes occurs when prevention techniques and treatment technologies are offered as the primary means to their reduction, a misattribution has been prone to continuous resurrection.

Building upon the sociological scaffolding fundamental cause theory provides, this research engages the extended case method to examine modes of care, prevention, and innovation as they have been produced on behalf of children with sickle cell disease in the U.S. and France. The extended case method employs the context effects of ethnography in order to "extract the general from the unique… and to connect the present to the past in anticipation of the future, all by building on preexisting theory" (Burawoy 1998:5). As such, this research applies the reflexive science of ethnography to refine fundamental cause theory by comparing differences in clinical practice, including in transplant access and utilization, at health care institutions providing comprehensive care for pediatric sickle cell disease in the U.S. and France. In engaging families and health care providers as they negotiated whether, when, and how to proceed with intensifying treatment for their children, this research attended to scientific research and clinical decision-making as intermingling worlds of incumbent moral reasoning, care, and practice.

Scientific and medical forums regularly attribute the underutilization of transplant to the clinical risks and pragmatic limitations of the procedure itself. This includes the paucity of matched sibling donors, to which Dr. del Toro and others proposed the remedy to, quite literally, conceive more. Yet many health care providers more privately voiced social, demographic, and other patient-based characteristics, such as "culture," educational attainment, immigration status, and socioeconomic status as proxies for why a family may decline the procedure (such as physician mistrust) or not be offered it altogether (e.g., "lack of social support," "non-compliance"). Reflexive science seeks out the contingencies, constructs, and fault lines of these concerns and presumptions.

Productive alternatives to the legacy of historical and social science accounts that reify a

"black underclass" and "cultures of poverty" (e.g., Moynihan 1965) include intersectional accounts of race, class, and gender-based structures (Mullings 2005, Martin 2006). This is also evident in Rouse's work (2009), where she interrogates the trope of sickle cell disease patients as a community of sufferers. Throughout this project, I have sought to identify how political contexts, bureaucratic protocols, advocacy opportunities, resource capacities, social imaginaries, and historical legacies (Nathanson 2007) have also conditioned the translation of experimental therapies to viable treatment options within health care institutions. Taking up standpoint feminism provides a means for *studying up* (Nader 1972[1969]; e.g., Harding 2008), by starting from the lives of women and post-colonial subjects as fundamental to scientific knowledge production, while taking seriously their politics during one's research. As such, in-depth interviews and oral histories were essential source material to meet the challenge of representing colonized subjects (Abu-Lughod 1991, Portelli 1991, Smith 1999).

This research also benefitted from anthropological contributions to social studies of science (e.g., Latour 1987, Fleck 1979[1935], Martin 1991, Martin 2001[1987]). The ethnographic work of Mol (e.g., 2002, 2008) provided particularly helpful examples for how to apprehend ontologically the scientific and clinical interactions that stabilize diseases and their therapeutic interventions as facts. Her work informs the instability of applying treatment intensification and other forms of care in the practice of sickle cell disease medicine. An ethnographic approach provided broad analytic areas to compare how the production of expert knowledges rendered transplant risks as knowable—and therefore governable—across research, advocacy, and clinical environments.

From 2012 to 2017, I conducted participant-observation across a range of clinical settings, research meetings, and advocacy forums. This enabled me to remain conversant with

the evolution of clinical practices over time. The primary clinical field sites included four pediatric centers—two in the U.S. and two in France—that provided disease-specific care for children with sickle cell disease, including transplant. My participant-observation encompassed a range of activities and clinical contexts in both countries. This included accompanying health care providers during their outpatient clinic, where they provided subspecialty care for their patients with sickle cell disease. I spent significant time with families in day hospital settings, where patients received post-transplant care and transfusion therapy. In the U.S., I had the opportunity to observe and get to know patients and their families during their inpatient stays on the transplant unit. I also attended the respective staff meetings, composed of interdisciplinary clinical teams, at all four centers. Participant-observation from the two French health care centers was temporally concentrated in 2013. The fieldwork I conducted at the two U.S. centers was intermittent and longitudinal, starting in the fall of 2012 and resuming in fall 2013 (upon my return from France) and on through 2015. In both countries, participant-observation at the respective centers often entailed alternating between sites within the same week, sometimes during the same day. In addition, since 2013, I have virtually attended a quarterly conference call conducted by French physicians as they discuss cases of patients with sickle cell disease who are potential candidates for transplant.

This study not only examines the technique of sickle cell medicine and transplant, but also attends to the discursive process of informing patients and families of their therapeutic options, negotiating the risks and benefits of treatment intensification, and obtaining consent for these procedures. In addition to clinical contexts, these discussions also took place at support group meetings and educational outreach events sponsored by local hospitals and advocacy organizations, where I had the opportunity to observe and engage in interactions among


Figure 1. Sickle cell disease awareness-raising event, partially sponsored by a commercial center in France. Banner reads: "*Drépanocytose (Maladie hereditaire du globule rouge)* [Sickle cell disease (Hereditary red blood cell disease)]."

community-based advocates, health care providers, and patients and their caregivers in local and regional contexts (see Figure 1). These debates also were prominent concerns at regional and international conventions of major professional and advocacy organizations, such as the Sickle Cell Disease Association of America (SCDAA), the American Society of Hematology (ASH), the Foundation for Sickle Cell Disease Research (FSCDR), as well as annual meetings of *le Congrès Drépanocytose* and the BMT Tandem Meetings.[14] These sites fielded international audiences, where social movements and advocacy projects intermingled, to varying degrees, with

basic science and clinical research presentations and served as foci to examine regional and trans-national flows of clinical and scientific knowledge production.

This project also draws upon archival materials from the scientific literature, including research presentations, on sickle cell disease and transplant medicine. Familiarity with these studies was crucial for recognizing their role as cited evidence within clinical environments and at scientific meetings, especially when the implications of newer scientific findings became contested sites for ongoing clinical practices and updating pre-existing care standards. By conducting fieldwork across a variety of care and research environments, I positioned this project to recognize and contextualize practice differences across institutions. Through a comparative ethnographic approach, I had the opportunity to observe where transplant and other forms of treatment intensification were being encouraged and discouraged, as well as the practices that produced their active and passive recruitment.

I recruited interview participants from outpatient specialty clinics and inpatient transplant wards; at community-based support groups and educational forums for affected patients and families; and regional, national, and international meetings involving sickle cell research, clinical care, and patient advocacy. A significant portion of these participants (who included patients, parents, and health care providers) also consented to the participant-observation component of this study. In turn, my participant-observation encompassed a broader cohort of providers, patients, and families who attended the U.S. and French health care centers that provided specialized medical care to children with sickle cell disease. Hence, this study's protocol was IRB-approved in the U.S. and France for all locations.

I am indebted to my study participants, who included adults with sickle cell disease, adult parents and their assenting children with sickle cell disease, community advocates, researchers,

and health care providers including physicians, nurses, psychologists, and social workers. In addition to participant-observation in clinical settings at large, I conducted longitudinal follow-up of 10 families as they underwent their transplant hospitalization and post-transplant care in the U.S., as well as semi-structured in-depth interviews that included 32 research interviews in France and 25 research interviews and oral histories in the U.S.[15] Oral histories will be gifted to the Columbia Center for Oral History of the Columbia University Libraries and available for the public record.

**Organization of the study**

This dissertation consists of four chapters. A summary of findings from this research follows:

Chapter 1, "Sickle Cell Disease [*La drépanocytose*]: Biopolitics, Old and New," explicates the contemporary contexts that made this particular study design possible. I describe the biomedical renderings of sickle cell anemia as a disease process and provide a brief history of its biopolitics, emphasizing the past 40 years in the U.S. and France. This includes civil and territorial struggles for recognition and rights, the transnational migration of patient populations and medical knowledge, and state-based provisions for health care services and research priorities that have been specified for sickle cell disease in both countries. Finally, I outline the major forms of treatment intensification available for sickle cell disease, including hematopoietic cell transplantation and provide the justification for comparison between the field sites.

In Chapter 2, "The Politics of Anticipation: 'Prevention As Treatment' and Making Care Matter," I introduce *anticipatory politics*, an analytic concept I employ to identify the affects and practices that respond to and recalibrate expectations for the future lives of children. This

includes their role in producing the diagnostic interventions, care practices, and health policies that are credited for improving childhood survival for sickle cell disease in high-income countries. Using newborn screening and stroke prevention as case studies, I enlist anticipatory politics to interrogate how their scientific and clinical knowledge production have been informed by affective economies. This chapter exemplifies the methodological implications of anticipatory politics as a research strategy that links orientations toward the future to ongoing and historic production of clinical strategies and disease categories. An excerpt from this chapter was published in *Science, Technology, and Human Values* (Jae 2018).

In Chapter 3, "'Just' Information: The Practice and Process of Making Treatment Intensification Possible," I demonstrate how efforts to intensify treatment for sickle cell disease become transposed as clinically viable practices and processes within health care institutions. Health care providers' duty to disseminate information to patients is often apprehended as compassionate or ethical performance. I argue, however, that the act of informing patients of their treatment options is inherently political and needs to be conceived as such to uncouple treatment technologies from the reproduction of social inequalities. Using the positive deviance research method, this chapter applies process theory (e.g., Brown and Deguid 2017[2002]) to inform how transplant knowledges are potentiated through institutional practices and politics.

Finally, in chapter 4, "Transplant Candidates, Treatment Collectives: Embracing the Problem of Belief," I address the "problem" of belief (e.g., Good 2003[1994]) as encountered in clinical and experimental contexts. I propose an alternate rendering of this concept as a constructivist relationship comprised of belief, hope, and risk. Here, I disentangle the structures of experimentation that are producing transplant strategies distinct to French and U.S. contexts. This includes elucidating how research environments, professional motivations, and health care

institutions act as *treatment collectives* (akin to Fleck's *thought collectives*, 1979[1935]) that work to expand and innovate but also protect and conserve existing experimental protocols and clinical care standards.

In addition to substantiating the complexity that new knowledge introduces to the care and practice of medicine, this study contributes to efforts in feminist science and technology studies to redirect attention to care as a significant constituent of scientific inquiry and its moral concerns (e.g., Harding 2008, Mol 2008, Puig de la Bellacasa's 2011, Mattingly 2013, Laugier 2014). In modern life, essential provisions such as vigilance and care are still relegated to domestic, feminine, and private spheres (Harding 2008); at best, these are underrecognized for their significance in promoting health and prolonging life, and, at worst, they are conflated as non-scientific concerns. Anticipatory politics is a research analytic that responds to these challenges, which I articulate through this multi-sited ethnography of scientific practice across historical, experimental, and clinical settings. The prospect of benefitting from life-prolonging interventions for sickle cell disease requires the availability of scarce resources, even after the necessary protocols and institutions had been sanctioned as national health policy. This research demonstrates the constraints of realizing benefit from preventive and treatment breakthroughs, whose success depended upon the labor and expertise composed from vigilance and care.

In this dissertation, I examine how researchers, clinicians, and patients and their families came to develop, follow, and promote the unconventional practice of hematopoietic cell transplantation as a treatment for sickle cell disease. This study contributes to scholarship on the biopolitical implications of introducing new knowledge to the material and discursive practice of medicine, with attention to health care systems that service vulnerable populations. An underlying goal for this project has been to trace the elusive manifestation of structural

inequalities in clinical care and practice. Undoubtedly, national and regional contexts matter. Yet the demographic predilection for sickle cell disease in the U.S. and France, and the comparable health policy commitments extended to pediatric patients in both countries, makes it possible to conduct this study as a comparison of institutional practices. As indicators continue to lag for racial and ethnic minorities to receive recommended interventions and best practices, even after accounting for socioeconomic and clinical confounders, this research distills how institutional power dynamics and patient-provider relationships become operationalized in the clinical setting. I demonstrate how the development of treatment practices reflects ongoing tensions between clinical power and decision-making and the ethical duty of patient autonomy and choice in treatment selection. Ultimately, the obligations of informed consent lie not only in ensuring that patients are educated on the risks and benefits of proceeding with an intervention, but how and whether these options are recommended to patients and families at all. Health care institutions that successfully recruit patients to intensify treatment produce unique processes that not only routinize the way families become informed about their care options; they also implement unique treatment collectives and praxis to support their delivery.

As this research demonstrates, the clinical impact of the scientific breakthroughs routinely credited for extending survival are also structured by national health policies, regional economics, local access to health infrastructure, and the institutional politics of caregiving that in turn produce variation to clinical practice downstream. Implications from this work include relocating secular scientific priorities toward innovation not merely as the embodiment of positivist objectives to improve health, but also a means for practitioners to advance professional interests and perform medical authority and expertise. This includes understanding the practices and processes that can determine whether information about treatment options is provided in

certain instances and withheld in others. In elaborating how complex treatment options, such as transplant medicine, were translated to clinical practice for sickle cell disease, findings from this study also suggest ways to make technologized care more equitably available.

As I elaborate in Chapter 1, both U.S. and French governments mandate comprehensive health care to children with sickle cell disease. The similarities in respective public health policies and health infrastructures for affected pediatric populations make it possible to conduct this ethnography as a comparison of health care centers. In order to understand how institutions come to produce their respective research priorities and clinical care standards, this work demands analytic frameworks that can account for the social, political, organizational, and interpersonal factors that are used to manage risk and access technologies such as transplant medicine. In this way, my examination of institution-specific differences in the utilization of hematopoietic cell transplantation and other forms of treatment intensification provides a unique lens to compare how divergent standards of care are emerging with the co-production of technological innovation, clinical knowledge, medical authority, ethnicized discourses, and state-level policy. With these contexts in mind, this multi-sited ethnography examines the translation of hematopoietic cell transplantation to the practice of pediatric sickle cell medicine at the locus of health care institutions in metropolitan New York City and Paris.

# 1

## Sickle Cell Disease [*La Drépanocytose*]: Biopolitics, Old and New

> *la maladie impossible de passer à côte, celle-ci vous rappel toujours à l'ordre: crises, colère, limites, frustrations, douleurs, incomprehension* [the disease impossible to ignore, that brings you to heel: crises, anger, limits, frustrations, pain, incomprehension]
>
> Leslie, *ex-drépanocytaire*,[16] 2013

According to most recent population estimates, sickle cell disease [*la drépanocytose*] affects nearly 100,000 individuals in the United States (Hassell 2010), 22,000 in France (Filière de Santé MCGRE 2018),[17] and millions worldwide. In the U.S., newborn screening detects sickle cell disease in approximately 2300 births annually; in continental France, this statistic has increased to over 400 births per year**.** By global comparison, an estimated 25,000 to 30,000 Brazilians are affected by sickle cell disease; whereas 100,000 infants are born with sickle cell disease each year in Nigeria alone. In high-income countries where newborn screening and access to comprehensive care are available, most children with sickle cell disease now reach adulthood. Even under these improved circumstances, however, mortality increases dramatically with each adult decade. Since 2000, adult life expectancy for sickle cell disease has plateaued, and the median age at death remains in the 40s (Platt *et al.* 1994, Powars *et al.* 2005, Lanzkron *et al.* 2013). In addition to a shortened adult life expectancy, people with sickle cell disease still face significant socioeconomic challenges, including inadequate education from lost days at school due to medical complications and poor health-related quality of life (McClish, *et al.* 2005, Panepinto *et al.* 2009, Amr *et al.* 2011). This research demonstrates how the conditions that have

improved outcomes for sickle cell disease in childhood concomitantly have shifted the risk tolerance of patients, families, health care providers, and researchers towards interventions to improve upon survival and anticipated quality of life in adulthood.

Sickle cell disease has predominated among self-identified Black and Latinx in the U.S., where it is estimated to affect 1 in 365 Black births (CDC 2017). As of 2012, as a result of more recent decades of migration, *la drépanocytose* became the most common genetic disease [*la première maladie génétique*] in France (Bardakdjian-Michau *et al.* 2009). France and the U.S. are affluent countries with complex economies that boast sophisticated health infrastructures and established research environments. Among advocates of sickle cell disease in both countries, however, inequities in health outcomes remain a significant concern. This is not only an artifact of the lower incidence of sickle cell disease relative to higher prevalence countries, but also in terms of popular recognition and dedicated professional and research attention, including pharmaceutical research and development. In the U.S., inadequate access to chronic care management continues to plague the adult population. Until recently in France, sickle cell disease was relegated a neglected disease (e.g., Lainé 2004, Filière de Santé MCGRE 2018) that was exoticized as a Third World malady by French physicians (Bachir and Galacteros 1990, Fullwiley 2011).[18] The U.S. and France continue to share in the symbolic and material production of a disease whose clinical care, scientific investigation, and political investments are intertwined with broader national histories and social contexts.

Against this background, I examine how the health care systems of two wealthy nations are making hematopoietic cell transplantation, a risky and expensive, but potentially curative, procedure available to children also largely drawn from minority and immigrant populations. In this chapter, I first summarize the biomedical pathophysiology for sickle cell disease and present

the three primary treatment methods of treatment intensification currently offered to patients, with specific attention to transplant. Next, I provide the premise for the comparative study design and introduce the field sites. Hematopoietic cell transplantation has been available to children with sickle cell disease in the U.S. and France for over two decades; to date, only about one thousand cases have been documented in the medical literature (Gluckman *et al.* 2017).[19] Remarkably, over half of the published cases have taken place in Europe, with the majority of these performed in France (Gluckman *et al.* 2017, Vermylen *et al.* 1998, Mischlitch and Walters 2008, Bernaudin, *et al.* 2007, Bernaudin, *et al.* 2010). This research interrogates how, despite the similarities in health care access and clinical care standards for their pediatric population, institutions that otherwise share leadership in research and clinical care in the U.S. and France have nonetheless produced divergent treatment intensification processes across their respective sickle cell centers, providing rich sites for comparative investigation.

**Sickle cell disease biopolitics**

Sickle cell anemia is the biomedical name given to a condition characterized by anemia and the appearance of sickle-shaped red blood cells that was first described in a case over a century ago (Herrick 1910). Today, the term sickle cell disease designates a category of inherited hemoglobinopathies, or pathologies of hemoglobin. The knowledge production for sickle cell disease is an enduring example of a biologically-based disease category that has co-produced social and scientific notions of race, heredity, and identity that have conflated with a racialized body politic and discriminatory public policies. This interdependence of social and scientific knowledge production spanned the recognition of its recessive mendelian inheritance pattern in

the 1940s (e.g., Neel 1947, Beet 1949); its characterization as a prototypical molecular disease in 1949 (Pauling *et al*. 1949); the identification of its evolutionary links to malaria resistance (e.g., Livingstone 1958); and its legacy as a racialized and ethnicized biomedical disease category (e.g., Wailoo 2001, Wailoo and Pemberton 2006, Tapper 1998, Nelson 2011).

The use of biomedicalized disorders and genetic conditions to stake claims for state recognition and improve access to care are examples of biological citizenship in the neoliberal era, as articulated by Petryna (2002) and others (e.g., Rose and Novas 2005, Creary 2017). My own project builds upon Foucaudian perspectives that interrogate the expert knowledges that brought modern concepts of risk into being (e.g., Lupton 2013[1999]). Foucauldian governmentality (1991) considers the ways that discourses and institutions, which initially provided biopolitical strategies for modernizing Western states, have implicated self-regulatory norms of health and behavior alongside the expansion of neoliberal economic policies and retrenchment of the welfare state. Useful articulations of Foucaudian technologies of the self have included "moral pioneers" (e.g., Rapp 1999, Franklin and Roberts 2006) and "flexible eugenics" (e.g., Taussig, Rapp and Heath 2003, Fullwiley 2004) that have emerged from contemporary entanglements with newer reproductive technologies, genetic research, social movements, and their private and public partnerships.

Alternatively, Novas (2006) more broadly conceptualized "political economies of hope," providing this umbrella phrase to characterize the activities of contemporary biosocial movements, composed of individuals and groups joined together by the commonalities in their biological selves. In turn, these organizations have asserted their advocacy or "biological citizenship" (Rose and Novas 2005) by means of capitalizing their scientific agendas and research expertise. Novas (2006) outlines case studies of patient organizations whose political

and economic activism served to de-territorialize and privatize more traditional practices in the conduct of scientific research, leading to as much a reordering of expert knowledge as of funding streams. Rabinow extended this logic in coining the term "biosociality" and predicted an eventual "overcoming of the nature-culture" divide (Rabinow 1996:99), when technoscience begins to apply its correctives directly upon the human genome. An ongoing example that calls upon biosocial analytic contingencies is the biocapitalized arena of gene therapy, which has been an active area of investigative research and investor funding, with recent clinical trials for children with sickle cell disease and thalassemia conducted in France and for adults with sickle cell disease in the U.S.[20]

Yet sickle cell disease has historically symbolized Black suffering in the context of civil rights foment and activism (e.g., Wailoo 2001, Tapper 1998, Nelson 2011) in the U.S., and this adds complexity to these more recently described biopolitical concerns. Sickle cell disease endures as an example of "old" genetic knowledge constituted as politicized illness experience, and contemporary iterations continue to carry over longstanding sociobiological categories of Blackness. Hence, biomedical histories of sickle cell disease demand analytic attention to the intersection of race and class-based disparities and their contribution to stratified care systems and research priorities (e.g., Vaughn 1991, IOM 2003, Duster 2003). In addition, local and national understandings of sickle cell disease also need to account for the post-colonial legacies and transnational political economies that inhabit the contemporary global health stage. For example, Creary (2017) has articulated the ongoing rights claims on behalf of sickle cell disease advocates by means of "biocultural citizenship," where redressing past neglect and under-recognition on the part of the Brazilian state has become an essential concern for the Black health movement. In articulating these politics as biocultural, Creary demonstrates the symbolic

and material exceptionalism that sickle cell disease has introduced into Brazil's public health agenda. The impetus for "racial health reparations" (Creary 2017:123) also serves as a rebuke to the violence of colonialism due the singularity of sickle cell disease genetics. In this role, sickle cell disease serves as embodied evidence of the nation's ancestral links to Africa and the repercussions of slavery.

Sickle cell disease is comprised of multiple genetic mutations to hemoglobin that produce analogous sickling deformities to red blood cells. The most common genotype for sickle cell disease is hemoglobin SS disease (Hb SS), also known as sickle cell anemia, and results from the autosomal recessive inheritance of a point mutation to chromosome 11 affecting the gene that codes for beta globin (β-globin). Beta globin comprises two of the four protein chains that make up the hemoglobin molecule. Together, these four globin chains coordinate with iron-containing heme groups, enabling hemoglobin to bind and release oxygen. Rich in hemoglobin, red blood cells procure oxygen from the lungs and transport this vital element via circulation to tissues throughout the body. With the substitution of a single nucleotide, this recessive mutation alters the folding structure and electrical charge of the β-globin protein to instead produce hemoglobin S within the red blood cell.

The typical hemoglobin molecule, called hemoglobin A, remains stable whether or not it is bound to oxygen. This permits red blood cells to maintain their pliant surface area even during periods of relative oxygen deficit. By contrast, when hemoglobin S molecules release oxygen, they clump together, or polymerize, to form rod-like structures that stiffen the red blood cell to the eponymous sickle shape. A range of environmental and embodied stressors can shift the proportion of unbound hemoglobin in the blood: physical exertion and exposure to colder temperature are common scenarios that prompt the body's organs and tissues to demand more

oxygen from red blood cells, while fewer oxygen molecules are available to red blood cells in the context of lung disease or at higher altitudes. In absence of inheriting at least one typical β-globin gene to produce hemoglobin A, which is protective, hemoglobin S polymers distort the red blood cells during these reduced oxygen states. By contrast, heterozygous carriers of the sickle trait, or hemoglobin AS, are (with rare exceptions[21]) considered healthy.

Genetic studies have identified at least five haplotypes associated with the mutation that produces hemoglobin S across the regions where sickle cell disease has been most prevalent over time, including Sub-Saharan Africa, the Mediterranean (including Southern Europe), the Middle East, and South Asia. The appearance of hemoglobin S mutations is hypothesized to have coincided with the development of agriculture-based societies that became malaria endemic regions. In these settings, the persistence of sickling hemoglobin mutations is attributed to the survival advantage conferred to heterozygous trait carriers, who still contracted malaria, but were protected against its fatal complications through the partial presence of hemoglobin S in the red blood cells (Allison 1954, Livingstone 1958).

Upon recognition of the five haplotypes for hemoglobin S came the initial expectation that could help predict an individual patient's disease severity or response to treatment (Gabriel and Przybylski 2010). The presence of polymorphisms in the promoter regions of the nearby fetal hemoglobin (γ-globin) genes have been associated with the Senegal and Arabian/Indian haplotypes of sickle cell disease. Because higher fetal hemoglobin levels can be protective to the complications of sickle cell disease, this led to the hypothesis that certain hemoglobin S haplotypes with this association were predictors of milder disease; however, "there is so much phenotypic variation among individuals with a common haplotype that this hypothesis has proven unreliable" (Gabriel and Przybylski 2010). Fullwiley (2011), whose work was based

primarily in Senegal, also addressed the challenge of extrapolating sickle cell disease severity according to mutation ancestry to implicate the complex social ecologies that ultimately contributed to patients' outcomes.

In an age of genome-wide association studies, Lock (2005) has argued recently for analytic vigilance against the neo-reductionism that accompanies data mining for genetic markers of disease susceptibility. As a case example, Lock identifies the limitations of ongoing efforts to demarcate prognostic significance to candidate genes for Alzheimers disease. Among the limitations inherent to these types of large scale investigations is that "given the current state of scientific knowledge, predictions about being at increased risk for complex, adult-onset neurological disease based on the presence of a specific susceptibility gene in one's genotype are no more accurate than fortune-telling" (Lock 2005:S48). Lock implicates the methodological contingencies that foreground genome-wide study and render the provisional significance of candidate genes as no better than "a return to divination" (2005:S47). A similar critique has borne out in the search for potential genetic modifiers of sickle cell disease severity. Unlike Alzheimers disease, the mendelian inheritance of sickle cell disease has been established. Nonetheless, phenotypic variation in disease expression on the individual level continues to resist predictive reductionism at the genetic level, however nuanced.

Hemoglobin SS disease (Hb SS), or sickle cell anemia, is the homozygous form of the S type recessive mutation. Hemoglobin $SB^0$ (Hb $SB^0$) is a form of thalassemia that is phenotypically indistinguishable from Hb SS disease, and therefore also eligible for transplant. By contrast, Hemoglobin SC disease (and its own phenotypic equivalent Hb $SB^+$ thalassemia), another relatively common sickling variant, has been characterized as a milder form of sickle cell disease. Today, the average life expectancy for Hb SC disease averages two decades longer than

for those with sickle cell anemia.[22] Yet even those who share the milder genotypes for sickle cell disease, such as Hb SC, still experience wide variations in their clinical course. At best, the observed variability in health outcomes can only be partially attributed to innate disease severity. As a result, the unpredictability of patients' clinical severity, complications, and long-term prognosis continues to thwart the search for a genotypical sickle cell disease, in spite of its monogenic inheritance. In response, my research articulates how the epidemiologic shift towards improved survival in children with access to comprehensive care resembles less an unnatural history of sickle cell disease than a stratified bricolage of interventions inextricable from their social and political worlds.

While not a focus of this study, scholars such as Tapper (1998), Wailoo (e.g., 2001), Nelson (2011) have analyzed the significance of sickle cell disease in historical context, where advocacy for improved health care for sickle cell disease became a matter of political concern and an example of embodied activism during the Civil Rights era. Sickle cell disease gained social and political attention in the U.S. as a symbol of black suffering when civil rights activists, including the Black Panthers, took up the cause of awareness-raising, and, with mixed success, community-based screening for the disease among African Americans (see Nelson 2011). These activities became co-opted by the federal government, when President Nixon signed the National Sickle Cell Disease Control Act into federal law, "pledg[ing] that this Administration would reverse the record of neglect on this dread disease" (Nixon 1972).

In their comparative analysis of ethnicity and race across genetic diseases in the U.S., Wailoo and Pemberton (2006) ascribe the uptick in research interest in sickle cell disease to the post-war discovery of its molecular defect (Pauling *et al*. 1949). This breakthrough had predated the identification of DNA, earning Linus Pauling his Nobel prize in chemistry, but it also gave

way to expectations for an efficient corrective, notwithstanding an outright cure. It was in the setting of heightened scientific and political expectations for sickle cell disease that Wailoo and Pemberton (2006) frame subsequent decades of unfounded hype for ultimately disappointing chemical compounds, such as urea and sodium cyanate in the 1970s. The proponents for these interventions, however, failed to convince scientific and clinical communities of their safety and effectiveness. Wailoo and Pemberton describe these treatments as examples of the unmet promise of sickle cell therapeutics commensurate with the pivotal discovery of its molecular and genetic properties. Indeed, the deceptive simplicity of initial scientific understandings of sickle cell disease genetics proved to undertheorize the implications of a complex pathophysiology that remains an area of ongoing biochemical investigation. I briefly summarize this below.

**A brief pathophysiology of vaso-occlusion**

The characteristic elongated appearance of sickled red blood cells was made visible to the human eye with the available microscopic instruments over a century ago (Herrick 1910). These earlier descriptive findings contributed to the initial, largely mechanical, representations of sickle cell disease pathology. Even today, the vaso-occlusive crisis (or VOC, most commonly experienced as pain crisis) denotes one of the fundamental pathophysiologic complications of sickle cell disease. A typical schematic of the phenomenon of vaso-occlusion still portrays a blood vessel splayed in cross-section, resembling a bobsled run piled high with crescent-shaped blood cells (see Figure 2). As illustrated in Figure 2, sickled red blood cells, distorted from oxygen deprivation, are depicted as mechanically obstructing the lumen of the blood vessels. This

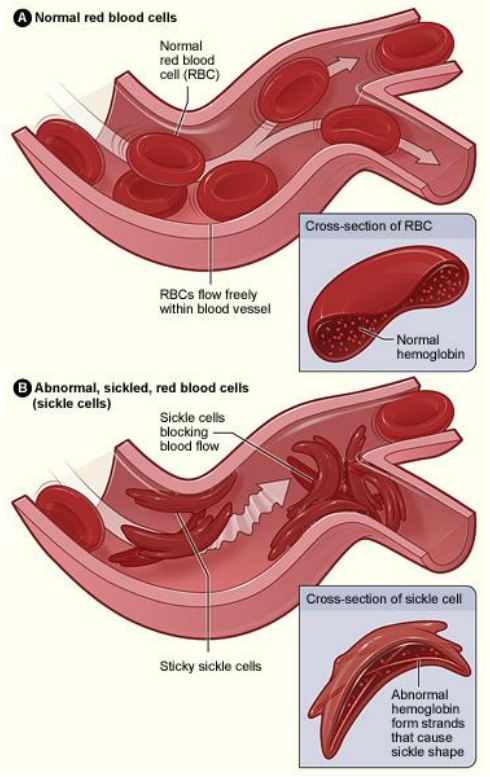


Figure 2. Schematic of sickling red blood cells. (Source: The National Heart, Lung, and Blood Institute (NHLBI), U.S. Department of Health and Human Services)

portrayal remains among the most widely recognized representations of the sickle cell pain crisis, which typically manifests as bone pain due to vaso-occlusion of skeletal circulation. The repercussions of vaso-occlusion, however, extend to organ systems throughout the body, and over decades of research, the understanding of the biochemistry of vaso-occlusive disease has gained significant complexity.

A more comprehensive pathophysiology of vaso-occlusion enlists the molecular biology of tissue inflammation and the clotting response as these interact with the "stickiness" of red blood cells that contain hemoglobin S. Hemoglobin S renders both mature red blood cells as well as immature forms, called reticulocytes, more prone to adhering to blood vessel walls. This stickiness even occurs when red blood cells are sufficiently oxygenated to maintain a rounded

structure. When reticulocytes and mature red blood cells adhere to the blood vessel wall, not only do they entrap rigid, sickle-shaped cells, but the occluded cells and ensuing damage to the vascular architecture attracts white blood cells and platelets to the region. Upon arrival, the activated white blood cells and platelets release their own inflammatory signals that further the cascade of tissue damage, inflammation, blood clotting, and oxygen deprivation (Manwani and Frenette 2013:3894). Furthermore, the physiologic means for reducing a clot within the blood vessel has its own consequences when blood flow is suddenly restored and induces reperfusion injury to tissues that had just been compromised by lack of oxygen. In this way, sickle cell disease provokes ischemia-reperfusion injury, a cycle of obstructed circulation followed by inflammatory stress with re-exposure to oxygen. Watershed regions—where the smallest veins exit the capillary beds of kidneys, lungs, brain, and bone—are especially vulnerable to these events.

Red blood cells laden with hemoglobin S also are more prone to breaking apart, an event called hemolysis. During hemolysis, the contents of red blood cells, including iron and other free radicals, are released directly into circulation and compound the inflammation within the blood vessel walls. The chronic hemolysis of sickle cell anemia also reduces the normal 120-day lifespan of red blood cells to fewer than 30 days. In response, the bone marrow's capacity to offset this constant premature loss of red blood cells is partial at best, leading to anemia. Furthermore, in the event of acute stressors such as blood loss and bone marrow suppression caused by certain viral illnesses and medications, these already overextended compensatory mechanisms can fall short, leading to a precipitous drop in red blood cells and potentially life-threatening organ failure.

Vaso-occlusion and hemolysis denote two of the pathologic events currently described as

prototypical in sickle cell disease. Either can occur in isolation, and each can induce the other during the propagation of vaso-occlusive crises. The bone pain indicative of skeletal involvement and more typical of the sickle cell pain crisis is but one of the severe complications of vaso-occlusion. Other sites of vaso-occlusive crises include the lungs during acute chest syndrome, a leading cause of death for adults, as well as the brain, due to strokes. The effects of hemolysis, ischemia-reperfusion injury, and inflammation incur cumulative damage to the blood vessels and the organs they service over time. Some of these sequelae include pulmonary hypertension due to the loss of elasticity of the lung vasculature and sickle cell nephropathy that can lead to renal failure that requires dialysis and kidney transplantation. As life expectancy for people with sickle cell disease has improved, due in large part to preventive interventions in childhood (see also Chapter 2), the long-term complications of sickle cell disease are becoming more prevalent, particularly among adults.

By the close of the twentieth century, two potential treatments for sickle cell disease were beginning to cross over from experimental realm to clinical practice for sickle cell disease: hydroxyurea, an oral chemotherapy that had been repurposed as a treatment for sickle cell disease, and bone marrow transplantation. Both interventions initially were developed to treat cancers and other blood and metabolic disorders, and as of the 1990s, their application to sickle cell disease was still relatively new and controversial. Wailoo and Pemberton's (2006) critique speaks to the advent of hydroxyurea and transplant trials during these earlier stages of their knowledge production, and reflected the uncertainties of efficacy, risk, and the unanticipated consequences of the clinical translation of these therapies from experimental trials. Two decades later, this dissertation offers an updating of both of these technologies.

**What is "treatment intensification" [*l'intensification thérapeutique*]?**

In 2011, I attended a grand rounds lecture reviewing the state of pediatric care for sickle cell disease, one that was part of a weekly educational series directed to physicians and trainees of a U.S. hospital. The invited speaker was a hematologist from a local pediatric sickle cell center. She began her presentation by noting that since the 1990s, there were only three available treatments for sickle cell disease: chronic blood transfusions; hydroxyurea (in France: hydroxycarabamide), an oral medication that can increase blood levels of fetal hemoglobin; and bone marrow transplantation. Twenty years later, she continued, these same three options remained the only ones available. Her remarks were intended to be provocative: that the absence of alternate treatments was a disappointing marker of the state of sickle cell disease therapeutics that, at best, could be taken as a call to action; at worst, as an invitation to cynicism.

Either assessment obscures that the applications for blood transfusions, hydroxyurea, and transplant for sickle cell disease have all undergone significant modification, expansion, refinement, and transformation, even as intervening decades failed to bring new drugs to the pharmaceutical market.[23] Consider the role of blood transfusion: previous longstanding practice called for the prompt administration of blood as the treatment of choice for painful crises, or vaso-occlusive crises. Today, blood transfusions are no longer a first line treatment for vaso-occlusive crises, and excessive exposure to blood products is considered an unnecessary risk to patients. Among the risks of blood transfusion are the possibility of exposure to blood borne infections, the toxic accumulation of excess iron, and as the possibility of becoming immunologically sensitive, or allo-immunized, to genetic differences in the donor blood, which

can lead to allergic reactions to blood products, especially after repeated exposure.[24]

As the indications for transfusion have become more stringent in acute settings, quality standards for the care of vaso-occlusive crises are measured by the timely administration of pharmaceutical pain killers in an emergency room, day hospital, or inpatient setting. The patients most likely to benefit from chronic transfusion programs are those detected to be at highest risk for stroke, as diagnosed by ultrasound and MRI (as I discuss further in Chapter 2). In addition, advanced transfusion technologies such as plasmapheresis and exchange transfusion[25] can reduce the risk of allo-immunization and iron overload, two serious adverse effects of repeated exposure to simple transfusions. These procedural variations fall under the rubric of "blood transfusion," yet they comprise a much wider field of treatment possibility than this category had implied two decades ago.

Clinical trials have also expanded the safety profile and clinical potential for hydroxyurea, an older chemotherapy medication that has been reclaimed as a disease-modifying treatment for sickle cell disease. Hydroxyurea is an oral medication that suppresses cell replication, including in the bone marrow. This effect can induce immature precursors, the less differentiated forms of red blood cells, to reproduce fetal hemoglobin, or hemoglobin F. Typically, hemoglobin F is produced during gestation, until hemoglobin production shifts to adult forms, primarily as hemoglobin A, after birth. Increasing the proportion of hemoglobin F within the red blood, due to its high affinity for oxygen, can reduce the red blood cells' propensity to deform in the presence of hemoglobin S. Hydroxyurea can additionally benefit those with sickle cell anemia by inhibiting their propensity to proliferate white blood cells and platelets, as both of these cell lines can propagate the inflammation that occurs with vaso-occlusive crises.[26]

Taken together, these effects contribute to how hydroxyurea has reduced the severity and frequency of patients' vaso-occlusive complications in clinical trials, as reflected, for example, by statistically fewer pain crises that lead to a visit to a medical facility (Charache *et al*. 1995). As a result, hydroxyurea received FDA approval in the treatment of adults with sickle cell disease in 1998. More recent studies have targeted very young children for intervention, starting from nine to 18 months of age (e.g., Wang *et al.* 2011, Thornburg *et al*. 2016). These trials have demonstrated hydroxyurea to be effective in not only reducing the number of painful episodes, but also in slowing the progression of organ damage to the kidneys. Experts' response to these findings has prompted recent guidelines to recommend initiating treatment intensification with hydroxyurea in children prior to the onset of more overt symptoms of vaso-occlusive disease.[27] Some centers have achieved very high utilization rates among their patient cohorts, where they have introduced hydroxyurea as early as nine months of age. The weight of these findings has also prompted clinical investigations that placed hydroxyurea head-to-head with chronic transfusion programs, heretofore the gold standard of care for preventing strokes in sickle cell disease.[28]

In keeping with the clinical variance in patients' symptom management and longer-term prognosis of their sickle cell disease, however, not everyone who takes hydroxyurea experiences unequivocal benefit. Some who have tried hydroxyurea may undergo a partial effect. For others, an initial robust response can wane over time or become gradually subsumed by the cumulative effect of chronic sickling. Although suppression of white blood cells can be of benefit in sickle cell disease, immune suppression is an adverse effect of hydroxyurea and limits the safety of achieving a therapeutic dose, sometimes even necessitating its discontinuation.

As a young adult with sickle cell disease, Carlton Haywood, Jr, PhD was among the

earliest beneficiaries of hydroxyurea. In our interview, Dr. Haywood reflected on this form of treatment intensification, twenty years later. At age 39, his account encompassed the full trajectory of hydroxyurea's experimental potential, clinical promise, and therapeutic limitations:

> I did have a long period where [hydroxyurea] was giving me great benefit. … I started taking it before it received FDA approval… . [M]y [pediatric hematologist] … initiated the hydroxyurea conversation with me, because at that point my condition had gotten so bad that he was afraid that I would not survive another [vaso-occlusive] crisis… . [H]e actually began to talk to me and my family about the possibility of bone marrow transplantation…I mean, this is 20 years ago now. Because of the risks involved [with transplant], and because he had just seen this study published about this drug called hydroxyurea, he said, "Well, why don't we do this? The transplant will always be here as an option. Let's actually just try this medication first." So I took hydroxyurea, and I am a big proponent of it. It did do a lot of good things for me. … I feel like it helped me get through my entire college career in Virginia with only one hospital stay that whole time.
>
> Unfortunately, … as time has gone on, … either [hydroxyurea] has started to get less effective, or my condition just got worse, because even on hydroxyurea … I started to have hospitalizations on a much more regular basis… . I started to have major crises that would wipe me out for long periods of time on a more regular basis. … [J]ust three years ago, I was in the hospital again. This time, my adult hematologist … said, "You've been hit so hard, especially recently. We have to give your body a break." So she put me on a [simple] chronic transfusion therapy. … for maybe a year or two. While it helped, it didn't keep me out of the hospital. I still had hospital visits…. …[N]ow I receive a red cell exchange transfusion every four weeks…. [I]t has kept me out of the hospital, but what I'm finding is that I still do have my acute attacks… [H]ydroxyurea has done nothing for my chronic pain and my chronic pain damage, so that has been flaring up these past few years, I guess, as I'm getting older. [Haywood, Jr. with Jae, 11 April 2015]

Dr. Haywood, Jr. had provisionally continued hydroxyurea at the onset of his chronic transfusion therapies. Though combining both forms of treatment intensification is occasionally attempted

on case by case basis, this practice has not been extensively studied. The paucity of published data supporting a clinical benefit when administering hydroxyurea simultaneously with transfusion therapy, in addition to evidence that Dr. Haywood, Jr. was beginning to experience neutropenia (a sign of possible immune suppression), ultimately led his doctors to suspend this treatment:

> They stopped [hydroxyurea] a year or two ago now. I was in the hospital. They did blood work, and my white cell counts were much too low for their comfort, so they said, "Well, we know hydroxyurea can suppress the white blood cells. We know that you're on red cell exchanges. We don't know whether red cell exchanges plus hydroxyurea has any additive effect, so let's just take you off the hydroxyurea." …I've actually been off of [hydroxyurea] for a couple years now. But I am personally a proponent of it, and I do think—at least for a long time in my life, … it did help me. [Haywood, Jr with Jae, 11 April 2015]

**"Surviving a transplant" versus surviving sickle cell disease**

> If sociobiology is culture constructed on the basis of a metaphor of nature, then in biosociality nature will be modeled on culture understood as practice.[29]
>
> Paul Rabinow (1996:99)

In 1990, Susan Stewart, herself a bone marrow transplant survivor the year before, founded the Blood and Marrow Transplant Information Network (BMT InfoNet). The name for the non-profit advocacy organization evokes its online presence and mission "to give patients and survivors a place they can turn to for accurate, easy-to-understand information" [30] about hematopoietic (stem) cell transplantation. In addition to maintaining its website, BMT InfoNet sends newsletters to its e-mail listserv and organizes opportunities for patients and their families to participate in webinars, regional and national conferences, and fundraising. In organizing

these engagements, BMT InfoNet not only enlists the expertise of health care professionals and researchers, but also the lived experiences of patients and their families, in the project of making transplant knowledge available to the public.

On October 28, 2011, the subject line from BMT InfoNet's e-mail to the listserv read, "Surviving A Transplant: What You Need To Know." The title is neither ironic nor overstated: to entertain the possibility of undertaking a transplant requires patients and health care providers to acknowledge the risk of a procedure-related death; the hope of extending life is by way of its hazards, including the possibility of long-term and potentially life-threatening complications. Transplant is a sociobiological technology made possible by immunologic and/or genetic compatibility between donors and recipients. Transplant is also a biosocial practice, where the shared experience of transplant risk interlaces the lives of those with refractory cancer to patients with a mélange of inherited and acquired blood diseases and metabolic disturbances. The prospect of "surviving a transplant" draws together biosocial commonalities across otherwise disparate disease categories, as the web of conditions being treated with hematopoietic cell transplantation continues to expand.

In the wake of World War II, bone marrow transplantation emerged as a blunt instrument of medicine in the nuclear age (Perry and Linch 1996, de la Morena and Gatti 2010) that has since proliferated in its experimental design and clinical complexity.[31] The first case of a bone marrow transplant performed on child with sickle cell disease was in the U.S. in 1983 (Johnson *et al*. 1984; for more details, see Chapter 2). In the decades that followed, pediatric sickle cell disease has become the most successful application of hematopoietic cell transplantation, both in terms of cure rates and treatment-related complications. When transplant is used to treat a high-risk cancer, such as acute myeloid leukemia, the malignancy itself usually carries a high

proximate risk of death at the outset. In such cases, transplant becomes an intervention of last resort, and its treatment-related mortality regularly exceeds 30 percent. By comparison, children who currently undergo transplants for sickle cell disease experience 95 percent rates of cure and event-free survival, provided that their donors are immunologically matched siblings and the recipients undergo a myeloablative conditioning regimen (Bernaudin *et al.* 2007, Bernaudin *et al.* 2010).

Hence, procedure risks for hematopoietic cell transplantation vary depending upon the disease or condition being treated, as well as according to the type of transplant being performed. A myeloablative conditioning regimen entails high dose chemotherapy, and sometimes radiation, with the intended consequence of eliminating—ablating—the existing bone marrow. This is in contrast to non-myeloablative regimens, which use reduced doses of chemotherapy, immunosuppressant medications and antibodies, and/or radiation. Because non-myeloablative regimens are less toxic, patients experience fewer of the severe side effects of transplant at the outset. Non-myeloablative regimens are being developed so that individuals with end organ damage and/or of advanced age can be considered for transplant. But because the recipient's bone marrow is not fully destroyed with a non-myeloablative conditioning, this form of transplant confers greater risk of relapse.

Even when the intensity of the transplant experience forges links between clients of diverse disease entities, their respective post-transplant course can still diverge along these short and long-term differences in treatment-related risks and outcomes. The variation in transplant recovery was sufficiently stark to be readily apparent to the health care providers I encountered in both the U.S. and France. My interview with a social worker from a US-based pediatric center reveals some of these nuances, when she described her impression of the impact of transplant on

her cohort of patients and their families:

> I think it's very intense. … if I were a parent going through that experience, … I think it's just a frightening form of treatment. … [T]he idea of …wiping someone[']s bone marrow] out entirely and then putting cells back into them is so scary. I see a lot of our families and patients … are not the same after the experience. … Some of their personalities end up being different. I don't know if that's the body's way of taking on a new … life. Or just the experience that they'd gone through creates such havoc over their ability to move on and heal and recover and regain strength… . I'm thinking about the first year—that year is like a blur. You don't know if you're going to get over that hump… . I think the patients that are getting sickle cell transplants are able to … better bounce back, and I like seeing that level of success, but I don't think that it's the same for oncology patients. [Sickle cell patients] can have a normal life after a transplant. … I still think it's so scary.

A nurse practitioner who worked in a different U.S.-based center also registered this difference early in her career, while providing post-transplant care in the outpatient clinic. Only the children with sickle cell disease "seemed normal" afterwards, she mentioned to me, echoing the remarks of the social worker. In France, the mother of an adolescent who underwent a successful transplant recounted how the nurses in the inpatient ward said that caring for patients with sickle cell disease was like "a breath of fresh air," because of their favorable outcomes in contrast to their counterparts in oncology.

The intended action of "wiping someone's bone marrow out entirely" is to destroy the host's own blood-forming stem cells. Signs that a conditioning regimen has produced this effect becomes evident with declining cell count measurements, resulting from the cessation of new cell replication. As the population of residual red and white blood cells and platelets reach their nadir, the transplant team orchestrates a rescue of intravenously infused hematopoietic stem cells, harvested from the donor's bone marrow or peripheral blood, and in some cases, from an

infant's umbilical cord at birth. When the newly emptied bone marrow provides space for donor stem cells to engraft, the new blood cell lines can potentially re-establish in the host. With engraftment, the donor's blood-forming, or hematopoietic, cells differentiate to the progenitor forms that can replace those of the host. The white blood cells that populate the immune system also need to develop tolerance within the host, in addition to regaining the full breadth of infection and immune response activities, and this process can take a year or more. Often there is at least some degree of mixed chimerism, where donor cells and the residual immune system of the recipient eventually co-exist. Mixed chimerism is the phenomenon of acquired tolerance between donor and recipient cells. This also means that a transplant that results in a donor cell contribution as low as 25 percent of the immune system cells can still produce sufficient quantities of normal red blood cells to halt the progression of sickle cell disease.[32]

Among the predictors of the desired transplant outcome is a younger age in the patient with sickle cell disease. The sequelae of sickling red blood cells, including the cumulative effects of infarcts and inflammation to blood vessels, compromises organs systems also vulnerable to the toxicities of most transplant conditioning regimens. On the one hand, certain health care providers have prioritized children with more severe complications of sickle cell disease (where strokes are a significant concern), or who have experienced a suboptimal response to hydroxyurea or transfusion therapy, for undertaking the risks of transplant. But because the longer-term impacts of sickle cell anemia to the brain, lungs, and kidneys accumulate with age, children tend to better withstand the potential toxicities of transplant at a younger age than they do as older adolescents. Hence the timing for conducting a successful transplant and the temporal effects of sickle cell disease are intimately linked.

As results from the earliest myeloablative transplants using matched sibling donors became available, some of these studies supported an observation that improved chances for an optimal outcome—namely, survival without lasting procedure-related morbidity or relapse to sickle cell disease—held an inverse relationship with the age of the patient. This trend towards better outcomes in younger children was starkly corroborated by the retrospective findings for the first 50 patients who underwent transplant for sickle cell anemia in Belgium (Vermylen *et al.* 1998). One arm of the study included 36 children and adolescents who also met disease severity criteria to qualify for transplant, such as frequent painful crises or evidence of increased stroke risk; this cohort's median age was 8.6 years. The second study arm was composed of 14 children who did not yet meet criteria for severe disease, whose median age was two years. In the first group, overall survival and disease-free survival with myeloablative transplant using matched sibling donors was 88 percent and 80 percent respectively; by contrast, the second group's overall survival after transplant was 100 percent and their disease-free survival (without relapse to sickle cell disease) was 93 percent. The rationale for allowing children who had experienced few or no overt complications of their sickle cell disease to proceed with transplant in the second arm was that "their famil[ies] had to return to Africa where medical care would not be optimal" (Vermylen *et al.* 1998:1-2). This non-conventional inclusion criteria served as the study's ethical justification for undertaking the risks of transplant when children of families were anticipated to leave Europe; it also posed a social and political indictment of the sub-Saharan African countries whose health systems were deemed of insufficient standard to provide the comprehensive care recommended for sickle cell disease.

As published series from North America (Walters *et al.* 2000) and France (Bernaudin, *et al.* 2007) demonstrated consistency around transplant outcomes for children with sickle cell

disease when using a myeloablative conditioning regimen and matched sibling donors, new practices emerged to consider who might be eligible for the procedure in the clinical, non-experimental, setting. Though the probability of a transplant-related death can never be eliminated, as mortality and rejection rates approached five percent, these risks became sufficiently low for a growing minority of providers to begin discussing this treatment with families as an elective option. Improving transplant outcomes for sickle cell disease was occurring in an era when comprehensive care for sickle cell disease ensured that most children in high-income countries would at least reach adulthood. In clinical practice, and as this research demonstrates, these conditions together created the clinical justifications for providers to introduce the possibility of performing a transplant before severe complications of sickle cell disease were apparent in their children.

Meanwhile, the results from trials that alternate protocols, such as unrelated donors and reduced intensity (i.e., non-myeloablative) conditioning regimens were proving dismal in terms of overall survival, with severe complications including fatal infections, chronic graft-versus-host disease, and rejection with relapse to sickle cell disease (e.g., Kamani *et al.* 2012, Radhakrishnan *et al.* 2013, Shenoy *et al.* 2016). For a subset of the providers who were willing to consider transplant for their patients who already demonstrated severe sickle cell disease, this support also hinged upon the availability of a matched sibling donor and a myeloablative conditioning regimen, as these protocols had produced the most reliable results to date. An even smaller subset of providers, however, were also willing to refer families of an as-of-yet asymptomatic child. The stabilizing argument for both cases weighed the procedure risks of transplant against the likelihood of disease progression in adulthood. For the latter group,

however, it was the availability of a matched sibling donor—not evidence of childhood disease—that justified a clinical decision to transplant.

The providers who were more vocal with their reluctance to recommend transplant for their pediatric patients argued for caution by citing these same statistics on transplant-related morbidity and mortality. Michael DeBaun, a U.S.-based researcher and pediatric hematologist-oncologist, interpreted the five percent risk of death and the possibility of severe complications such as chronic graft-versus-host disease, as an intolerable risk for most children with sickle cell disease, especially given the emerging success of hydroxyurea in reducing symptoms and slowing disease progression (DeBaun with Jae, 11 April 2015; see also Chapter 4). A physician from a French sickle cell center made the point not to minimize the one in 20 probability of a procedure-related death by exhorting, "When you are dead, you are 100% dead!" Serious reservations among health care providers towards the inherent risks of transplant also translated to clinical and interpersonal processes that had impact on whether and how families become informed of this and other treatment intensification options; these instances are detailed further in Chapters 3 and 4.

In the strictest sense, for a transplant to "cure" sickle cell disease, enough donor stem cells need to remain engrafted to sufficiently replace the circulation with healthy red blood cells. By this measure, one can be cured of sickle cell disease, while experiencing significant complications of transplant, including life-threatening or difficult-to-treat infections or GVHD. Transplants have been shown to halt the progression of sickle cell disease, but they do not usually reverse previously incurred organ damage, and patients who have already experienced irreversible complications such as bone infarctions or avascular necrosis of the hip may continue to experience chronic pain or require joint replacement. While an elevated risk of stroke may be

corrected by a transplant, rehabilitation for a prior stroke still needs to be addressed after transplant.[33]

Hence, deliberations between health care providers and families on whether and when to transplant—when these discussions did occur at all—weighed the specificities of patients' past medical history and their ongoing state of health against the uncertainties of their short and long-term prognosis on current management and the known risks, possible benefits, and unpredictable course of transplant. Though the majority of transplants were successful in terms of cure, the unexpected hardship of complications weighed upon the minority of families who experienced extended hospitalizations, sometimes for months on end, due to slow engraftment, prolonged viral infections, and GVHD. I asked a mother, whose son with severe sickle cell disease had undergone a matched sibling transplant in the U.S., that was nonetheless plagued with a difficult infection and complicated recovery, if she would consider the same procedure for her other child who had a milder course of sickle cell disease. She responded without hesitation, "No." Another parent recounted how their health care provider had framed the risk-benefit calculation of undergoing transplant for her school-aged child: "She said that Aliyah had a greater chance of being alive for the next ten years without having a bone marrow transplant, but that she had a greater chance of being alive beyond that if she had one."[34]

**From transnational study to inter-institutional comparison**

Usually by this point in explaining the premise of a U.S. and France-based comparison, two interjections inevitably arise: the first, Surely the differences between the respective national health care systems can explain much of the difference in their transplant utilization; and the

second, Aren't these different patient populations? In answer to the first argument, and despite a lack of universal health insurance coverage in the U.S., both the U.S. and French governments require that children with sickle cell disease receive access to health care services, including transplant medicine. This is due to the federal title that mandates access to health insurance for this and other forms of pediatric chronic illness (see also Chapter 2), and both Medicaid and private insurers in the U.S. cover the cost of established (i.e., non-experimental) forms of transplant for children with sickle cell anemia.

Thus, an important point of comparison I draw for this study is of practice variation across health care institutions, within both countries. This is made possible by the existing similarities in patient demographics, access to advanced medical technologies, professionalization standards, and the respective national health policies that produced the pediatric care I observed in New York City and metropolitan Paris. That both countries afford children the right to access health services for sickle cell disease made it possible to conduct this study primarily as a comparison between health care institutions where differences in transplant utilization were primarily the product of locally derived pediatric care practices. And as I found, the practices and processes specific to institutions can produce striking similarities in their approach towards treatment intensification across national borders and just as vast differences in utilization between the health care centers within them. Though the clinical and scientific research environments particular to the respective countries have an impact on the production of novel transplant protocols (or worked to conserve existing ones; see also Chapters 3 and 4), whether transplant was promoted and utilized clinically was primarily a reflection of institutional structures, practices, and processes that could be observed across health care centers in both countries.

Beyond pediatric care, the challenges of obtaining insurance coverage and identifying trained adult health care providers are both formidable obstacles in the U.S. Though the French government does provide health care to adults with sickle cell disease through its public system, comparable ruptures occur during the transition from pediatric care for this and other chronic illnesses that require specialized health services (e.g., Rouse 2009). In the U.S., pediatric sickle cell centers tend to "hang on" to patients well into adolescence and early adulthood. This was the case for Carlton Haywood, Jr., whose pediatric hematologist had initiated the course of hydroxyurea therapy that helped maintain his college career. The transition from pediatric to adult medicine specialties often occurs much earlier in France, beginning after age 16. Even centers that are committed to providing specialized chronic care services to adults in both countries do not tend to engage in the degree of "hand holding" observed in the pediatric setting and expect greater independence from patients, such as in making and meeting their appointments or obtaining and taking their medications.

At the health care institutions where I conducted participant-observation in New York City and Paris, both locations also reflect the more recent migration of people from areas of high sickle cell disease prevalence, particularly Sub-Saharan Africa and the Caribbean, as part of colonial and post-colonial legacy. A fairly recent study reported that nearly two thirds of the 1, newborns diagnosed with sickle cell disease from New York State since 2000 were to foreign-born mothers (Wang *et al.* 2013):

> From 2000 to 2008, 1,911 New York State newborns … [or o]ne in every 1,146 live births was diagnosed with sickle cell disease. Newborns of non-Hispanic black mothers accounted for 86% of sickle cell disease cases whereas newborns of Hispanic mothers accounted for 12% of cases. … Newborns of foreign-born non-Hispanic black mothers had a twofold higher incidence of sickle cell disease than those born to US-born non-Hispanic black mothers

(Wang *et al.* 2013:222).

During this period, the estimated incidence for sickle cell disease by race and ethnicity was 1:230 births to non-Hispanic Black mothers, 1:2320 births to Hispanic mothers, and 1:41,647 births to non-Hispanic White mothers (Wang *et al.* 2013). As such, pediatric sickle cell centers in New York City also draw from immigrant population, with demographic similarities more comparable to Paris than elsewhere in the U.S.

Unlike in the U.S., however, French law prohibits the collection of population statistics that identify race or ethnicity.[35] This erasure has been politicized to the extent that, in 2018, the National Assembly voted to remove mention of race from the French constitution, a decision broadly based on an argument that there is but one "human" race.[36] Critics of color-blind politics have argued that denying a means to quantify the contribution of racism to economic and social disparities hinders the State's accountability to anti-discrimination projects: "The endless paradox created by a color-blind census lies in the disconnect between the official rhetoric about racial categories and the less official practices of racial enumeration and the social realities: by denying the existence of racial categories and the social significance of race, it also denies the existence of racial minorities in France and of their precarious social standing" (des Neiges Léonard 2014). As social constructs, race and ethnicity have an impact on the historical representation and quotidian realities of multicultural French society, and this includes their manifestations during the clinical encounter. My own fieldwork corroborated the findings of Nacu (2010), whose ethnographic work in Parisienne maternities found that patients were broadly categorized and stereotyped as "migrant women" by health care workers in juxtaposition with their White, middle class**,** female counterparts.

Sickle cell disease does provide legal grounds for affected individuals to receive full health insurance benefits and maintain legal residence in France.[37] Not only are health care costs covered "*cent pour cent*" [100 percent] for sickle cell disease,[38] it is also one of the medical conditions that can justify political asylum for non-citizens, provided that their country of origin is unable to provide the standard of health care that is available in France.[39] In addition to being among the medical exceptions recognized by the French government as grounds for asylum,[40] *la drépanocytose* also poses a clinical exception to the State's race-blind politics. Since the 1950s, migration from outside of Europe has increased steadily in France. These demographic repercussions have been reflected by data collection within the public health care sector in ways that are unique to sickle cell disease, including the practice of newborn screening.

Because early detection can confer significant survival benefits, newborn screening has become a critical diagnostic intervention in the practice of sickle cell medicine. Chapter 2 details the scientific history and policy development of newborn screening for sickle cell disease in the U.S., which also established this practice as standard of care in other high-income countries. Newborn screening for sickle cell disease is performed universally for all births in certain overseas departments in France, as in Guadeloupe since 1985. Since then, however, the preponderance of affected individuals in mainland France began to exceed its incidence overseas. As sickle cell disease became increasingly recognized as a significant health problem, newborn screening underwent pilot testing in metropolitan Paris, Lille, and Marseilles in the early 1990s.

In 2000, newborn screening was implemented nationally in mainland France, but remains a practice that still targets "at risk" populations (Bardakdjian-Michau *et al.* 2009) rather than performed universally. In order for a program of targeted screening to successfully capture

infants affected by sickle cell disease, and seemingly paradoxical to the prohibitions of French law, potential candidates for testing need to be identified by eliciting an infant's parental origins outside of France. Current public health guidelines recommend that health care providers refer infants for newborn screening when at least one parent reports a family history of "at risk" ancestry. This is defined by geographic boundaries elicited when parental family history originates in one of the overseas French departments and territories; from Africa, including "African ethnics" from the Americas; Southern Europe (including Portugal, Corsica, Southern Italy and Sicily, Greece); the Near and Middle East; and the Indian sub-continent (Bardakdjian-Michau *et al.* 2009:32).

In practice, however, targeted newborn screening inevitably leads to referral bias, where health care providers' diagnostic suspicion is owed, at least in part, to their response to parents' apparent markers of race and ethnicity[41] (Rochette and Charbit 1990:152). Using targeted screening, over half of births in metropolitan Paris (Île de France) undergo testing for sickle cell disease (Bardakdjian-Michau *et al.* 2009:32). These practices notwithstanding, missed diagnoses have occurred, usually due to screening and referral lapses on the part of health care providers (Thuret *et al.* 2010). In fact, two of the families I met during this fieldwork had children born in Paris who had not been referred for newborn screening and whose sickle cell disease had gone undiagnosed until their first pain crisis.[42] Sickle cell providers in France have advocated for universal screening, not only for the clinical benefit to patients by reducing missed diagnoses, but also for social costs of maintaining this practice. As Galacteros argues:

> *Mais la faisabilité du ciblage actuellement effectué repose sur la notion, totalement erronée mais solidement installée dans les esprits, que la drépanocytose ne touche que les personnes à peau noire. Les conséquences en sont désastreuses. Tous les pays à situation comparable, et pour les mêmes raisons, ont opté pour un dépistage non sélectif* [But the feasibility of targeted screening as

> carried out presently is based on the notion, misplaced but firmly established in people's minds, that sickle cell disease only affects black people. The consequences are disastrous. All other countries comparably situated, and for these very reasons, have opted for non-selective (newborn) screening]. (Galacteros 2012:311)

Despite the dearth in their demographic statistics for race and ethnicity, the French public health system collects a great deal of data on its patients. More insidiously, the annual reports for sickle cell newborn screening have been appropriated by far-right and White nationalist groups as proxy for evidence of demographic replacement (i.e., *le grand replacement* [the great replacement]) in France[43] due to non-European migration.[44] Newborn screening data collected and presented by the public health system, for example in the map published from 2010 (see

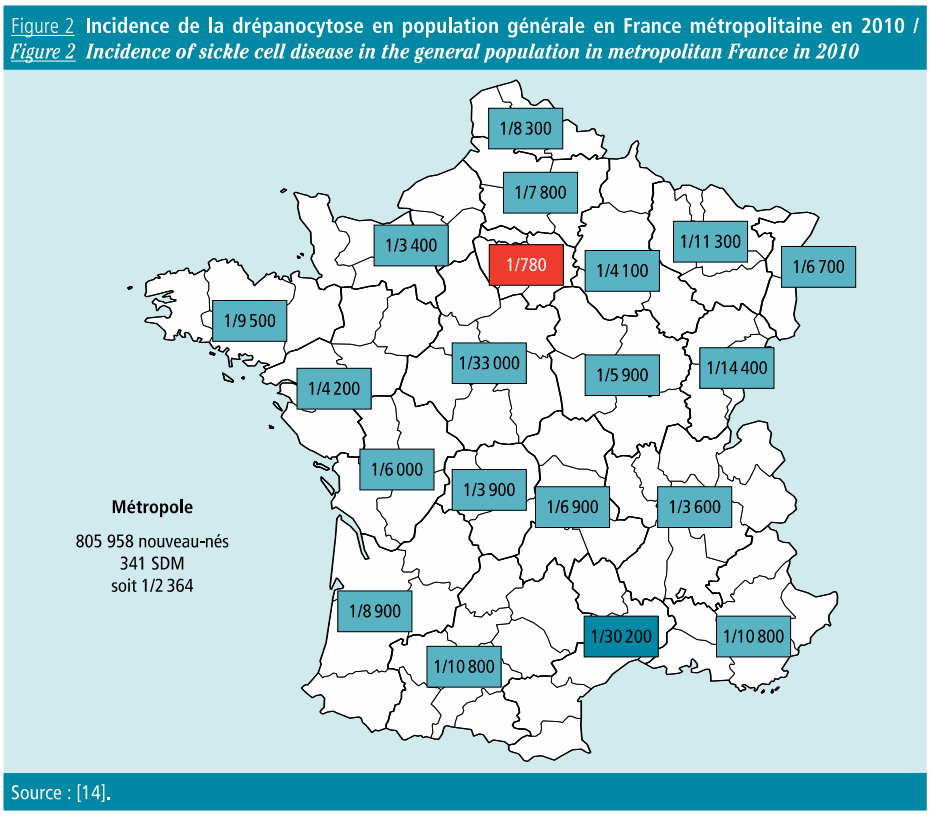


Figure 3. Statistical rendering of the incidence of sickle cell disease in mainland France, as extrapolated from 2010 newborn screening results (Bulletin épidémiologique hebdomadaire, Institut de Vielle Sanitaire, 3 July 2012:315; Source: http://www.afdphe.org/ewb_pages/a/administration-1347.php, no longer available)

Figure 3), to produce epidemiologic data to has extrapolated the proportion of sickle cell births as a statistical representation of disease incidence in mainland France. In absence of national population statistics for race and ethnicity, this and similar figures published in national newborn screening program reports also have been disseminated on anti-immigrant websites.[45]

In France, I was a participant-observer in two sickle cell reference centers that had produced very different approaches to comprehensive care, including how, when, and whether to refer families to transplant. One center, Hôpital B, had a catchment of over 1,000 patients primarily drawn from the periphery of Paris; a second, Hôpital Y, was located in the suburbs, with a cohort half the size. Yet Hôpital Y had transplanted over one fifth of its patients and, rather optimistically, anticipated 15-20 patients would undergo the procedure annually. Despite being the larger sickle cell program, and with access to an active pediatric transplant center on-site (which the other center, housed in a community hospital, did not), Hôpital B had transplanted fewer than two percent of its own patients—a rate similar to the single digit percentages I had observed being estimated at sickle cell centers in the U.S.

In New York City, I was a participant-observer at two health care institutions that housed sickle cell centers of small to moderate size, and between them shared fewer than 300 pediatric patients. Due to the inter-departmental dynamics at other local medical centers at the time of this fieldwork, University Hospital was one of the few regional centers that were regularly performing transplants for sickle cell disease. Between the two U.S.-based centers, the sickle cell program at Community Hospital was smaller and of more limited resources, both in terms of its physical plant and institutional support. Nonetheless, Dr. H had leveraged outsized ambitions to cobble together grants and extramural funding to conduct community-based programs, hire additional staff, and enhance the clinical offerings at Community Hospital's sickle cell program.

Across the four centers, I had the opportunity to observe a range of institution and provider-specific approaches towards the outpatient management of sickle cell disease. At Hôpital Y and University Hospital, and to a lesser extent at Hôpital B, this fieldwork included direct vantage points to observe transplant care in clinical and experimental practice. These included opportunities to be present during discussions between health care providers with families whose children were potential candidates and as an observer of outpatient follow-up and post-transplant care during their recovery. At University Hospital, I had the opportunity to spend significant time in participant-observation with families during their initial hospitalization and over the course of their post-transplant outpatient care. While the ideal transplant hospitalization typically lasts about a month, an inpatient stay can extend much longer in the event of infections, slow recovery of blood cell lines, graft-versus-host disease, and any combinations thereof. Prolonged hospitalizations also occurred with regularity among the patients who underwent higher risk experimental protocols, including transplants that procured unrelated donors. Across these settings, I conducted oral histories and research interviews with transplant practitioners and the families of longer-term survivors.

The populations of transplanted patients from Hôpital B and Community Hospital were smaller in relative and absolute numbers compared to their study counterparts; I also met former patients from Hôpital B and Community Hospital while they received their post-transplant care at Hôpital Y and University Hospital. These inter-institutional movements sometimes occurred by direct referral, for example when families from Community Hospital were recommended to discuss transplant options with the specialists at University Hospital. In the course of fieldwork at the respective sickle cell centers of Hôpital Y or Hôpital B, I also met families who formerly had been followed at the other hôpital, but since transferred care to their current sickle cell

program. In some instances, families had relocated to different region of Paris and attending the new center became a matter of convenience; others expressed that their move was also an intention to transfer the management of their child's care elsewhere. In a few instances, the movement of patients and their families was also occurring between the U.S. and France.

Similarly, the composition of personnel at each institution was not static. Staffing responded to changes in leadership and team dynamics; the availability of funding streams and salary lines that led to new hires and terminations; as well as individuals' professional opportunities and personal priorities. At three of the four centers, those who held leadership roles while I conducted this fieldwork have since moved to new institutions or changed career paths at the time of this writing**.** Many of the practitioners I met were passionate about their work as caregivers and researchers, and for some, their career in sickle cell disease medicine was also a calling; but this was not the case for all. At an annual meeting of the American Society of Hematology, I veered toward an entrance to attend one of the research sessions, amidst a throng of fellow attendees, when someone announced her realization that she was in the wrong place, upon reading the signage: "'Hemoglobinopathies'! I am *done* with hemoglobinopathies." The kinds of work and emotional labor that are required of many clinical fields can be the source of their greatest reward, but also lends to burn out. The affective difference between providers who came to practice sickle cell medicine because it was the only available option, rather than of their own accord, was sometimes palpable.

Transnational knowledge flows have been intrinsic to the expansion of hematopoietic cell transplantation as a site of scientific innovation and technical practice. What began as a highly experimental treatment concept has since been translated, if unevenly, to the clinical realm as an growing but still contested practice in pediatric sickle cell medicine. The transnational movement

of knowledge and practice included the professionalization of health care providers. A number of the French-trained providers I interviewed had spent a period of post-graduate training gaining clinical and research experience in North America. In addition to reading each other's publications in the medical literature (albeit in the English language journals on the part of the U.S.-based providers), international conferences for professional organizations such as the American Society of Hematology (ASH) served as recurring points of interaction for practitioners and researchers from both countries to convene and disseminate preliminary findings from unpublished research in the basic sciences, ongoing clinical trials, and health services investigations. Shortly before attending my first ASH meeting, a U.S.-based pediatric hematologist told me that the presentations on sickle cell disease from France were "always the best." International attendance also regularly occurred at regional scientific and advocacy meetings, such as the Sickle Cell Disease Association of America annual convention or *Le Congrés Drépanocytose*. In some cases, these professional ties helped to foster trans-Atlantic collaborations in research trials.

Participant-observation did demonstrate a striking difference between the U.S. and France in the organization and attendance of scientific meetings: the degree to which leadership in research, clinical care, and policy making for sickle cell disease has been assumed by Black and Latinx scholars and physicians in the U.S. The visibility of sickle cell disease in France today is partly the product of more recent demographic change; the lack of parity in certain professional spheres of sickle cell medicine implicates the opportunities available for affected groups to participate as organizers of the scientific and research agenda in France. The differences in minority professionalization that I observed between countries is at least partly attributable to a longer history of social mobilization around sickle cell disease in the U.S.

Interviews I conducted with certain U.S.-based providers elicited a more-than-intellectual-interest in their field. These individuals found in sickle cell medicine an opportunity to develop research expertise and dedicate clinical effort that overlapped with a more personal social mission or a desire to contribute to a greater good.

For some, these concerns were more explicitly connected to civil rights era activism and its immediate aftermath, particularly as sickle cell disease was becoming formally funded by the U.S. government and federal research institutions as of the 1970s. For a younger generation of providers, their professional engagement was a more direct reflection of contemporary second wave social justice movements. The work of sickle cell disease medicine also afforded the specificity of shared racial experience between certain health care providers of color and many of their patients, in addition to servicing populations who have been broadly and disproportionately burdened by the systemic abuses that underlie disparities in access to care and health outcomes. Black and Latinx clinicians, scientists, and social scientists in the U.S. have gained scholastic and scientific recognition for their contributions to sickle cell research through their professional careers. Some of these roles, as in the case of Carlton Haywood, Jr., PhD, have been assumed by individuals who themselves have sickle cell disease.

That anticipatory politics became a central analytic frame for this project also benefited from multi-sited fieldwork. As Chapter 2 elaborates, the methodological possibilities of anticipatory politics are afforded by participant-observation sustained across space and over time, including the research and advocacy meetings that promoted clinical care and scientific investigation. During the preparatory phase of my fieldwork, I had met with a senior anthropologist who noted how repetitious these meetings became while conducting ethnographic research on sickle cell disease. The point is still fair. These sites are not solely a place to present

new findings or the next cutting-edge technologies (though even discussions on the research pipeline can become redundant with speculation and unmet promise). These were also locations where the history of the science of sickle cell medicine continues to be recounted and remade (Sharp 2013). Not only are decades old diagnostic and therapeutic breakthroughs, such as newborn screening and prophylactic penicillin, still practiced as the clinical standard in pediatric care today, but their story is still retold and summarized on the secular scientific stage. Yet, the political and social contexts for these interventions and how they came to be implemented broadly through public policy are often muted in their retelling, post-hoc. Hence, this research also benefited from oral histories that revisited the debates that led to consensus building around the scientific validity of these interventions and subsequently justified health policies that would underwrite the gains in childhood survival for sickle cell disease observed in high-income countries today. Anticipatory politics provides a conceptual framework to explain how expectations for the future have the capacity to shift stakeholders' tolerance for risk in the present: that improving upon survival in children concomitantly transforms high-risk interventions, such as transplant, into viable treatment options.

## 2

## The Politics of Anticipation: "Prevention As Treatment" and Making Care Matter

At the 2012 annual convention of the Sickle Cell Disease Association of America (SCDAA), Kwame Ohene-Frempong read from a prepared statement. He was among a panel of patients identified as the earliest beneficiaries of scientifically proven interventions for sickle cell disease, technologies which included newborn screening, bone marrow transplant, chronic transfusion therapy, and hydroxyurea. Kwame's father, Dr. Kwaku Ohene-Frempong, who had organized the panel, introduced his son by noting he only recently learned that Kwame was quite possibly the first child in the U.S. to be tested for sickle cell disease at birth.[46]

Kwame was born in May 1972, while his father was a medical student at Yale University. The inventory of hospitals where he received his pediatric care also mapped the academic career of his father, now an emeritus professor at an Ivy League medical center. Kwame recounted a life of milestones met in spite of his chronic illness, and he credited family, friends, and health care providers for supporting these achievements. In the years after finishing college, he found steady employment, enjoying a 15-year career in telecommunications. Kwame spoke of the centerpieces of his life: "I have a house. I have a wonderful girlfriend, four beautiful children," stirring a wave of applause from the audience. He paused before adding, "I live a pretty normal life." Kwame scarcely allowed the clapping to fade before concluding, "And I owe that to my father, who has dedicated his life to working with sickle cell disease. Through him, I was fortunate enough to be surrounded by some of the best hematologists, some of the best facilities,

and I have benefitted from research that has now saved the lives of so many children, and I am extremely thankful for that."

Seven months after the SCDAA meeting, I learned that Kwame had died. This news reached me while I was conducting fieldwork in France, through a bulk e-mail from the Foundation for Sickle Cell Disease Research. The announcement reverberated across the sickle cell disease community, including among the doctors I had met in Europe. Because Kwame was the son of Dr. Ohene-Frempong, a renowned physician-researcher and political advocate for sickle cell disease, the shock was particularly acute. I would later learn that Kwame had collapsed at home, while in the presence of his mother, due to complications of his disease. He was forty years old.

Crediting scientific discovery for prolonging life—as Kwame had in his closing remarks at the SCDAA convention—is pervasive in biomedical histories of sickle cell disease. Kwame's life also spanned the introduction of the other technologies embodied in the lives of his fellow panelists. Among them was Kimberlin Wilson-George. Born in 1974, Kimberlin was two years old when her sickle cell disease was diagnosed. In a polished account, Kimberlin recounted a spirited childhood that was still hindered by frequent and debilitating sickle cell pain crises. Her parents and grandmother tended to her during her painful episodes, and her private school was supportive. Despite significant absences from school due to her condition, Kimberlin was determined to keep up with her peers and never repeated a grade. Yet even as a young child, she recalled feeling resigned to a future of recurrent pain.

That future took an improbable turn in 1982 with a second, unrelated, diagnosis: acute myelogenous leukemia (AML). At eight years of age, Kimberlin had a sickle cell pain crisis that she "would never forget." When doctors detected leukemia in the days that followed, Kimberlin

was not expected to survive the ensuing months. Yet she responded to the initial chemotherapies, providing doctors at St. Jude Children's Hospital in Memphis, Tennessee the chance to propose bone marrow transplantation.[47] At that time, bone marrow transplantation offered a hypothetical—but still untested—treatment strategy to resolve the red blood cell deformities caused by sickle cell disease. Kimberlin was fortunate to have two siblings who could serve as stem cell donors. Though the risk of dying from the transplant was high, so was the likelihood of succumbing to AML.

Kimberlin underwent the transplant at the University of Alabama in Birmingham, where doctors prescribed an intensive regimen of chemotherapy and radiation to destroy Kimberlin's doubly diseased bone marrow. Chemotherapy and radiation are blunt instruments; however, deliberately injuring the bone marrow in this way not only destroys all blood cell lines, but creates the physical space for a donor's blood-forming (hematopoietic) stem cells to engraft. As Kimberlin's blood cell counts reached their nadir, indicating the elimination of her own blood-forming cells, her younger brother's stem cells were infused, with the hope that they would "take" and begin producing normal white and red blood cells.

While awaiting engraftment of their donor's hematopoietic cells, patients are dependent on transfusions of red blood cells and platelets to keep them alive. Successful repopulation of blood cell lines requires careful titration of medications to modulate donor and host immune systems, not only to encourage the proliferation of the donor graft so that it is not rejected by the residual host immune system, but also to suppress donor white blood cells from attacking the host body. During this period, patients take myriad antibacterial, antiviral, and antifungal medications to protect them from opportunistic infections. Kimberlin endured a difficult year largely spent in hospital at St. Jude due to the complications of her transplant, including graft-

versus-host disease (or GVHD; Johnson, *et al*. 1984).

In Kimberlin's own words, "the outcome of my transplant was miraculous": since the transplant, her blood cells have remained free of leukemia and of sickle cell disease. No longer the anonymous child from a case report in the *New England Journal of Medicine,* Kimberlin provided the audience a resplendent update of the next 30 years of her life. She completed her college education, taught grade school and founded her own business, married and raised a family. Against her own expectations of infertility as a consequence of the chemotherapy and radiation, she gave birth to three children.

Kwame and Kimberlin's lives were thus briefly juxtaposed on a convention stage. Kwame's life and words testified to the success of early diagnosis and supportive treatments for children with sickle cell disease, though his precipitous death was also prescient of the uncertainties that can follow in adulthood. Kwame had been a model for living well with sickle cell disease; Kimberlin demonstrated an essence of a life without it.

**Anticipatory politics**

Scientific and clinical innovations have transformed sickle cell disease from a genetic disorder that had been largely fatal in childhood to a chronic, but still life-shortening condition. As recently as 50 years ago, the majority of children born with sickle cell disease were not expected to reach adulthood. In low and middle-income countries where the disease is prevalent and newborn screening and comprehensive care practices are unavailable, sickle cell disease remains a significant cause of childhood mortality. In high-income countries such as the U.S. and France, however, where public health systems have implemented newborn screening and disease-specific

comprehensive care practices, the likelihood of surviving childhood with sickle cell disease has never been better. Epidemiologic studies of U.S. children born with sickle cell disease since the 1980s report upwards of 95 percent surviving to age 18 (e.g., Quinn *et al.* 2010). Indeed, centers in the United Kingdom and elsewhere in Europe have cited survival through childhood that approaches 98 to 100 percent (Telfer *et al.* 2007).

Unique to sickle cell disease is that its prevalence predominates among groups that are disadvantaged minorities in high-income countries like the U.S. and France, where life chances already are stratified by race, ethnicity, immigration status, and class. An estimated 100,000 people have sickle cell disease in the U.S., and this population is largely composed of Black and Latinx identified individuals (Hassell 2010). With recent decades of migration, particularly from sub-Saharan Africa, sickle cell disease is now the most common genetic disease in France (Bardakdjian-Michau *et al*. 2009), affecting one in 1900 Métropole births. As such, interpersonal and inter-institutional power dynamics as well as broader social and economic structures inevitably have co-produced clinical outcomes for these populations.[48] These social contexts generate human capabilities[49] to remake worlds and to envision viable futures. Among these imagined or anticipated futures are the world-making possibilities that adults conjure on behalf of children. In turn, expectations for the future shape what kinds of treatments, research, and clinical decision-making are being proposed and practiced on behalf of patients.

This chapter deploys an anthropologically informed notion of *anticipatory politics* to provide an epistemological account of two ground-breaking interventions for sickle cell disease: first, the now well-established clinical practice of newborn screening; and, second, the emerging scientific evidence for identifying and treating silent cerebral infarcts, or silent strokes. I offer anticipatory politics as an analytic to conceptualize these clinical and experimental spaces as

they have been informed by stratified expectations, in this case, for the future lives of children. In providing an ethnographic historicity of the scientific knowledge production of newborn screening, I elucidate how comprehensive care practices for sickle cell disease became accepted as clinical standards and operationalized as national health policy. Biomedical efforts to extend and improve upon patients' life chances are fraught with overt and implicit assumptions about researchers, health care providers, and families' intentions and capacities when seeking care and pursuing treatment options. Yet even conflicted and contradictory desires among these stakeholders ultimately align with modes of care to define and justify who is eligible for higher risk treatment interventions, and under what circumstances.

Given that blood travels throughout the body, the biomedical assumption is that the sequelae of sickling red blood cells occur everywhere. These effects become cumulative when left unmitigated by disease-modifying therapies. Because sickle cell anemia provokes incremental changes to the body, identifying who is at risk of complications involves recognizing and defining evidence of disease progression, ideally prior to the appearance of overt symptoms. Currently, no treatment outside of hematopoietic stem cell transplantation halts the progression of sickle cell disease. Transplant practitioners have noted that the extensive diagnostic testing that precedes a bone marrow transplant can lead to "discovering" previously undetected signs of organ dysfunction. Learning to anticipate these signals of future pathology while they are still amenable to circumvention has underwritten the success of life-prolonging interventions for sickle cell disease.

Nonetheless, predicting the future health of people with sickle cell disease continues to defy scientific explanation and clinical expertise. Even when they share the same genetic mutation, patients' symptom presentation and clinical course can vary. For some, the red blood

cells' predisposition to distort and accumulate in blood vessels manifests predominantly as painful crises or the life-threatening syndrome known as acute chest. For others, strokes or leg ulcers present as the primary complications of the body's long-term exposure to the contents of ruptured blood cells due to chronic hemolytic anemia. A subset of patients may experience relatively quiescent symptoms as children until the effects of long-term organ damage become apparent in adolescence or young adulthood. In other words, outward signs of suffering—and the lack thereof—during childhood are imperfect forecasters of disability and early mortality in adult survivors.

Much clinical knowledge is operationalized today as practice-based prognostication. This blending of anticipation, care, and practice has a specific name in Anglophone Western medicine: "anticipatory guidance."[50] As performed in medical contexts, anticipatory guidance denotes a range of predominantly—though not exclusively—preparatory strategies. Anticipatory guidance is a form of care that is inherently oriented to the future. As such, anticipatory guidance is especially prominent in the parlance and practice of pediatric health care professionals. The latitude for defining what counts as performing anticipatory guidance ranges from the specific and self-limited preparation of a patient for a single procedure to capacious forms of support—informational, material, emotional—that implicate open-ended futures.[51] Seeped in potentiality, anticipatory guidance transfers knowledge and expertise for an ever-widening breadth of conditions. While anticipatory guidance can assume secondary and tertiary forms,[52] its role in preventive medicine and child development exemplifies the pediatrician's primary care orientation, where the imaginable future for a child holds an inverse temporal relationship to the life course.

In conceptualizing anticipatory politics, I incorporate the affective elements of medical

innovation, where expectations for improving upon mere survival empowers "speculation the authority to act in the present" (Adams, Murphy and Clarke 2009:249). Building upon Ahmed's (2004) theory of affective economies, these future-looking, non-individuated emotions that are subsumed in care work and research expertise surface to underwrite social and political projects. In order to articulate the "politics" of anticipatory politics, the case studies presented below employ an analysis of sickle cell disease medicine that is conversant with the historical contexts and political conditions of its knowledge production. In practice, anticipatory guidance generates new matters of clinical and experimental concern by instilling affective states of preparedness, "a strategy that must continually keep uncertainty on the table" (Adams, Murphy and Clarke 2009:250). That is, even as stakeholders implement anticipatory guidance with the objective to mitigate future risk and forestall complications, this form of expertise remains oriented toward inherently uncertain futures. Tacking between the practice and affect of anticipatory guidance, this chapter considers how patients, parents, and health care providers are actively entangled in "affective economies of fear, hope, salvation and precariousness oriented temporally towards futures already made 'real' in the present" (Adams, Murphy and Clarke 2009:260). In this way, the clinical interventions that shape lives in the present also relocate expectations for the future.

In assembling the case studies for this chapter, I draw methodologically from Mol (2008) and Puig de la Bellacasa (2011) in their efforts to apprehend the sciences by attending to their practices and politics as "matters of care." Both scholars foreground constructivist efforts to account empirically for human and non-human agencies and associations that produce the multiplicity that is the sciences and thereby make room for their politics and ethics (e.g., Latour 1987, Latour 2005). Mol's fieldwork-based accounts of atherosclerosis (2002) and diabetes (2008) provide a methodological basis for doing science and attending to its care logics. Puig de

la Bellacasa extends Latourian "matters of concern" (Latour 2005) so that "[u]nderstanding caring as something we do extends a vision of care as an ethically and politically charged practice" (Puig de la Bellacasa 2011:90).

In bracketing praxis and care, I write against reducing the critique of clinical decision-making to categories of scientific versus non-scientific expertise, such as in the way "the art and science of medicine" tends to dichotomize value-laden interpersonal relationships and value-neutral scientific knowledge. To this end, I utilize oral histories and in-depth interviews, draw on participant-observation in clinical settings and research and advocacy meetings, and engage in document analysis of the medical literature. Using these research methods, I first explicate how newborn screening became deemed scientifically valid and therefore actionable as social policy. With this brief history of sickle cell disease medicine, I then introduce how the conditions that improved survival in childhood have made the proximate risk and deferred promise of transplant a plausible research and treatment proposition. For the second case on the more recent medical research to advance the detection of silent strokes, I locate the affective and future-seeking attributes of clinical work as a key impetus for producing new knowledge and forms of care. Both case studies employ the analytic of anticipatory politics to recognize how orientations toward the future, as in the practice of anticipatory guidance, are subject to structural relationships that contribute to whether and how scientific knowledge becomes empowered to act upon patients' futures.

**Blackboxing childhood survival: the success of newborn screening**

In 2014, the American Society of Hematology bestowed special recognition to Dr. Michael

DeBaun for his career achievements in clinical research for sickle cell disease. This honor included an invitation to give the Ernst Buetler memorial lecture at the Society's annual meeting, a conference that convenes over 25,000 international attendees. Among the colleagues Dr. DeBaun commended during his lecture was Dr. Elliott Vichinsky, whom he described as "a pioneer that initiated newborn screening for sickle cell disease." DeBaun cited Vichinsky's findings, now three decades old, involving a cohort of 81 children in Northern California whose sickle cell disease was identified through newborn screening, and how they experienced 1.8 percent mortality over seven years of follow-up. By comparison, the 64 children who had not undergone newborn screening and attended the same comprehensive sickle cell center experienced eight percent mortality (Vichinsky, *et al*. 1988).

The children in the second group received their diagnosis of sickle cell disease after three months of age: on average, by 21 months. Of the five children who died in the second group, two were diagnosed only at the time of their fatal septic illness, typically the culmination of a precipitous and overwhelming bacterial infection and resultant multi-organ failure. Vichinsky's paper quietly proffered that both groups from their center nonetheless fared better than the much higher mortality of 15-30 percent reported in other study cohorts and geographic regions (Vichinsky, *et al*. 1988:753). I asked Dr. Vichinsky, over e-mail correspondence, what had explained the difference in mortality between his study groups, apart from the timing of their diagnosis, given that the same sickle cell program had followed all families. He noted that teaching parents how to provide anticipatory care operated differently when children were diagnosed later in life, and particularly when their sickle cell disease was detected while *in extremis*. For families who were proximate to a child's life-threatening crisis at the time of their diagnosis, attempts to transfer preventive knowledge seemed less successful than with the family

of an infant who had not yet manifested signs of illness (Vichinsky, personal communication, 2015).

The benefits of newborn screening to individuals and populations affected by sickle cell disease are no longer subject to dispute. This claim is made with confidence by physician leaders in sickle cell disease medicine, like Michael Debaun, Elliott Vichinsky, and Kwame's father, Kwaku Ohene-Frempong, who advocates for making newborn screening available in low-income countries, including his native Ghana. Newborn screening programs have been credited with increasing survival for children with sickle cell disease in the U.S., and these results have been replicated worldwide. A notable exception is a recent study that found no significant reduction in childhood deaths due to sickle cell disease in Minas Gerais, Brazil, despite federally mandated newborn screening (Wang 2015). As this chapter expounds in further detail, the success of newborn screening programs is limited by multiple structural factors, including access to anticipatory guidance and comprehensive care practices, as was found in the Brazilian case.

Because the fetal form of hemoglobin is still present at birth, newborns are temporarily protected against the effects of sickling red blood cells. From delivery onwards, the sickle hemoglobin varieties begin replacing the residual fetal circulation in earnest. Sickling red blood cells predominate by four to six months of age, when children may begin to display signs of illness, depending on the severity of their disease. To obtain a diagnosis of sickle cell disease in early infancy within the purview of an intact public health system provides families the occasion to receive expert evaluation and counseling, ideally well in advance of the emergence of symptoms and complications. Among the key interventions of newborn screening is retention of families to health care institutions specialized in the practice of sickle cell disease comprehensive care, where future risk is managed and contained through enhanced forms of vigilance,

attentiveness, and care.

My framework for analyzing newborn screening for sickle cell disease draws from Latour's important observations on *blackbox*[53] processes and "the way scientific and technical work is made invisible by its own success":

> When a machine runs efficiently, when a matter of fact is settled, one need focus only on its inputs and outputs and not on its internal complexity. Thus, paradoxically, the more science and technology succeed, the more opaque and obscure they become [Latour 1999:304].

In an analogous fashion, newborn screening for sickle cell disease assembled new matrices of care and practice that were vital to its success as a screening technology. Here I explore further how public health systems recruited families to health care institutions that would in turn enlist these caregivers' expertise to act as first responders to potentially lethal complications of sickle cell disease in childhood. The term, "newborn screening," implies a diagnostic technology to test an infant at birth for an existing and often (as of yet) unapparent condition. Newborn screening is in fact the accepted shorthand for an assemblage of coordinated practices that operate across multiple institutions, within a specific period of time, and under a particular health policy mandate. The newborn screening test is performed on blood drawn from a pinprick to the infant's heel, blotted to a filter paper card, dried, and sent on to a laboratory facility to detect hematologic markers of sickle cell and certain other diseases. Taken alone, however, the heel-prick test is insufficient to comprise an efficacious newborn screening program.

This limitation was substantiated when newborn screening for sickle cell disease was first implemented in 1975 in New York State. The initial rollout of newborn screening in New York City was "dismal" (Grover 1989:819), as nearly half of the positive filter paper tests never underwent confirmatory testing, leading to numerous missed diagnoses. In a case-by-case

analysis of the eight children known to have died of sickle cell disease in New York City between 1976 and 1978, all had succumbed after fewer than 48 hours of infectious illness, and none were receiving regular medical care. Five of the families were unaware of their children's underlying condition. Four of the children who died had undergone screening for sickle cell disease at birth, but only one had their initial abnormal test confirmed. These findings strengthened the conclusion that "accurate screening of newborns in the absence of a comprehensive follow-up program is of limited value" (Grover 1989:821). Not until additional federal funding was secured in 1978 did newborn screening in New York begin to function as intended. Hence, a successful newborn screening program is comprised of interlocking practices that include reliable initial and confirmatory testing, effective conveyance of results to families, and the efficient linkage of affected children to health care institutions capable of providing disease-specific training and care.

Two anticipatory care strategies linked to newborn screening remain unchanged since the 1970s. Both entail recalibrating families' and health care providers' thresholds for evaluating and treating episodic illness. The first approach induces caregivers to detect and respond to fever more aggressively than they would for an otherwise healthy child. With each instance of fever, parents are coached to immediately bring their children to a health care institution for urgent evaluation. The second strategy teaches parents how to palpate the abdomen to detect an enlarged spleen, whose sudden appearance can indicate a precipitous extravasation of blood into the organ, a life-threatening condition. These practices do not necessarily reduce the occurrence of complications; rather they compel families to seek care in the earlier stages of an acute illness, while still responsive to antibiotics or blood transfusion.[54] This heightened vigilance coupled with more assertive attention from the health care system ultimately reduces the risk of a fatal

outcome.

The role of anticipatory guidance in preventive medicine and child development exemplifies the pediatrician's primary care orientation, where providing "well baby" and "well child" care are hallmarks of the practice of general pediatric medicine.[55] In this way, anticipatory guidance assumes greatest import during the earliest stages of a child's life. This is also the case when the trajectory of disability or chronic illness overlays the expected development of a child. Dr. Ohene-Frempong pointed to how newborn screening allowed health care workers not only to provide anticipatory guidance for children before they showed symptoms, but to reimagine the natural history of sickle cell disease:

> I think health workers were also learning that this disease was not necessarily a death sentence … [E]ven when we didn't have any major innovative therapies, taking good care of them in an ordinary sense, and anticipating their problems—good "well baby" care, good "well child" care, making sure they get all their immunizations—were saving lives. [Ohene-Frempong with Jae, 16 April 2013].

In a similar vein, Serjeant indicates that the instrumental interventions linked to newborn screening are also an adjunct to the new knowledge that comes with diagnosis, when "[t]he mother [*sic*] also receives an important psychological message that although her child has a currently incurable disease, much can be done by close observation and simple interventions to improve its outcome"[56] (Serjeant 2013:3). Articulating newborn screening as the assemblage of anticipatory care practices not only resists blackboxing an efficacious medical technology, but also considers its structural politics. In the paradigm of anticipatory politics, the capacity to provide enhanced vigilance became a "matter of care" (Puig de Bellacasa 2011), an affective practice, and a vital resource that was co-productive with—not merely adjunct to—the distribution of economic and social capital required for newborn screening's success. This

affective appeal to the expectations of families and health care practitioners instilled the capability to imagine and nurture alternate futures, thereby undoing prior assumptions of what sickle cell disease should look like.

Whereas early reports of significantly improved child survival were being ascribed to newborn screening, as the initial experience in New York demonstrated, these gains were not uniform. As of 1981, the Cooperative Study of Sickle Cell Disease, a nationwide multi-center observational study organized and funded by the U.S. National Institutes of Health (NIH), had not observed a decline in the (still unacceptable) 30 percent case fatality rate for sepsis among the children in their sample who were born during these earlier years of newborn screening (Gaston 1986:1594). While a handful of U.S. states had adopted newborn screening (as did the French overseas department of Guadeloupe in 1985[57]), another technology was being added to the armamentarium for pediatric sickle cell disease: prophylactic penicillin. Penicillin does not modify the effects of sickling red blood cells to the body; rather, it attenuates infection from certain kinds of bacteria that are better-contained with a normally functioning spleen.[58] Though penicillin was no longer a new drug in the 1980s, some practitioners began prescribing it as a daily medication for infants and children with sickle cell disease.

The Cooperative Study itself held no intervention component, but one of the Study's organizers, pediatrician Marilyn Gaston, pushed leadership at the National Heart Lung and Blood Institute (NHLBI) to fund the Prophylactic Penicillin Study (PROPS), a multicenter randomized, blinded, placebo-controlled trial of penicillin prophylaxis for children with sickle cell disease (Vichinsky with Jae, 15 April 2013). The 215 participants were drawn from a national sample of 23 centers across the U.S. After 15 months of follow-up, the results of PROPS were compelling enough to end the study prematurely: thirteen episodes of sepsis due to pneumococcal infection

occurred in the placebo arm, compared with two cases among children in the prophylactic penicillin arm (Gaston *et al.* 1986).

Dr. Vichinsky stressed the underlying importance of experimentally demonstrating an unequivocal survival benefit among the children who were assigned twice daily doses of penicillin.[59] As he explained during our interview:

> [N]ewborn screening is the critical thing, and penicillin was the tool that allowed public health departments to accept it, because you had a pill to give them. What [families] really needed was not a pill. What they really needed was counseling, education, [knowing] when to come in [to the hospital], how to manage pain, how to feel for the spleen … . They needed comprehensive care, and no one wanted to support that as an indication for newborn screening. It was too kind of touchy-feely stuff, so … no one would support it from the traditional schools. [Vichinsky with Jae, 15 April 2013]

Experimentally demonstrating the effectiveness of penicillin in reducing fatal sepsis recursively justified the presence of the newborn screening programs already in existence and added impetus for their expansion. It could no longer be argued, especially by those who dismissed the "touchy-feely"-ness of comprehensive care practices, that sickle cell disease was untreatable and therefore unworthy of an early diagnosis. In response to the PROPS findings, a NIH Consensus Conference recommended universal newborn screening for sickle cell disease (NIH 1987). Congress approved additional funds to support state-sponsored newborn screening programs during the same year.

Penicillin's historic contribution to sickle cell disease care and practice exceeded its direct antimicrobial effects. Prior to PROPS, only five states had required newborn screening for sickle cell disease. By 1990, newborn screening programs expanded to 20 states; within a decade of the NIH Consensus Conference, 40 states implemented universal newborn screening (Benson and Therrell 2010). As of 2006, universal newborn screening reached all 50 United States. The

clinical study of penicillin had provided the policy justification to broadly implement newborn screening programs across the U.S., and it was through the process of newborn screening that children with sickle cell disease would obtain the anticipatory care they needed.

Newborn screening's importance as the vehicle to comprehensive care became evident to me even outside my more narrowly defined field sites. While waiting for my son to finish his dance class, another parent, pointing to the conference bag I was carrying, approached me. "Are you a hematologist?" she asked. The mother explained that her young son had sickle cell disease, and he was "doing great."[60] She mentioned that her family had refused vaccinations and adhered to a vegan diet to maintain their son's health but still endorsed their close relationship to the large hospital-based sickle cell center, where her son was first referred as an infant. "Because he is doing so well, they leave us alone," she interpreted as the doctors' response to their unorthodox treatment choices. Before we parted, she said, "I just wanted to ask, do you know Dr. S?" In fact, Dr. S was among my study participants, though he no longer worked at the sickle cell center they attended. She was delighted. "He was the doctor who first explained sickle cell disease to us. He taught us how to feel for the spleen. We would come back [for our follow up visits], and he would make sure we knew how to do it right. We'll never forget him." In an evocation of Mol's "logic of care" (2008), I pose this as an example where the "medical home"[61] was successfully maintained in the presence of conflicting stakeholder positions, where the health care institution continued to care for the patient, despite his family's decision to forego recommended comprehensive care practices. As Mol explains, "… even in moments that leave a lot to be desired, health-care professional do not write people off as bad investments. … In the logic of care, patients are not a target group, but crucial members of the care team" (2008:26).

**Ambiguities of improving longevity: childhood survival, adult mortalities**

> The biggest challenge for families going forward is this sense of hope. Families want to know that their child … – when I see the 1-month-old or 2-month-old who has just been diagnosed … they want to know that their 18-year-old is going to finish high school and that they are going to have a normal life. … I look to that future for every one of those newborns…. I look the parents in the eye and say, "Your child, as a result of medical advances, research that has been done by others prior to your child's birth has greatly increased the chances of your child reaching her 18th birthday, and I hope to be able to celebrate that day with you when it comes."
>
> Dr. Michael DeBaun, 2013

In the U.S., gains in life expectancy dramatically increased since the early 1970s, when the average age at death for sickle cell disease was reported as 14 years. The National Heart Lung and Blood Institute (NHLBI) of the NIH has promoted this narrative of progress through biomedical discovery, as rendered in an oft-cited slide of average life expectancy for people with sickle cell disease (see Figure 4). The timeline begins in 1910, when the first clinical case report for sickle cell disease was published in the U.S. (Herrick 1910) and ends in 2000. The graph depicts a modest rise in life expectancy until 1970, when the curve angles sharply upwards. Annotated near the base of this surge is the National Sickle Cell Disease Control Act. Signed into law by President Nixon in 1972, the Act allocated specific federal funds for sickle cell disease health care services and medical research. The remainder of the timeline is punctuated by interventions asserted as effective by clinical research trials. Yet newborn screening, which gained ground in urban centers in the 1970s and reached nearly half of U.S. states by 1990, is curiously absent from the Figure.

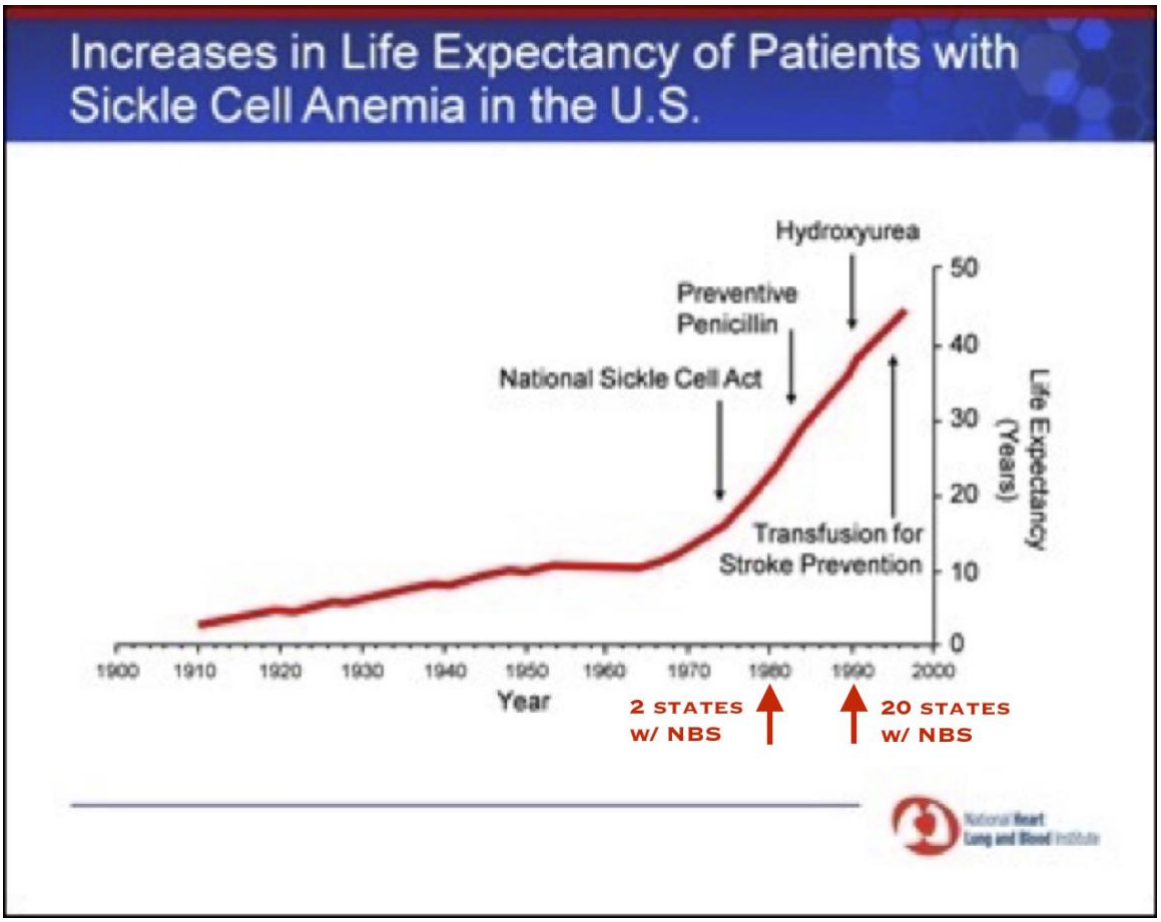


Figure 4. Sickle cell anemia (Hemoglobin SS) life expectancy (Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services). Annotation added: U.S. states mandating newborn screening (NBS) for sickle cell disease.

Also notable is the relentlessly smooth rise in the life expectancy curve, whose slope predates any of the scientific proofs—for penicillin, hydroxyurea, or chronic transfusions—that the graph means to highlight. These interventions scarcely register as inflection points against the timeline; yet this portion of the life expectancy curve does hew to the expansion of newborn screening and comprehensive care programs for sickle cell disease (neither of which were represented in the unannotated slide). When I queried Dr. Ohene-Frempong about the NHLBI slide, which he has used in his own presentations, he readily acknowledged the inadequacy of representing the impact of scientific discovery in this way:

> [T]he 'smooth rising thing,' some of it is not justified, because we haven't done something beyond newborn screening and chronic transfusions that has in a major way affected the potential for dying for young adults with sickle cell disease. .... They're living longer with many, many challenges. [Ohene-Frempong with Jae, 16 April 2013]

Like Kwame Ohene-Frempong and Kimberlin Wilson-George, Carlton Haywood, Jr., PhD, was born with sickle cell disease in the 1970s. Dr. Haywood, Jr., now entering his fifth decade, recalled desperately seeking reassurance from his parents as a child, after happening upon pamphlets that informed him the lifespan of a person with sickle cell disease was 20 years (Haywood, Jr. with Jae, 11 April 2015). The life expectancy cited in the 1970s proved to be a moving target, and Dr. Haywood, Jr. and others of his generation found themselves crossing over this epidemiological line. Since 2000, and for those who have reached adulthood during the past twenty years, however, median life expectancy has remained stubbornly in the 40s (essentially unchanged since Platt *et al.* 1992). These statistics never sit well for the generation of patients who first benefitted from early childhood interventions but now find themselves catching up to the life expectancy curve.

The available epidemiologic data suggests that childhood mortality has shifted to young adulthood (Quinn *et al.* 2010, Lanzkron *et al*. 2013). In this way, the achievement of a child surviving to adulthood and the tragedy of an adult life foreshortened become "two sides of the same coin."[62] Whereas death certificate data demonstrate a consistent annual reduction in childhood mortality from 1979 to 2005, adult mortality due to sickle cell disease in the U.S. has steadily increased compared to the general population, with an average age at death of 42 years among females and 38 years for males[63] (Lanzkron *et al*. 2013). A large adult sickle cell center in France elicited similar findings, and among their patients who had died between 2001 and 2013, their median age was 36 (Ngo *et al.* 2014). Today, sickle cell disease mortality is regularly

invoked to justify research objectives or advocate for improving health care services for adults. At scientific meetings, projected life expectancy statistics often inhabit a presenter's background slide. Halima, who had recently entered her fifth decade with sickle cell disease, mentioned to me as we left one of these sessions together, "I always tear up a little bit, when they mention mortality."[64]

Improved outcomes in children have shifted advocacy discourse to the disparities between pediatric sickle cell disease patients and their own prospects for accessing appropriate services as adults. Improving the survival of pediatric patients makes the public health system a victim of its own success, when these systems are unequipped to provide comprehensive care for their adult population. Disease-specific specialists are often readily available to pediatric populations in the U.S.; even in geographic regions without overall physician shortages, however, obtaining optimal care for adults remains a challenge. This is partly due to a lack of dedicated providers and institutional support,[65] but also a result of losing federally mandated health insurance. Depending on the state, loss of Title V coverage for children with sickle cell disease (and other special health care needs) contributes to lapses in health care coverage in adulthood. As the authors of a study of emergency department discharge data in California grimly observed, young adults with sickle cell disease become high utilizers of emergency room services soon after losing their pediatric health insurance (Wolfson *et al.* 2011).

The NIH Consensus Conference that had endorsed newborn screening for sickle cell disease produced rights-based language to advocate for the appropriate clinical management of children: "Comprehensive specialized care should be the right of every child who is affected by a clinically significant hemoglobinopathy. Economic, social, cultural, or geographic concerns should not limit access to this care but should be taken into account when structuring a follow-up

program" (NIH 1987:1207). This rights-based language was not extended to the adult population 30 years ago. Today, the need to maintain disease-specific care in adulthood—a time when the long-term effects of sickling red blood cells manifest as damage to kidneys, lungs, bones, brain—is greater than ever. The Affordable Care Act of 2010 may benefit adults with sickle cell disease in accessing health insurance in certain states; its impact, especially given the current Trump administration's attacks on this legislation, is as of yet unknown.

**Ontologies of cerebrovascular disease: the enactments of silent stroke**

Strokes are a significant complication for people with sickle cell disease, with 25 to 30 percent of patients experiencing this complication. By two years of age, children with sickle cell disease experience a significantly higher risk of stroke (Ohene Frempong *et al.* 1998). Although sickle cell disease confers a higher likelihood of strokes throughout the life course, for many, this risk peaks during the first decade of life. Beginning in the late 1980s, doctors began investigating a non-invasive diagnostic technology to predict which children were at greatest risk for stroke. Placing the ultrasound Doppler probe transcranially against the bony windows of the temple and under the jaw, Adams *et al*. (1992, also Adams *et al.* 1997) defined a subset of patients whose blood flow velocity in the large arteries supplying the brain had markedly increased, usually due to a pathologic narrowing of these blood vessels. Followed over time, this group also experienced dramatically higher rates of stroke. The predictive value of the ultrasound Doppler to stratify future stroke risk is one of the few instances where a degree of consensus has coalesced around categorizing certain sickle cell patients as "high-risk."[66]

Clinical researchers continued to explore the limits of diagnostic technologies such as

ultrasound and magnetic resonance imaging (MRI) to interpret, prevent, and ameliorate the acute and chronic complications of stroke in sickle cell disease. In a subsequent trial, the patients diagnosed as high-risk after screening with transcranial Doppler were randomized to receive regular blood transfusions in an effort to dilute the proportion of sickled cells circulating in the blood stream. Compared to those receiving the comprehensive care standard for sickle cell disease, without regular transfusions, the chronically transfused group demonstrated over 90 percent reduction in the incidence of a first stroke (Adams, R *et al*. 1998). Additional centers in the U.S. and France confirmed the benefit of chronic transfusion programs for preventing strokes in children. Since implementing their chronic transfusion program in 1992, a French cohort reduced their rates of overt stroke from 11 percent to less than two percent from birth to age 18 (e.g., Bernaudin *et al*. 2011). The impact of chronic transfusions as a secondary prevention standard was also measurable at the population level: between 1991 and 2000, the state of California experienced an 80 percent drop in hospital admissions for stroke among children with sickle cell disease (Fullerton *et al*. 2004).

Children who experience strokes in childhood can sustain dramatic changes to the appearance of their brain on diagnostic imaging, even when the neurologic system demonstrates its plasticity with recovery. These lasting visual changes to the brain can readily re-emerge as a source of physician concern, in spite of intervening years and rehabilitative therapy. In an informal discussion in the outpatient clinic, one of the hematologists mentioned that the appearance of a young patient's brain on MRI looked "like Swiss cheese." When an interdisciplinary team deliberated the emotionally challenging informed consent discussions they had with an adolescent patient who was in the preparatory stages of bone marrow transplantation, a doctor raised the question of whether a cognitive delay due to his prior stroke

was impeding his understanding of the consent process: “Have you seen his MRI? It’s not pretty.” These examples illustrate some of the ways in which the practices that identify patients as at increased risk for stroke and its recurrence simultaneously generate fears and concerns for the future that circulate as affective economies. Indeed, the evidence of cerebrovascular disease is among the less contested clinical justifications for undertaking a transplant for sickle cell disease.

Research concerns for cerebrovascular compromise as a complication of sickle cell disease recently broadened to include not only overt strokes, but silent cerebral infarcts, also called silent strokes. Recent studies have detected that nearly 40 percent of children will have evidence of a silent stroke on MRI by the time they reach adulthood (Bernaudin *et al.* 2011). Though chronic transfusions have been the standard of care for reducing the occurrence of overt strokes in high-risk patients, they do not diminish the progression of silent strokes. As a result, certain researchers are reframing transfusion programs, heretofore considered the care standard for overt stroke treatment and prevention, as palliative, due to their relative ineffectiveness in reducing the progression of silent strokes in sickle cell disease (e.g., Hulbert *et al.* 2011). I outline the emergence of silent stroke as a diagnostic category to demonstrate the anticipatory dread and ontological tenuousness with which clinicians regard the brain. Preoccupations with stroke and its sequelae also pose discomforting linkages between cerebrovascular disease and cognitive impairment. The specter of silent strokes not only implicates the consequences of sickle cell disease to the maturing brain but also recalibrates the thorny prospect of forecasting children’s potential for thriving in adulthood.

Silent strokes are in a process of becoming—of being understood and recognized as a pathologic process in sickle cell disease, both as a diagnostic entity and as an object of

therapeutic debate. Here I employ Mol's important study of the praxis of atherosclerosis (2002) to characterize the multiple and performative ontologies of silent strokes. Mol's ethnographic contribution demonstrates how scientific practices are enactments that perform the aim of scientific concern. Mol redirects the object of our study to specific research processes and diagnostic practices to demonstrate the inherent multiplicity of the scientific object. Similarly, the ongoing emergence of what constitutes silent cerebral infarcts and how they come to matter in sickle cell disease is being enacted across collectives of clinicians, researchers, educators, patients, MRI technologies, and neurocognitive testing.

As its name suggests, the antecedent event that provokes silent stroke can elude detection during routine clinical evaluation. On the one hand, silent strokes are defined by their lack of resemblance to overt strokes. Silent cerebral infarcts are believed to result from severe anemia or other physiologic states that cause low blood oxygen. On radiologic imaging, they are expected to appear smaller in size than overt strokes and also to be located in distinct regions of the brain. The search for silent strokes has revised radiologic diagnostic parameters, as infarcts present differently on the brain MRIs of children than they do for adults. Moreover, as MRI scanning technologies improve upon magnetic field strength, so does the detection of more subtle lesions, again readjusting what counts as a significant radiologic finding (DeBaun *et al.* 2012).

Silent cerebral infarcts on MRI are "silent" by virtue of their lack of radiologic correlation to discernable neurologic deficits that can be elicited by history or by physical exam. If historical or persistent neurological exam findings could explain the radiologic presence of the lesion, the infarct is no longer considered a silent stroke but is deemed overt. Thus, distinguishing cerebral infarcts as silent requires the corroboration of MRI findings with clinical input from the hematologist and neurologist. The clinical physical examination is needed to rule

out the possibility that an unrelated condition is mimicking the radiologic appearance of an infarct on MRI. Moreover, among the contingencies for eliciting a neurologic defect on physical exam is the fact that pediatric neurologists are more likely to detect a subtle finding than their counterparts in hematology.

Silent strokes need to be established as radiologically distinct from clinically apparent overt strokes. Yet to make the claim that silent strokes matter—that they are consequential and therefore *not* "silent"—demands measurable deficits. Current research supporting the significance of silent strokes targets their potential influence on behavior and cognition. This research has primarily elicited these outcomes through neuropsychological testing and through indirect measures such as school failure. Hence, the search for consequential effects of silent cerebral infarcts also requires researchers take into account other potentially more potent social confounders of cognitive impairment.

A 1963 study by Chodorkoff and Whitten found no significant differences in IQ between children with sickle cell disease and their unaffected siblings; since then, the effects of sickle cell disease to cognition, school performance, and "intellectual status" has been an ongoing clinical research concern. Participation in Chodorkoff and Whitten's study required the absence of a prior history of overt neurologic disease, and the 19 children with sickle cell disease who met the selection criteria otherwise varied in their disease severity. Affected children and their sibling controls were found to have comparable IQ scores and rates of school failure. In their discussion, the authors added that they "think the incidence of average and below average I.Q.'s in our sample results from the fact that these children are from a large, culturally deprived area of a metropolitan city" (Chodorkoff and Whitten 1963:33).

Subsequent studies published in 1970 and 1989, however, began to detect a performance

gap against healthy controls (Swift *et al.* 1989). Swift *et al.* pointed out that despite the variation in testing measures employed across the research groups, the scores elicited from children with sickle cell disease had been relatively stable over time; rather, it was in the healthy siblings that scores were rising. They postulated that the broader impact of changing educational opportunities for African American children since the 1960s was "causing the cognitive impairment of sickle cell anemia to become more apparent" (Swift *et al*. 1989:1083). Swift *et al.* discuss further:

> If [children with sickle cell disease] manifest immaturity and poor school progress in comparison to their peers and siblings, their problems should not be simply attributed to poor adjustment to chronic illness. Rather, they should be seen as symptoms that may be a manifestation of the illness… .
>
> The research implications of this study point to the need to discover when and by what process cognitive impairment occurs in children with sickle cell anemia." (1989:1084)

Both of these studies predate the recognition of silent strokes as a putative indicator of cognitive impairment. These historic findings also bring into relief the confounding role of socioeconomic status when performing neuropsychological testing. The contribution of education as clinical variable resurfaced when DeBaun and colleagues sought to measure the impact of silent strokes to cognition by comparing children with and without a history of silent strokes (King *et al.* 2014). Their regression analysis attributes a five-point deficit in IQ scores to the silent cerebral infarcts, a finding that DeBaun has termed the "cognitive morbidity" of silent strokes (e.g., Schatz *et al*. 2002). This is demonstrated in the Figure by the difference between the "No infarct" and "Infarct" study subjects, whose parents' education included "Some College or more" (see Figure 5 annotation). And yet, the five-point decrease in IQ attributed to silent strokes was exceeded by the six-point decline for children without silent strokes, but whose

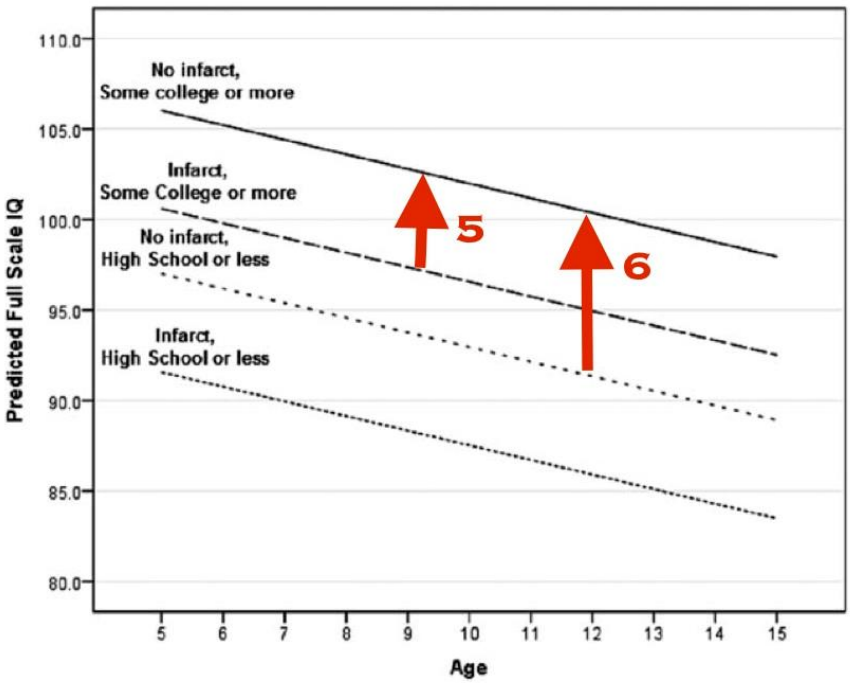


Figure 5. Effect of age, presence of silent cerebral infarct, and head of household education on predicted full scale IQ, with per capital household income and hemoglobin oxygenation held at mean values (King *et al*. 2014, 164). Annotation added: 5-point effect of silent to IQ measurement; 6-point effect of parental education ("some college or more" compared to "high school or less") in children without infarcts.

parents had not exceeded a high school education (see Figure 5 annotation). In other words, the parents' educational attainment had as great an impact on the children's IQ scores for this study as the presence of a silent stroke. Even children with demonstrable infarcts scored higher than their counterparts without silent strokes, provided their parent held a college education. Moreover (and not commented upon by the authors in this study) is that the regression extrapolates an age-dependent decline in IQ across *all* subgroups of children with sickle cell disease. By comparison, IQ measurements in healthy children are expected to rise as they age through young adulthood.

Through his research with King *et al.* (2014), DeBaun brings the Chodoroff and Whitten

(1963) and Swift *et al.* (1989) findings full circle. DeBaun recasts the social as not merely a confounder, but a determinant of sickle cell disease outcomes:

> I think, from the point of view of being a physician who takes care of children with this disease where … 60-70% of the children that I provide medical care to with sickle cell disease, receive Medicaid as their form of insurance. … poverty is a major component of this disease. As we construct our models regarding biological determinants of the disease, I have, in the past, been less sensitive to the social determinants of the disease and have focused almost exclusively on the biological determinants. I think, in the future, as we try to identify strategies to improve the care for this population, we cannot isolate the biology from the social determinants of this disease. [Michael DeBaun with Gibbons 2013]

Advocating for the clinical significance of silent strokes necessarily brings poverty, parental education, household income, and other markers of socioeconomic status into the methodologic and interpretative field, even as these may fall short in accounting for the critical intersection of variables such as racism, housing discrimination, and educational segregation.

In response to these findings, Dr. Debaun has collaborated with colleagues in the adult sickle cell service of his medical center to advocate for adults with symptoms of silent strokes to qualify for the existing comprehensive cognitive, behavioral, and emotional rehabilitation programs that have benefitted patients with traumatic brain injury (DeBaun with Jae, 11 April 2015). DeBaun elaborates on the impetus to implement this practice change with the adult patient care providers at his center:

> I have the ability to hire psychologists totally devoted to patients, children and adults, with sickle cell disease. …[T]he psychologist does cognitive testing in children, and she started to do cognitive testing in adults. And what we started to see was that a number of the adults had significant cognitive limitations—full scale IQ in the sixties, seventies that were affecting their medication adherence, instructions, ability to keep appointments. … [T]hey tested around forty adults, and over the course of eighteen months, I said, "Look,

> we're expending resources and doing the cognitive testing. What are you all doing after … the test? Are we scheduling them for rehab?... You have a patient with a global IQ of seventy, and you expect them to make their appointment for rehab in a part of the hospital they've never seen before. Is that right? … We're the ones that need cognitive testing, if this is our expectation. We have to close the loop…. Let's cut off the cognitive testing for the adults, and you all demonstrate that this service is making a difference in the lives of your adults." [DeBaun with Jae, 11 April 2015]

Elliott Vichinsky has bemoaned the "too rosy picture" of sickle cell disease that pediatric hematologists can present to their patients and families today. If a perception has been advanced that sickle cell disease is relatively benign or even "gets better" in adulthood,[67] I suggest that this is less an artifact of pediatricians painting an untroubled future than the current state of affairs: childhoods with sickle cell disease have become more manageable and predictable, and the existing care systems that have produced these outcomes concomitantly obscure knowledge of the likelihood of decline in adulthood. Even pediatricians with more intimate knowledge of the historical legacy of sickle cell disease biopolitics or of the challenges ahead in the life course will eventually relinquish their role as their charges' primary health care providers.

In both the U.S. and France, most adult and pediatric services are dichotomized in the care of sickle cell disease and other chronic conditions. This is among the reasons that Vichinsky advocates for improving upon anticipatory care practices for the adult population, akin to those performed in the pediatric setting, and promotes his center's model for a comprehensive sickle cell program that serves children and adults. To an earlier iteration of this work, Vichinsky responded: "I strongly believe that one could develop anticipatory guidance for young adults and their family about the future… they are not really told the likelihood of progressive organ failure and what steps they can take before that happens… to be effective [this] needs to be done in a steady-state situation, when the patient and his [*sic*] family are at ease and have time to prepare

for the future. …" (Vichinsky, personal communication, 2015).

**"Prevention As Treatment"**

The subtitle of this chapter is an inversion of treatment as prevention (TAP), one of the care strategies to reduce human immunodeficiency virus (HIV) transmission in the post-antiretroviral treatment (ART) era. When the clinical objective of ART is to suppress the virus to undetectable levels in the body, HIV treatment itself becomes an effective means to prevent spreading the disease to others. Hence, TAP poses a critical shift in the goals of care for already vulnerable populations: a programmatic goal like preventing mother to child transmission of HIV takes on new politics when a one-time dose of nevirapine during childbirth—an intervention that prioritizes the health of the newborn to the potential detriment of the mother (who is placed at increased risk of drug resistance with this intervention)—is replaced by ART for pregnant women in order to induce an undetectable viral load.[68] As such, TAP becomes more than a clinical concern, but a political proposition whose success depends upon social commitments to systems of care that promote health equity, akin to the processes that made comprehensive care available to children with sickle cell disease in the U.S.

Anticipatory politics provides an analytic response to a call in the study of science for "greater temporal and spatial reflexivity … that … move[s] away from normative futures and … sees expectations [as] rooted in particular times and places" (Brown 2003:18). Translating scientific knowledge to clinical practice (and its study, dubbed today as "implementation science"[69]) is rarely a linear process. Nor do scientific questions emerge outside of the soupy milieu of ongoing practices, embedded in their own social and material contexts and affective

concerns for the future.

In organizing scientific knowledge production as constitutive of practices and affective economies, anticipatory politics provides a methodological grounding to articulate abstract and contingent hopes for the future, as they become located in the present and the past. Ground-breaking interventions for sickle cell disease, such as newborn screening, prophylactic penicillin, and other comprehensive care practices, also are preventive strategies whose success is mediated by expertise in vigilance and care. Care and vigilance require, and are themselves, resources that are subject to social and economic stratification: those who are resourced to care for these futures preferentially stand to benefit from preventive intervention. In practice, care and vigilance also inform expectations for the future lives of children in clinical and experimental spaces. These paradigm shifts are made explicit through the analytic framework of anticipatory politics.

In this chapter, I have employed anticipatory politics to unpack the Latourian blackbox of research priorities, clinical practices, and public health policies that transformed sickle cell disease from a fatal disease of childhood to a chronic condition. With a diminishing hazard of dying in childhood, families and caregivers, patients and advocates, researchers and health care providers are redirecting concerns and expectations to the longer term, including the deferred potential for children to thrive as adults. The very likelihood that children with sickle cell disease reach adulthood is proliferating uncertainty for the longevity and health quality of adult lives—uncertainties that also produce grounds for considering novel and risky interventions. Unlike in 1983, the urgency of a more pressing affliction, like Kimberlin's leukemia, is no longer required for patients with sickle cell disease to assume the risk and hardship of undergoing a transplant.

Understanding why health care providers have proposed that children undergo a procedure that exposes them to the short- and long-term risks of chemotherapy, prolonged

hospitalization, and months of social isolation—and why families agree to undertake it—takes on new valences when the goal of treatment is not an express effort to stave off a more proximate death, but the hope and expectation for a durable cure. To opt for a child to undergo transplant in an effort to circumvent morbidities in adulthood is to extend the politics of anticipation to its logical conclusion. As in the case of silent and overt strokes, the project of defining who is at risk for cerebrovascular disease also produces a persuasive constituency of potential candidates for transplant. The appeal of embracing the risk of hematopoietic cell transplantation is not to improve upon survival in childhood, but to imagine a life without sickle cell disease.

# 3

## "Just" Information: Practice and Process in Making Treatment Intensification Possible

> Now, witchcraft is spoken words; but these spoken words are power, and not knowledge or information.
>
> Favret-Saada, Jeanne (1980:9)

In Chapter 2, I introduce the analytic of anticipatory politics to reframe the research priorities and public health policies that transformed sickle cell disease from a fatal disease of childhood to a chronic condition, albeit one with significant disability and premature mortality in adulthood (e.g., McClish, et al. 2005, Powars et al. 2005). There I bracket praxis and care to approximate how clinical practices and their affective economies co-produced the comprehensive care systems that improved upon childhood survival. For this chapter, I pare down praxis—the embodied actions and reflections that materialize ideas and theories (including biomedical constructs)—to specific acts of clinical decision-making and caregiving. From fieldwork I conducted at health care centers in the U.S. and France, I identify a range of practices as necessary—if insufficient—to persuade expert knowledges into actionable treatment processes at the level of the health care institution. These processes have the potential to translate to the recruitment of clinicians and families to new modes of care, including high-risk interventions, like transplant.

To elicit practice differences across the health care centers, I conducted participant-observation using a positive deviance approach. First described as a research method in a study of childhood malnutrition in Central America (Wishik and Vynckt 1976), positive deviance has since been operationalized to conduct health services research and social interventions, from

decreasing rates of hospital-acquired infections to programs (Bradley *et al*. 2009) to alleviate the impact of poverty. By definition, positive deviants are beneficial outliers, whose own outcomes surpass those of the prevailing population. Because positive deviants possess resources comparable to their peers, the reasons for the resulting disparity can appear opaque at the outset. For an obstinate problem like malnourishment in a resource-poor setting, why might certain families of similarly limited means *not* experience this complication? Upon identifying the outliers, researchers can study their specific contexts to elicit the practices that produce unexpected yet advantageous outcomes. These practices have the additional benefit of being "indigenous" (Wichik and Vynckt 1976:38), thereby improving upon the possibility of transferring this expertise locally and to analogous contexts. For this study, I employ positive deviance to identify atypical-yet-indigenous practices in institutional contexts, where treatment intensification for sickle cell disease is occurring at higher rates than the norm.

When "The Bell Curve" appeared in *The New Yorker* (2004), Gawande's essay attempted to press together two problematic strands that continue to vex health services research: first, how to explain the variance—the bell curve—in patient outcomes as a meaningful reflection of individual health care providers' practices; and second, how to use quality measures to reduce these observed disparities in patient care across institutions. When the article was updated as a book chapter (2007), Gawande rebranded his portrayal of one of the informants with a social science paradigm: "Matthews"—a physician whose innovative and unconventional practices for cystic fibrosis radically extended the life expectancy of his patients compared to his peers—"was what we'd now call a positive deviant" [2007:210]. Gawande's journalism provided a compelling example of positive deviance operationalized as a qualitative method. Positive deviance research focuses attention to the exception as a means to decipher the rule. To

demystify the unexpected success experienced by a small but significant minority of clients and institutions, a qualitative examination of positive deviants can help identify and distinguish unique and effective practices that would otherwise go underrecognized.

In turn, I draw from organizational theory to identify individual *practices,* such as the transfer of information and knowledge among health care providers and families, and distinguish whether these practices become incorporated or systematized as institutional *processes*. A process is generically defined as "[a] continuous and regular action or succession of actions occurring or performed in a definite manner, and having a particular result or outcome."[70] Process theory prioritizes sequence and linearity: an input leads to an output through a series of causally defined steps.[71] The historical link between process theory and mass production is not coincidental. For example, engineer and mathematical physicist W. Edward Deming proposed process-based interventions to improve quality control that revolutionized the Japanese manufacturing industry after World War II (Young 2011). Deming's insight was that limiting inspection to the final product provided insufficient information to redress the steps leading to a poor product or undesired outcome. Only when management systematically examined each step of the manufacturing process could potential errors be identified and mitigated: "Control the steps of the process and the final product will largely take care of itself" (Young 2011:118). A fundamental characteristic that distinguishes an organization's process control from its practices is this reproducibility.

The success of comprehensive care programs in the pediatric sickle cell disease population is an example of practices that, taken together, produce a process-based outcome. For example, in the U.S., state policies that implemented universal newborn screening combined with federally mandated health care access for children with sickle cell disease also linked with

practitioners' efforts to establish and disseminate comprehensive care standards, thus producing the processes whereby improved pediatric survival became a replicable outcome. This predictability breaks down, however, as observed with the burden of mortality that has shifted from children to the young adult population. This breakdown is due in no small part to the dearth of comprehensive care processes for the adult population—a deficit that is occurring just as the accrual of the long-term sequelae of sickle cell disease accelerate and intensify.[72]

In this examination of the practice and process of intensifying treatment for sickle cell disease [*l'intensification thérapeutique*], I focus on the transfer of knowledge and expertise that is necessary to enroll health care providers to offer and patients to accept more aggressive treatment options.[73] Genetic counseling illustrates the modern ethos of many Western health care professions that scientific evidence should be presented dispassionately. As such, the goal of conveying medical knowledge is to engage patients in informed decision-making that is autonomous and "free of coercion,"[74] while remaining respectful of their own desires and beliefs. I argue, however, that the sickle cell centers that achieved high rates of treatment intensification rarely did so by a dispassionate recommendation to enroll in a chronic transfusion program, initiate hydroxyurea therapy, or be referred for bone marrow transplantation consultation. Rather, what was required to achieve recruitment for these therapies was quite the opposite and included the convergence of interpersonal, clinical, and political support to produce the conditions that made treatment intensification possible.

**Practices and processes**

Though transnational differences in day-to-day clinical practices for sickle cell disease were not vast, I elaborate an exception: while conducting participant-observation in the French pediatric centers, I learned that children undergoing certain procedures, such as phlebotomy for laboratory testing, could receive a premixed combination of inhaled nitrous oxide and oxygen to keep them sedated. When I discussed this practice—and its lack thereof in the U.S.—with doctors and nurses from both countries, their respective surprise was palpable. French pediatricians were astonished that their U.S. counterparts had not adopted such a helpful adjunct to pediatric care. The use of MEOPA[75] had alleviated a daily source of stress to inpatient and outpatient practice, when health care providers use needles to draw blood from children or insert intravenous lines for fluids and medications. In contrast, providers I spoke with in the U.S. were struck by the perceived excess of using an inhaled anesthetic for these relatively mundane procedures.

Notably, using MEOPA had not transferred to adult medicine within France at the time of my fieldwork. In 2013, a nurse I interviewed at a pediatric center was exceptional among her colleagues and found the practice to be problematic, citing her experience working with sickle cell patients on the adult service at another hospital. Of MEOPA, she said, "*C'est trop*" [It's too much], while shaking her head. She recounted cases of older adolescents who presented to the adult outpatient clinic or inpatient hospital ward and were unprepared to undergo routine phlebotomy or placement of IVs without MEOPA and became anxious to the point of agitation. Moreover, this rupture in continuity between pediatric and adult care practices can further complicate an already challenging transition for patients. I pose this example of practice differences to consider a broader set of questions for how to explain the variation in clinical

practices observed within and across institutions. What are the conditions that lead to the proliferation of a practice, even across national boundaries and health care systems? How do these contexts differ for a process that has embedded within a local constituency, as occurred with the adoption of MEOPA among French pediatric practitioners, not to crossover even to adult providers in the same specialty?

Using health care institutions as the locus of comparison, this chapter elucidates some of the processes that make treatment intensification for sickle cell disease feasible and acceptable to its stakeholders, often in spite of its risks, costs, and limitations. This chapter also considers how new treatment technologies introduce complexity to the social, material, and discursive practice of medicine (e.g., Rapp 1999, Sharp 2006, Mol 2008), including how transplant discussions become routinized and resisted both as practice standards and institutional processes. Finally, these examples elicit some of the vulnerabilities of these mechanisms as they operate within organizations that treat historically underserved minorities, immigrants, and children.

Centers that became heavy prescribers of hydroxyurea have noted dramatic shifts in the types of care that their patients require. Holly, a nurse practitioner for the sickle cell center at University Hospital in the U.S., recounted that when she began her career in pediatric hematology over a decade ago, her outpatient practice resembled a day hospital, with children regularly appearing to the clinic in acute pain crisis. At the time, their hematology service maintained a regular census of hospitalized patients. Since their sickle cell practitioners made hydroxyurea widely available to their clinic patients, while pushing doses to the maximum tolerated, hospital admissions became infrequent. Patients taking hydroxyurea still require regular outpatient visits to monitor for potential side effects, but at University Hospital, they rarely appeared to the hospital in acute pain. “I believe in hydroxyurea,” Holly, stressed to me,

"because I have seen it *change lives*."

Despite gaining approval from the U.S. Food and Drug Administration in 1998, hydroxyurea is still considered underutilized among adults with sickle cell disease. More vocal proponents of hydroxyurea have argued that this underutilization is fueled in part by informed consent practices for this medication, where health care providers place undue emphasis on hydroxyurea's rare or hypothetical adverse effects, while underselling its established benefits for sickle cell disease. When I asked some of the clinical staff why University Hospital was able to convince so many of their patients to take hydroxyurea,[76] a nurse practitioner from the transplant team interjected, "I know exactly why. It's because of—" and pointed to Holly, who was sitting at the adjacent work station. In the clinical hierarchy, attending physicians supervise the nurse practitioner's work; nonetheless, University Hospital's sickle cell patients recognized Holly as their primary health care provider in the hematology practice. A staff member from the transplant division mentioned to me that Holly had a preternatural ability to involve herself in the lives of her patients and provided them support much in the way a social worker did. This colleague noted that as a clinician, this made Holly a unique asset to the hospital, and she would not be easy to replace, if and when she retired.

In our interview, Holly elaborated how during every patient visit, she not only addressed the current status of a child's disease, but constantly sought out opportunities to perform anticipatory guidance in the broadest sense. She iterated that in contrast to an annual physical or comprehensive care visit, that her approach was one of "continuous comprehensive care." When asked what distinguished her approach to comprehensive care as "continuous," she explained that with "every subsequent little visit, I'm taking those comprehensive components and weaving them into the visit." This meant that a monthly or quarterly maintenance visit for a child's sickle

cell disease also addressed a range of comprehensive care concerns, however mundane. A follow-up visit had as much potential to address a patient's exposure to second-hand smoke as it did to review the significance of the results for diagnostic test. Within this model of continuous comprehensive care, Holly also gave shape to short and long-term expectations for the future, including the impact of disease-modifying treatment options, such as hydroxyurea and transplant, to survival and quality of life. For Holly, these conversations took place over the course of multiple patient encounters and across the years of a child's growth and development.

The parents I met through University Hospital's transplant service who also had been referred from the pediatric hematology practice credited Holly for introducing the subject of transplant to them. Holly not only was a conduit for families to learn about transplant as a treatment option; she also helped prepare them for meeting with the transplant team:

> I spend months talking … to families before they go to transplant. … When you go to meet these new big doctors, … these specialists that they don't know, it can be intimidating. So I want them to have an understanding of some words, so they're not intimidated. I want them to practice saying "graft-versus-host disease," so they can say those words and feel comfortable saying those words. I want them to understand a transplant is a transplant and not [a surgical] operation. I want the basics to be clear before they walk into that big room. Then, depending on the families' dialogue and understanding, just depending again on this synergy that I have, I may say to families, "Let's together write out some questions you want to ask, so that when you go meet the people, you're going to walk in with a list of questions that you're going to ask." And then I'm going to tell the family, "And the next visit, you bring those questions back to me and we're going to talk about the answers that they told you."

To receive and possess knowledge about transplant did not equate with being in a position to act upon that information. The idea of treatment intensification became incrementally more concrete, when families were encouraged to meet with the transplant team. For those meetings to

achieve a productive exchange of information, Holly took steps to attenuate the potential mismatch in power dynamics between families and the transplant specialists.

In the example of reducing cerebrovascular complications in sickle cell disease, decisions to intensify treatment can respond to an overt decline in a patient's health status, such as a stroke, or with a measurable physiologic impairment, as detected through diagnostic testing. When Doppler ultrasound is used to detect abnormal blood flow to the brain, this form of expertise produces a proximate form of anticipatory practice[77] where the intervention—regular, often monthly, blood transfusions—can help reduce the likelihood of future strokes. Because strokes confer significant mortality and long-term morbidities, cerebrovascular risk became a clinical justification for undertaking the treatment-related risks of transplant.

As described in the previous chapter, diagnoses for cerebrovascular disease are undergoing a recalibration to include silent strokes, which are not preventable by transfusion therapy. Hence, the parameters of cerebrovascular risk are being redefined to attribute more subtle findings, including long-term cognitive deficits and behavioral difficulties, to silent strokes. This paradigm shift also is occurring within a clinical context where children with sickle cell disease increasingly are expected to survive to adulthood. With improved childhood survival, stakeholder desires to prolong adult longevity and improve upon the quality of adult lives become more active anticipatory and therapeutic concerns during pediatric care. Put another way, certain parents' and health care providers' desires to provide a "normal" life for their children produce opportunities to uncouple treatment intensification from the presenting severity of a child's disease. In this manner, having sickle cell disease at all can become an indication for its own treatment intensification. Precisely this capacity to elicit expectations for a future without sickle cell disease makes it possible to approach transplant as an attainable

treatment option.

Nonetheless, transplant remains a difficult and expensive procedure, requiring a diverse and deep pool of experts to oversee the prolonged recovery period within an intact social welfare system. The professionals who comprise transplant care teams extend beyond the doctors and nurses that provide direct patient care to include social workers and psychologists. Transplant programs rely upon a range of institutions to provide state-of-the-art diagnostic equipment, technicians, and radiologists; hospital-based surgical and intensive care facilities and sub-specialists; local and transnational blood banking systems; hospital and home-based teachers and educational support; and transportation and housing assistance for patients to access these during recovery.

Even in the best of circumstances, an uncomplicated transplant is both intense and lengthy, requiring at least one year for recovery. As Holly also indicated, simply holding the conversations that are necessary for informed decision-making takes time. This was consistent with the histories I elicited from families I met in both the U.S. and France, and it was common for these discussions to take place over the course of years before proceeding with a decision to transplant. Time is also needed to undergo the extensive diagnostic testing and psychosocial assessment to ascertain patients' (and their families') candidacy for transplant and, whenever possible, to mitigate findings that can pose a risk to tolerating the transplant itself or might compromise recovery.

Typically, first degree family members will undergo HLA testing as potential stem cell donors. When an unrelated transplant protocol is being considered, the transplant team will perform a preliminary search for potential matches through international marrow and cord blood registries. Depending on the underlying health of the child and the ongoing complications of

their sickle cell disease, their work-up includes consultations with a range of sub-specialists to identify potential complications, optimize patients' physical condition, and redress reversible physiologic deficits and reduce the risks of transplant. In addition, patients and families undergo psychological evaluation in preparation for the procedure. Due to patients' profound immunosuppression during recovery, the transplant team conducts evaluations for cleanliness and safety of the home environment and advocates for housing support when these conditions are found to be inadequate.

Hence, transplants not only demanded significant material and professional resources, but also reserves of space and time from families during this lengthy period of assessment. These deliberations included planning what portion of a child's life should be committed to a yearlong removal from school, friends, and activities. These negotiations were also economic, including questions of how to maintain a household where at least one parent or caregiver can be present with the child during the months spent in the hospital and home-based quarantine. At the same time the family is met with loss of income when one or both parents are required to reduce work hours or take family leave, they often must identify and enlist additional caregivers for their other children. The need to extend post-transplant expertise outside of the clinic often entangled parents and ancillary family members to make themselves available for an extended period of home-based care and often required them to cross state lines and sometimes national borders that were subject to local immigration policies.

At the time of this fieldwork, the U.S. public health insurance known as Medicaid, reimbursed the initial inpatient hospitalization for hematopoietic cell transplantation at $250,000; however, this figure and the real costs incurred to institutions can vary widely based on the type of transplant being performed, the length of the hospital stay, and whether or not short-term

complications arise.[78] In the U.S., private insurers tend to reimburse at higher rates than Medicaid, incentivizing health care institutions that perform transplant to seek out commercially insured patients to offset losses anticipated from Medicaid. In France, the approximate reimbursement to hospitals for transplants was €505,000 inclusive of the first six months of care (circa 2013, over $650,000 at the historical exchange rate). Medicaid's compensation of $250,000 was an unworkable sum in the eyes of the French doctors: "That's really not much money," one of the hematologists had marveled, when we compared the respective reimbursements through the French and U.S. state health care systems. In turn, she quoted an out-of-pocket charge of €750,000 (close to one million U.S. dollars in 2013) to a foreigner (in the example given: "a rich Saudi") undergoing a transplant in France, including the initial hospitalization and follow-up care. These figures also challenge the presumption of an inherently more cost-effective health care system in France.

Despite these obstacles, a minority of health care institutions have significantly increased the availability of transplant to their patient populations. A notable outlier is a French sickle cell reference center that has transplanted over twenty percent of its 600 patient cohort—a startling figure, as rates of transplant for sickle cell disease are in the single digits at most centers in the U.S., as well as elsewhere in France. The health care providers I met in the U.S. who were aware of the French transplant studies through the medical literature often presumed that "everyone" in the sickle cell community in France must be hearing about transplants. In absence of this information being disseminated broadly, how else could the French cohort, now approaching 300 cases, be explained? To address this question, I sought out Docteur Dani at Hôpital Y.

The sickle cell program at Hôpital Y had been led by Docteur Dani for nearly three decades. She had built up the program from the windowless basement offices they occupied

during its earliest days to the current cadre of full-time pediatric specialists. This clinical team provided comprehensive care for several hundred pediatric sickle cell patients and supervised a day hospital for the several dozens of children who received chronic transfusion therapy and coordinated the comprehensive diagnostic testing, such as blood work, carotid dopplers, and MRIs, that each patient with sickle cell disease underwent annually (*le bilan annuel*). Although Hôpital Y did not have their own transplant facility, Docteur Dani trained her clinical team to provide the intense first months of post-transplant care at the day hospital after patients were discharged from the inpatient transplant wards in Paris.

Anticipating her own retirement from clinical work, Docteur Dani had persuaded Docteur Justine to assume her role as chief of medical services for sickle cell program at Hôpital Y. Over a period of years, Docteur Dani finally persuaded the younger colleague to relocate from the smaller sickle cell center that she formerly headed elsewhere in France. By the time I began fieldwork at Hôpital Y, Docteur Dani had begun to relinquish many of her administrative duties and had curtailed her patient case load, in order to devote the remainder of her career to conducting clinical trials and preparing manuscripts for publication. Docteur Dani had maintained a distinguished research portfolio and publication record alongside her clinical responsibilities—a significant achievement for a physician, whether in the U.S. or France. That Docteur Dani was retiring from patient care but continued to work for Hôpital Y as a researcher was a departure from the usual trajectory for a clinician. She attributed her productivity as a researcher to the data analysis, grant writing, and manuscript preparation that she conducted "during the evening and on the weekends," in addition to maintaining her duties as the sickle cell center's programmatic chief and raising multiple children.

It was during the first month of participant-observation at Hôpital Y that a question was

being posed for the second time in the course of an afternoon of outpatient consultations with Docteur Justine: “How do they treat sickle cell disease in the United States?” The adolescent patient, a parent at her side, sat across the desk from Docteur Justine. She had been discussing her plans to visit relatives in the U.S. over the summer, and her tone struck me with its mixture of earnestness and curiosity. The French doctor’s reply was curt, and both of Docteur Justine’s hands cut the air above her side of the desk: “It’s the same!” Despite Docteur Justine’s exasperation, the question was fair: pediatric care at large between the two countries, while similar, was not exactly “the same.” The likely source of Docteur Justine’s annoyance became apparent when a parent at the day hospital gestured to the bag of blood that dangled on the IV pole above our heads and mused, “I would have thought that they would be doing something more advanced than this [for sickle cell disease] in the United States.” Docteur Justine’s response was in defense to the assumption that the treatments for sickle cell disease in U.S. were more sophisticated or technologically advanced than the ones available in France.

I learned to anticipate this question when I met with patients and their families in the presence of their health care providers, when I spoke with parents privately in the day hospital, and when I conducted interviews with families in their homes. Sometimes the question was addressed to the provider I had accompanied, sometimes directly to me. When meeting families in the hospital, the French physicians would sometimes introduce me as “a colleague,” who was visiting from the United States. My designation would also alternate between pediatrician, researcher, and anthropologist—furthermore, an American—who was interested in how sickle cell disease was cared for by the health system in France. When I started to explain that I was interested in learning about differences in the care of sickle cell disease, the parent or patient often completed the sentence: “—between the United States and here.” Parents sometimes

responded with surprise after I explained that, in fact, I came to Hôpital Y because of the preponderance of patients from their center who were undergoing transplants, at rates far higher than any institution in the US. Moreover, as I argue in this chapter, some of the distinctions between treatment intensification processes that had been attributed to transnational differences actually were indicative of practice variations across health care institutions, even within the respective countries.

Because she was still relatively new to Hôpital Y, I had the opportunity to observe Docteur Justine during a period when families were meeting her for the first time. Though she tended to speak quickly, Docteur Justine's demeanor was friendly and professional. She had devised a brief script that she used to introduce herself to patients as a new physician at the sickle cell center. Whenever possible, and as if by way of introduction, she also mentioned the three available treatment intensification possibilities for sickle cell disease: blood transfusions, hydroxyurea, and transplant. Docteur Justine described each option briefly, but with enough detail to explain how each method worked and some possible reasons for trying them, even if these did not necessarily apply to the patient present in the room. Though the mechanics of Docteur Justine's approach at Hôpital Y differed from Holly version of "continuous comprehensive care" at University Hospital, I posit that over time, their effects are similar, provided that the practice of transferring knowledge interacts with longitudinal care processes that supported treatment intensification.

Conversely, not every health care provider had a systematic means for broaching the topic of treatment intensification with their patients. In absence of a methodical practice for sharing this information, hydroxyurea or transplant can go unmentioned indefinitely, until a physician is prompted by a family's own questions or prodded by a decline in the patient's health

status. This became apparent to me at Hôpital B, a children's hospital whose patients with sickle cell disease drew from a catchment area roughly twice that of Hôpital Y. At Hôpital B, I was given the opportunity to observe Docteur Eugenie and her colleagues from the sickle cell reference center during their outpatient consultations and staff meetings. The families I met and interviewed were largely recruited from routine visits to the sickle cell clinic, during their scheduled transfusions at the day hospital, and at the transplant team's long-term outpatient follow-up.

As the head of the sickle cell center at Hôpital B, Docteur Eugenie was a polarizing figure among her colleagues: outspoken, exacting, and thorough. During consultations with her patients, Docteur Eugenie's interviews were deliberate and sometimes unhurried to the point that appointments regularly ran overtime. Near the end of a morning outpatient session, an adolescent girl was one of these later appointments. Accompanied by her mother, they had driven over an hour from their home outside of the city. Docteur Eugenie interviewed the patient and mother together, and then, as was customary for the French providers with their teenage patients, asked her mother to step out of the room for the physical examination.

Near the close of their session, the mother rejoined her daughter; meanwhile Docteur Eugenie excused herself to attend to an issue outside the consultation room. In her absence, I chatted with the family, explaining in more detail my presence in the clinic and the topic of my research. The patient and her mother had heard about transplants as a potential treatment for sickle cell disease, but not from any conversation with a physician. The patient's mother explained that her daughter wanted to have a transplant, and that her older brother was even "ready to donate," though they had never actually discussed the possibility with a doctor. When I asked why not, the mother replied that she did not know, but perhaps the doctors did not think

she would be a candidate for the procedure.

Docteur Eugenie returned to the room to dispatch the family. After they left the room, she turned to me and explained that this patient had a "very bad [Hemoglobin] S Beta$_0$ thalassemia," a genetic variant that is clinically indistinguishable from the Hb SS form of sickle cell disease.[79] I asked Docteur Eugenie if the transplant procedure had been discussed with this patient. Docteur Eugenie furrowed her brow, tallied some instances of familial strife that could have affected the patient, and concluded, "—and I don't think they want it." As I began to relate what the patient's mother had told me, Docteur Eugenie ran out of the room, leaving me mid-sentence. She had left to call the family back to the room. I smiled weakly when Docteur Eugenie gestured towards me and explained to them that I had brought their interest in transplant to her attention, all the while thanking me a bit too profusely for doing so. Docteur Eugenie modified the schedule for their follow-up visit, which would be in three months' time and extended the appointment to an hour in length rather than the usual 30 minutes, to allow for more time to discuss the procedure.

After they departed for the second time, Docteur Eugenie exclaimed, "This is very bad!" She openly acknowledged the disconnected expectations of this family with those of their health care provider. Docteur Eugenie ruminated that at their center, conversations about *l'intensification thérapeutique* often began at their weekly staff meetings. At these meetings, the physician, social worker, and psychologist members of the sickle cell team discussed patients that they considered notable or challenging. Perhaps, she wondered aloud, this protocol also delayed informing patients about treatment intensification options? Docteur Eugenie noted, however, that this patient also had had a good response to hydroxyurea and was not taking the medication consistently. "I don't think she needs it," she said finally, referring to the transplant. We gathered up our belongings. The morning clinic session was over.

**Ethnicized discourses, racialized affinities, and intersections with class**

In 2015, I presented the case of this adolescent from Hôpital B, among others from my fieldwork in France, to a meeting of U.S.-based clinicians. When the mismatched expectations between the family and the health care provider around the transplant became apparent, the meeting participants bubbled over with questions. The ethicist who had organized the session also happened to be French and phrased her own inquiry with care: "Where were they from?" I interpreted the question behind her question as an extension of my participant-observation and the ways that race and ethnicity were simultaneously voiced and silenced. In asking where this family was from, the assumption had been that their origins were outside of France. The expected answer was more than a geographic location: it would also stand in as a suggestion of their immigration status and the extent of their acculturation, a proxy for their educational attainment or socioeconomic status, an implication of the cultural or linguistic barriers that might explain why a conversation had not yet transpired with their health care provider, despite the family's apparent knowledge of and interest in a transplant for their child. My answer mirrored both the evasiveness and pregnancy of the question: "The mother was French. And blonde."

Here, I pose some possible reasons for why Docteur Eugenie and the family of the adolescent with $SB^0$ thalassemia had not had a prior conversation about transplant at Hôpital B. Docteur Eugenie had identified one contributing circumstance: the practice at their center had been to discuss patient cases at the staff meeting prior to intensifying therapy, including referrals for families to consult with the transplant service. The mother, too, had offered another: perhaps her daughter's physician did not consider her a candidate for transplant. That is, even a discussion among the health care providers at Hôpital B was still contingent upon the doctor's

subjective threshold for intensifying treatment for this particular patient.

Similar thresholds have been identified as sources of health care provider bias that has contributed to the underutilization of hydroxyurea. Examples of provider-originated barriers included their stated concerns for potential patient non-compliance with maintenance diagnostic testing, providers' stated fears about the possibility of carcinogenic side effects,[80] and providers' stated assumptions that their patients' lack of interest in hydroxyurea have been cited as reasons for not prescribing this medication to otherwise eligible patients (e.g., Lanzkron *et al.* 2008, Brandow and Panepinto 2010). This family from Hôpital B had already begun conversations about transplant in their own home. If they had received their care at Hôpital Y, where Docteur Justine mentioned the three treatment intensification options as a matter of routine, could this practice have provided an opening to extend the transplant conversation into the clinical sphere? Moreover, does this interpretation sufficiently account for the fact that this patient's mother was educated in France, middle class, and White?

Back in the U.S., the transplant service at University Hospital held their own weekly staff rounds, and a portion of each meeting was devoted to discussing "the candidates": the list of patients (and their families) who had undergone a consultation with the transplant team. The candidates were in varying stages of assessment for hematopoietic cell transplantation, as appropriate to the patients' disease process and overall health status, and as pertinent to the transplant physicians' experience and expertise. When it was evident that a family was meeting with multiple transplant centers or seeking a second (or third) opinion, this practice was sometimes termed "doctor shopping." My fieldwork in France also elicited examples of families who had consulted multiple sickle cell centers simultaneously or in sequence. When I described "doctor shopping"[81] to Docteur Justine at Hôpital Y, I asked her if a similar term existed in

French. She thought for a moment and responded that in France, this phenomenon has been called "*nomadisme medicale"* ["medical nomadism"].

When multiple providers become involved in the care of a patient, this situation inevitably creates conditions that can produce multiple recommendations—sometimes repetitious, sometimes conflicting, and often to the confusion and frustration of all parties. It is noteworthy that health care providers in both the U.S. and France perceived this practice as a redundancy of medical services. Although medicine is also a paternalistic and hierarchical field in the U.S., there is a certain acquiescence among providers in current practice that patients are the consumers of care and therefore entitled to approach these services as a marketplace. Even when doctor shopping was considered within the scope of patient choice, however, physicians in both countries acknowledged the burden that this duplication of services posed to the greater health care system, as when it generates a superfluous repetition of diagnostic testing.

While the metaphor of doctor shopping invokes the pervasiveness of capitalism in the U.S., the French analogue of *nomadisme medicale* implies this behavior as foreign and exotic. Yet I do not wish to overstate the implications of contrasting imageries, as they play out as everyday praxis. I did encounter examples where, when it became known to staff at Hôpital B that a patient was also consulting another center, the provider asked the family to decide upon one location for their ongoing care. Nonetheless, similarly involved (and exasperated) providers in the U.S. have made comparable requests of their patients. Upon identifying infants with sickle cell disease through newborn screening, French health care policy recommends families to sickle cell reference centers whenever possible to provide long-term specialized care. While the French public hospital and outpatient system provides the safety net, class and socioeconomic status remain a significant determinant of patients' options for how and with whom they manage their

care. Those with the means to cover copays and out-of-pocket fees, for example to a private physician or hospital, can exercise the option to obtain care elsewhere.

As in the U.S., the possibility for patients to exert choice in their care options was more attainable in regions of France where medical expertise was densely populated. Yet even in metropolitan Paris, certain families found it necessary to overcome the geographic constraints of their health care access. For example, when I spoke to the parents of Ayo, who was the receiving chronic transfusions at Hôpital Y, his mother explained that when her son started to experience the painful complications of sickle cell disease during his first year of life, she began to question the care he received at the local hospital after he was discharged with a prescription for *Doliprane* (a brand of paracetamol, an over-the-counter pain reliever, known as acetaminophen in the U.S), only to return to the following week, again in pain. Initially, she sought out sub-specialty care for Ayo at Hôpital B, but her impression was that the place was "frankly, more like a factory." During another conversation we shared, she mentioned how she even found the physical plant of Hôpital B discomforting, such as the emergency department, where the cubicles (*des box*) felt too small and narrow.

Though Hôpital B was constructed during the late twentieth century, its mismatched furnishings of heavy wood, steel, and fiberglass seemed to predate the building by additional decades, sometimes forming awkward angles and tight corridors within the consultation rooms. By contrast, the campus at Hôpital Y, though smaller, had been undergoing more recent staged renovations. At the time of my fieldwork, the outpatient clinics and day hospital for the sickle cell program were located in new buildings. The exam rooms remained modest but also bore the mark of globalized mass-production, the furniture constructed from modern plastics and the walls painted in bright solids. On her friend's recommendation, Ayo's mother learned about the

pediatric sickle cell center at Hôpital Y. As she had a portable career in informatics and despite self-identifying as "*cent pour cent Parisienne*," she moved to the suburbs. Shortly after transferring to Ayo's care to Hôpital Y, he was found to be at increased risk for stroke on his screening intracranial ultrasound and was placed on a chronic transfusion program. This intensification in her son's sickle cell management was a significant adjustment, but Ayo's mother also felt put at ease with the information she received from the team of care providers at the day hospital, who also helped to normalize this form of treatment.

Moreover, the metaphors of doctor shopping and *nomadisme medicale* place undue onus on the agency and preferences of patients and families, when health care providers also have a role in recruiting patients to their respective centers. Docteur Eugenie gave a terse example of a patient who had missed a routine outpatient follow-up appointment. By the time the team reached the family to reschedule the visit, not only did they learn the patient had transferred their care to another center, but that the family had decided to transplant their child. Through the grapevine, Docteur Eugenie took note of similar accounts from comparably miffed colleagues. Another doctor in France conveyed her own shock (her term) when she observed this practice occur at her own center, relating an instance of a family who had been referred for consultation by a sickle cell provider from an outside center. Because the child "didn't look so good"—i.e., it appeared that the patient's sickle cell care had not been optimized—the team proceeded to "just keep him," without warning or apology to the referring provider. When performed outside of perceived bounds or norms (akin to "stealing patients," in the U.S.), this practice was excoriated by some of the French health care providers I spoke with —as well as one parent—as a violation of professional courtesy.

In both the U.S. and France, assumptions about race and ethnicity, while pervasive in the

course of clinical work for sickle cell disease, typically operate in these settings as unspoken implication or veiled in euphemism. Giving voice to race or ethnicity during patient care was also contingent upon the interpersonal dynamics of the parties to the conversation. Clinical contexts produced their own ethnicized discourses and racialized affinities that overlapped with class and power. For instance, when French physicians performed case presentations of their patients, such as during the national multidisciplinary case conference to discuss potential candidates for transplant, the relative professionalism of this forum provided a clinical indication to invoke the family's country of origin or ethnicity. In analogous professional settings in the U.S., health care providers' evocation of their patients' race (e.g., Black / African American) was more readily invoked than in France, in addition to their ethnicity (e.g., Hispanic / Latinx) or country of origin.[82]

Staff meetings were less formal, and in these contexts, patient cases were presented as abbreviated clinical summaries, where providers' references to race, ethnicity, or country of origin often shed their specificity. In these instances, health care providers in France regularly defaulted to vague identifiers as "*d'Afrique*" ["from Africa"] or "*au pays*" ["back home"][83] such as when discussing their plans to optimize a child's sickle cell disease with transfusions or prescription medication prior to travel *au pays* for the summer. In France, families and health care providers did find ways to invoke race during informal clinical interactions. These ranged from discursive proxies amounting to oblique references to racial or ethnic distinction in some instances, while other contexts produced opportunities to mention racial difference explicitly. The following examples demonstrate how either instance can occur when using spoken as well as non-discursive language.

When I accompanied Docteur Dani during her outpatient consultations at Hôpital Y,

some parents had asked, in response to my presence as the American visitor, "Is there very much sickle cell disease in the United States?" Docteur Dani sometimes offered as explanation that sickle cell disease in the U.S. was a legacy—"*malheureusement"* [unfortunately], she qualified—of slavery. On another occasion, I spoke with an older adolescent patient after meeting her in the outpatient clinic at Hôpital Y; she had been transplanted several years prior.[84] I asked if she had belonged to a community-based organization or support group for her sickle cell disease or during the transplant experience. She did not. In her experience, she had to explain sickle cell disease, let alone the transplant, to her acquaintances, for example with her current boyfriend, who was very supportive but had no prior knowledge of the disease. "Your boyfriend is French?" I asked. "Yes," she replied. She and paused before adding, "He's White," so there was no misapprehension that they were an interracial couple. Near the end of a lengthy interview, a mother offered that she had heard of sickle cell disease occurring among White Europeans, "But where were they?" She had attended multiple health care centers in France (that included both Hôpital B and Hôpital Y, among others) in the care of her daughter, as well as for treatment of her own form of sickle cell disease. From her vantage, all of the other people with sickle cell disease (*drépanocytaires*) that she could see "were Black."

One of the families I met and interviewed in France I had actually first heard about, years earlier, in the U.S. While seeking out potential field sites during the preparatory stages for this research, I had the opportunity to explain my proposed project to the clinical teams in the pediatric hematology and transplant divisions at University Hospital. One of the hematologists mentioned that a family from France was visiting New York some years prior and had consulted their sickle cell program for their daughter, in anticipation of a possible move to the U.S. Given her condition and history of complications, the team mentioned the option to transplant and

recommended having her siblings undergo HLA testing to determine their status as potential bone marrow donors. The team eventually lost contact with the family, but not before providing them the name of a lead author of several French transplant studies to contact upon their return.

In a serendipitous turn, I met the same family on the first day of my participant-observation at Hôpital Y, during outpatient consultations with Docteur Dani. Nina's mother and I were astonished and delighted by the coincidence. I obtained an initial, abbreviated account of what had transpired in the intervening years. The family had remained in France but also made good on investigating their options for transplanting Nina, which had taken place just over a year ago. Afterwards, I mentioned to Docteur Dani that I had been struck by the drive that had consumed their search to resolve Nina's sickle cell disease, also resembling accounts from certain families I had met in the U.S. of the years spent researching treatment options while seeking out second (and third) opinions. Docteur Dani nodded as she listened, but added, "That really does not happen much here." I was learning that transplant remains an exceptional practice, in both countries, and I was also meeting families who were exceptions to this perceived norm.

Previously followed at a neighboring hospital and now considered an *ex-drépanocytaire* since her transplant, Nina continued her follow up at Hôpital Y, where I later had the opportunity to interview her mother in depth. Her account also alluded to the nuance that race and class produced in the clinical setting, including in the performance of professional propriety. Both of Nina's parents held private sector careers with international firms before she was born. Nina's mother had requested prenatal testing, though not out of an initial concern for sickle cell disease (of which neither parent had prior knowledge), but due to family member's trisomy disorder; the amniocentesis, however, led to a diagnosis of sickle cell disease during the second trimester.

In France, when the fetus is deemed to have a severe and unremitting illness, including

sickle cell disease, abortion is permitted until just before birth. After consulting a highly regarded adult sickle cell specialist to discuss the options, Nina's mother decided to proceed with the pregnancy and in doing so, to "never look back"—advice from the specialist that she had taken to heart. She also recalled his mentioning that if the family was of some means, this would be beneficial in caring for a child with sickle cell disease. In preparation for the birth, Nina's mother had researched and selected a pediatrician beforehand. After the birth, and as the state public health system had intended, Nina's abnormal newborn screening result also triggered a referral to the local sickle cell reference center. Her mother recounted receiving a call from a hematologist who had phoned to persuade her to transfer her care to their sickle cell service, but also to discontinue her care with her current pediatrician, who was not affiliated with their hospital. By then, however, Nina was five months old and her mother had developed a good relationship with their pediatrician. Put off by the attitude of the hematologist, Nina's mother refused the transfer, a request she found objectionable, in part, because it was rude to her current provider.

Since infancy, Nina experienced frequent, often daily, complications of her sickle cell disease, including learning and motor difficulties that were not typical for her illness. Nina's mother also continued contact with the adult sickle cell specialist who had provided their prenatal counseling, and on his recommendation, she met a hematologist she trusted, Docteur M, who followed Nina over time, supervised her hospitalizations, and coordinated care with Nina's general pediatrician. Docteur M was initially reluctant to recommend transplant for Nina due to the risks of the procedure. In fact, since their family returned from their consultation at University Hospital, Nina's transplant had taken years of lobbying on the part of her parents before she was permitted to proceed with the procedure in France.[85] For Nina's father in particular, the decision to transplant hinged largely upon the question of her longer-term

prognosis, expectations that were already being informed by Nina's ongoing health and education struggles despite the care she had received thus far.

As of 2011, Docteur Eugenie and some of her colleagues in the field began a quarterly teleconference for pediatric sickle cell providers across France and its overseas departments to present cases of patients who were potential candidates for transplant, discuss related ethical and clinical concerns in complex sickle cell management, and encourage consensus in this decision-making. Nina's family had consulted Hôpital Y about transplanting Nina, and her younger sister was found to be a match. Although the clinical committee required to review all proposed cases of transplant in France had approved proceeding with Nina's transplant, participants on the teleconference recommended trying other forms of treatment intensification first. One of the participating physicians on the teleconference recalled the discussion of Nina's case and remarked on her large number of extra-curricular activities—"as many as a [government] minister's daughter"—in a tone that sounded more skeptical than complimentary. After a yearlong trial of transfusions and hydroxyurea that did not significantly improve Nina's condition, Docteur M's attitude toward the transplant, at least in response to her parents' frustrations, began to shift. At their subsequent meeting, she argued forcefully for the transplant, and the dissenting colleagues relented.

Since her transplant, Nina's overall condition and motor issues dramatically improved; some of her learning difficulties, however, persisted. At the time we spoke, Nina's mother was still composing e-mails of introduction and scheduling appointments with specialists to discuss these concerns. The search for answers was not over, and Nina's mother expressed a desire for her daughter to have a future that was "without limitations." She also kept in touch with Docteur M, for whom Nina had become a kind of "*publicité vivante*" [walking advertising] for transplant.

“It’s so funny,” Nina’s mother said as she recalled asking Docteur M what she thought of the procedure now, since Nina’s recovery. Docteur M told Nina’s mother that her own practice had shifted, and she had begun bringing up the possibility of transplant to her other patients and encouraging families who were more hesitant. Near the end of our interview, Nina’s mother produced her cell phone, explaining that she wanted to show me a picture of Docteur M. In the photograph, she was in profile, silhouetting hair that was arranged in neat twists. Because I had not met Docteur M, Nina’s mother wanted me to know her not only by name, but also to see that she was also Black. She smiled at the photo, before turning off the screen to place the phone to her bag and conclude, “She’s a very good doctor.”

In the U.S., a significant portion of medical labor and expertise has shifted from physicians to include nurse practitioners and other non-physician health care providers (e.g., physician assistants). Nurse practitioners in hematology and oncology assume much of the everyday management of patients, and the demands of specialized knowledge in these fields are high. The acuity and severity of the complications that regularly befall patients of inpatient oncology and transplant ward, as well as the potency and complexity of their medications and cancer treatments, often exceeds the experience and capacity of the residents covering the inpatient floors. This degree of task shifting of clinical responsibility from physicians to nurse practitioners had not yet occurred in France. When I attempted to explain the distinction between nurse practitioners from traditional nursing staff in the U.S., some French physicians expressed surprise with the extent to which the professional lines between medicine and nursing had crossed: “Sure, they take the blood pressure, but they don’t auscultate heart sounds [with a stethoscope], do they?” While staff nurses in both countries are expected to collect vital signs like blood pressure, U.S.-based nurse practitioners perform physical exams to assess their

patients' clinical condition and, with varying degrees of physician supervision, direct care management decisions accordingly.

Though the nurses in France did not task share to the extent that Holly and the transplant nurse practitioners did with their physician colleagues in the U.S., nurses I met at both Hôpital B and Hôpital Y demonstrated their potential to integrate themselves as crucial patient advocates within the processes of treatment intensification. When I interviewed the families of transplanted patients who had received their comprehensive care for sickle cell disease at Hôpital Y, they invariably cited Docteur Dani as the person who had informed them about transplant. When I asked if there was anyone else who provided support with their decision-making, almost as frequently they mentioned Lena, one of the nurses. Even when parents did not recall her name, they attempted to identify her, sometimes referring to her as "the nurse from the Antilles."[86]

After graduating from her nursing school in overseas, Lena and gaining additional experience abroad before specializing in pediatric nursing in France. She began working in general pediatrics at Hôpital Y, before transferring to the day hospital to work with Docteur Dani for the sickle cell program. Prior to this, Lena was unfamiliar with sickle cell disease, the field to which she has since devoted these last two decades of her career. Lena's work with the sickle cell program spanned the ground-breaking French clinical trials that supported the efficacy of a chronic transfusion program for stroke prevention and the feasibility of transplant using matched sibling donors. When I met Lena, she still worked as a member of the clinical team and was an active sickle cell advocate in the hospital and the community at large. I had the opportunity to observe Lena at work in the day hospital and as a volunteer in regional awareness-raising events. Lena helped to organize the *groupes de parole* (support groups) that were made available to transplanted patients and their family members. When Docteur Dani produced an informational

video that featured patients from Hôpital Y who had successfully undergone transplant, a form of *téimoignage* (testimonial) to introduce and recruit other families to undergo the procedure, it was Lena who conducted the on-screen interviews.

What was the source of this connection between Lena and the families she met at Hôpital Y over the past two decades? Lena started to respond, "Maybe it's because…," but then tugged at the skin of her forearm, gesturing to its dark tone. When I started to mention the name of one of the doctors who was also Black and among the current physician staff, she shook her head and pointed a finger in air, "She doesn't have the history!" Lena maintained that when she first arrived at the day hospital, and during the earlier years of the sickle cell program, she was the only member of the sickle cell team who was also Black. In Lena's words, families often approached her as *une compatriote* (a compatriot); her visibility to the families at Hôpital Y, at least initially, was not based on ethnicity or country of origin, but by her race. In our interview, she elaborated that while her appearance helped the parents to approach her, Lena's affinity with the families over time was the product of the effort she made to listen to them. She also cited her manual dexterity in accessing their children's veins with ease, for example when introducing intravenous catheters for transfusions and drawing blood. Both were examples of practices and professional qualities that lent confidence to families.

As put forward at the beginning of this chapter, the transfer of knowledge about disease-modifying therapies like hydroxyurea or transplant is a necessary-though-insufficient practice in a process for implementing these treatments as interventions. For the practice of informing patients about their therapeutic options to operationalize and shift into a change in care management, across even a single institution, required significant material resources (as in the case of transplant or chronic transfusion therapy), but also human ones, in terms of interpersonal

relationship and experience. These latter reserves are less quantifiable and more ephemeral and include the uniquely adept support that Holly at University Hospital and Lena at Hôpital Y provided for their patients over time. That Holly and Lena took substantive measures to support families as they moved forward with even the high-risk intervention of transplant was integral to the treatment intensification process at their respective institutions. Lena acknowledged that she did not foresee continuing to work as a nurse for many more years, and she anticipated nearing her own retirement. Echoing Holly's colleague at University Hospital, Lena was concerned for her own legacy at Hôpital Y. How to replicate the apparent expertise and singular drive of certain health care providers? Lena had been looking for another nurse with a similar level of commitment, someone she could train to eventually take her place. "I haven't found that person yet," she told me.

**Getting from "It's just information…" to informational justice**

Since her arrival at Hôpital Y, Docteur Justine was becoming attuned to the interpersonal tensions that had produced some of the differences in clinical practice that I was observing at Hôpital Y and Hôpital B. "It's just information," Docteur Justine offered, as she rifled through charts during a pause between patient appointments, "Why not tell them?" She was responding to my comment that her practice of regularly mentioning the three methods of treatment intensification to patients was not the norm. Docteur Justine framed her approach in this way: if doctors do not let their patients know about the treatment options available to them, their patients will search for the information themselves anyway. And from the perspective of most physicians I asked, whether in the U.S. or France, "that's worse." As evidence, they readily cited examples

of internet and social media-derived content that had been the source of troubling health misinformation to patients and the community at large, ranging from anecdotal to apocryphal.

Brown and Duguid have illustrated the unique obstacles of re-engineering an organization at the management level, as compared to a production floor. These challenges apply also to the innovation of care processes within health care institutions, and both are examples of organizational culture where "…life is less linear, inputs and outputs are less well-defined, and information is less 'targeted.' These are, rather, areas where making sense, interpreting, and understanding are both problematic and highly valued—areas where, above all, meaning and knowledge are at a premium" (Brown and Duguid 2017[2002]:90). To exert process control in these contexts demands negotiation of the implicit politics and power dynamics within health care institutions that have an impact on the movement of knowledge and practices across domains occupied by patients and families, as well as the hierarchy of their practitioners.

Even where institutional processes are strong, health care providers develop individualized practice styles as drawn from personal experience and professional training. That is, approaches to patient care are far from uniform, and this practice variation is readily observable when comparing interactions between health care providers and families. In addition to the multiple ways to practice medicine is the latitude for what counts—and is accepted by colleagues and patients—as good care. Here I revisit how the ontological experience of caregiving can prompt innovations in practice that compel health care providers to adopt and disseminate, as well as resist or reject, these departures from pre-established modes of care. In response, I provide an example in the work of medical record keeping and documentation.

Providers across different institutional settings, whether in the U.S. or France, had site-specific methods for reproducing their patients' histories and clinical interactions as medical

records. These practices served both to document past patient care[87] and to help guide future clinical management decisions. For patients with chronic diseases, being able to produce a written summary of their medical history that was thorough yet also succinct made lasting impressions on new and unfamiliar providers. Physicians at the sickle cell center at University Hospital, for instance, specifically mentioned to me the medical summary they were presented by a family from France who had consulted them some years prior. At the time I observed Dr. S at Community Hospital in the U.S., he produced and updated medical summaries for his patients that were independent of the charting required by his institution.[88] However appreciated this written document was by the health practitioners who received them, preparing consult reports and maintaining medical summaries required practices at odds with an optimal bedside manner.

At Hôpital Y, a significant portion of outpatient visits involved transferring patient metrics and lab results to a spreadsheet program. When test results from the annual exam were clipped to the front of a chart, the providers I observed spent a considerable portion of the patient encounter entering these data points into the spreadsheet, for future extraction, aggregation, and statistical analysis. Often the provider and family sat across from each other in silence, the quiet of the room interrupted by clicks from the keyboard of the desktop computer. At times during this portion of the consultation, I assumed the role of a chatty outsider and made small talk with patients and families. When appointment schedules ran behind, I was sometimes enlisted to help expedite the process of data collection by measuring the height and weight of the children or checked their blood pressure.

At Hôpital B, the outpatient consultations produced an amalgam of paper-based charting and hard copy records, such as of diagnostic test results and hospitalization notes, that cohabitated with the electronic record system that referenced the dates of their testing, doctor

visits, and inpatient stays and, when possible, included archived consultation notes. Providers did not have to edit their clinical notes in real time, and, for some providers, this meant a larger proportion of the visit was spent in direct conversation with the family members and physically examining the child. Some of the sickle cell providers at Hôpital B dictated their consultation notes into a tape recorder, for the administrative assistant to transcribe afterwards. Depending on the physician, this occurred immediately after the patient left the room or, more awkwardly for this researcher, while the family waited to be dismissed. The updated note subsequently was uploaded to the hospital's electronic record system, and a hard copy was mailed to the child's primary care pediatrician.

Prior to Hôpital Y, Docteur Justine was the clinical director for a much smaller sickle cell program elsewhere in France. She recalled to me that while at her previous hospital, the patient records she had inherited from her predecessor were in serious disarray. Docteur Justine took it upon herself to manually reorganize and update every patient's chart in her practice. It was a tedious project, but in doing this, she came to know her patients and their clinical cases exceedingly well. Docteur Justine prided herself that not a single patient on chronic transfusion therapy from her former center suffered from iron overload, a common and challenging to treat complication of repeated blood transfusions. By tailoring each child's transfusion schedule meticulously to their symptoms and interval blood testing, she was able to prolong the duration between transfusions for many of her patients, thereby retaining the benefit of stroke prevention and improved quality of life, while reducing their exposure to blood products.

Patients with Hb SS disease who did not require more frequent monitoring for transfusion or hydroxyurea therapy customarily underwent maintenance outpatient visits on a quarterly basis. This was the conventional practice I observed both at Hôpital Y and Hôpital B, as well as

in the U.S. At Docteur Justine's former sickle cell center, however, she found that getting to know her patients' conditions as well as she had enabled her to conduct the comprehensive care for her patients with Hb SS over fewer sessions. As a result, she reduced the frequency of outpatient visits to every six months; her patients with less severe symptoms of Hb SC disease were able to extend the interval from every six months to annually. Because she had been the principal sickle cell provider at her previous institution, Docteur Justine was empowered to modify their clinical management efficiently, as these practices were under her direct control and supervision. When I asked what explained this difference between the standard three-month interval between outpatient visits at Hôpital Y (and Hôpital B and in the U.S., for that matter) and the six-month interval she had implemented at her former center, she answered, "*Par habitude*" [Out of habit].

By contrast, the larger census of patients at Hôpital Y required multiple physicians to supervise routine outpatient care and long-term management, provide post-transplant care in the clinic, as well as manage nearly one hundred patients undergoing regular transfusions and post-discharge transplant care at the day hospital. Nearly all of the patients receiving transfusion therapy underwent a standard practice of simple transfusions[89] that were scheduled every four weeks. Did adhering to what had become Hôpital Y's established schedule for transfusion therapy expose their patients to preventable iron overload? Docteur Justine noted that she wanted to introduce the more individualized patient care that she had developed at her previous institution to Hôpital Y, but even from her position as the sickle cell center's new clinical leadership, modifying the pre-existing protocols when they were already entrenched as routine practice proved challenging.

With these examples, I underscore how the proliferation of practices that produced new

knowledge and inspired novel practices were also subject to the particularities of institutional history and interpersonal context. Moreover, bringing the practices that began as novel interventions to scale as processes across institutions can flatten and homogenize the nuance that made these modifications beneficial in the first place. Brown and Duguid describe the push and pull between practice and process as a relationship where "[th]e process [gives] shape and direction to an organization. It always risks, however, blinding the organization to improvisation and new ideas…. // Practice suffers from the opposing danger—of allowing itself to evolve too independently and so become too loosely 'coupled' to the organization" (Brown and Duguid 2017[2002]:107). This "balancing act" was also true of the health care practitioners I observed and their institutions, and innovative practices "require[d] … coupling loose enough to allow groups to develop their own new knowledge but tight enough to be able to push that knowledge along the lines of process" (Brown and Duguid 2017[2002]:115).

Back at University Hospital, Holly related an example of how her own tinkering with pain management protocols in the outpatient setting led to practice change for this patient care process at her sickle cell center:

> When I came here, any kid that came in with sickle cell pain automatically got an IV and … [intravenous] fluids. After … watching this for a few years, I said …, "You're sending the message that they need an IV and IV fluids. … Instead, let's figure out how to treat the pain without the IV … because if we can do that successfully, I can keep that kid at home and keep that family intact, versus pulling a mother or a father away to be with this child [in the hospital], and then what happens to the other children?" So all of us have the goal to preserve the child, but also to preserve the family. … [I]n the beginning that was really hard, because … everyone was used to getting an IV. And then all of a sudden Holly stopped giving them an IV: "[W]hat do you mean you're not giving me an IV? You're withholding care." No, I'm not withholding care. I'm going to do the IV a little bit differently, with a bottle of water or a bottle

> of juice. Because you can get that same fluids in you faster … if you drink it. … [I]t was … very easy … for the young kids, …. because if they didn't know [to expect] the IV, they just thought that was the way it is. For the older kids [who already expected intravenous fluids], that was really hard. So I had to get the trust of the child first. The parents were going to fight me, but once the parents realized that the child trusted me, and once the parents realized that I was on the child's team, it all got better.

This instance of practice innovation was not made at the outset of Holly's arrival to the center, but after she had provided patient care multiple years, gaining the trust of her patients as well as of her colleagues. Nor was this an arbitrary or top-down measure, and as a nurse practitioner, Holly had to gain backing from her physician colleagues to implement this successfully within the existing clinical hierarchy. When I asked Holly how she had presented her proposed change to colleagues at the time, some seven years prior to out interview, she could not recall the request explicitly: "I mean, I'm sure I said to them, This is what I want to try and this is what I believe. And the truth of the matter is, at the end of the day, I had to make it work, okay? So my colleagues were great in terms of 'Yes, Holly, you can try it,' but I had to make it work." For Holly, the processes of patient care at University Hospital responded to and accommodated variations in approach among the health care providers: "[The attendings] have different formulas. They all have the same goal. Everyone gets there a different way. So everyone calculates things a little bit differently, but it's the same in the end." This shared goal, Holly explained, "is a really good level of health" for their patients.

In another fieldwork example, I demonstrate how the practice of presenting new findings can speed or slow its own uptake within the process of treatment intensification. Here I present the dissemination of the initial results from the haploidentical transplant trials for sickle cell disease, as this information became available to providers at research meetings and to patients in

the clinical setting. At Hôpital Y, among the patients I observed meeting Docteur Justine for the first time was an older adolescent who was accompanied by her mother. Docteur Dani previously had informed the patient of the possibility of participating in a new transplant protocol that was being piloted in France. The trial was led by a U.S.-based group and used haploidentical or "half-matched" relatives as donors—a significant shift from limiting transplant donors to fully matched siblings, as had been the practice for sickle cell disease in France. Haplo transplants already had been performed for other severe disease conditions; this approach was a radical enough departure for sickle cell disease that the first published results were presented with fanfare at the Annual Society of Hematology annual meeting in 2012 (Bolaños-Meade *et al.* 2012).

A benefit of haploidentical transplants is the potential to expand the available donor pool, which to this point had posed a substantial limitation of hematopoietic cell transplantation for sickle cell disease. Haplo transplants also pose an advantage to unrelated donors for patients who belong to non-White ethnic groups, as these individuals are the least likely to encounter a sufficiently matched donor through existing bone marrow registries. Hence a patient's mother, father, sibling, or even child—anyone who shared at least half of a patient's genetic material—can potentially be a candidate donor of hematopoietic cells for transplant. Because the haplo transplant protocol for sickle cell disease used a reduced intensity conditioning regimen, the study also recruited adult candidates, whose cumulative organ dysfunction usually excluded them from the morbidity of myeloablative conditioning regimens. The haplo trial results also generated interest for a very low reported incidence of graft-versus-host disease and no deaths during the initial phase of the trial (Bolaños-Meade *et al.* 2012). The significant downside to the procedure was that roughly half of patients rejected their graft; this was the tradeoff: a relatively

low morbidity of reduced intensity haplo transplants in exchange for a much lower cure rate than the myeloablative conditioning regimens.

Even some of the sickle cell providers I had met who already supported the myeloablative transplants using matched sibling donors regarded the new study findings, at least initially, with suspicion. The very same morning at the American Society of Hematology meeting, shortly after these results had been presented, I was speaking with a U.S.-based hematologist-oncologist with a longstanding and prominent career in sickle cell research. Unprompted, he both brought up and dismissed the new protocol as "that crap haplo transplant." Sometimes the initial distrust towards novel treatment modalities could be assuaged over time, by means of familiarity and repetition. I spoke with the same physician-scientist ten months later, after results from the haplo trial had disseminated over subsequent sickle cell advocacy and research meetings; during this interval, he also became one of my study participants. In the interceding months, he conceded that there were potential benefits to the haplo transplant protocol, with the caveat that patients needed to be sufficiently informed of the risks and benefits, as with any new procedure.

When I observed Docteur Justine in the clinic with her patient, it was still within six months of the first published results of the haplo trial. Docteur Justine was noticeably guarded when discussing this protocol with this adolescent. During the consultation, she pointed out the ongoing uncertainties regarding the procedure, as well as the complications of sickle cell disease that were required for a patient to be a candidate for this trial. Surprised, bordering on mystified, the patient remarked that the way Docteur Justine was explaining the haplo transplant sounded completely different from how it first had been proposed to her by Docteur Dani. When Docteur Justine spoke with me afterwards, she questioned the indications for referring this patient for a

haplo transplant, pointing out that the cerebrovascular findings from this patient's MRI could have been due to an alternate diagnosis (a reversible brain disease) and not necessarily a stroke. Docteur Justine wanted discuss the case with Docteur Dani, before they referred the patient for the trial.

As exemplified here, the available information about haplo transplants for sickle cell disease were never drawn from a depository of objective content. Nor were the practitioners for these knowledge transfers engaged in a value-free practice. Here, the conveyance of knowledge also were enactments of interpersonal relationships and their structural constraints, giving shape to quotidian politics. Folbre has pointed to the gendered power dynamics between care and coercion: "[C]hoice is a funny thing, affected by both moral values and by social pressures. Often what we choose depends on what we think other people will choose" (Folbre 2001:7). The information about the haplo trials that did transfer across stakeholders also doubled back to conserve or retrench ongoing practices as well as to modify and realign them with reconfigured expectations for the future. "Just" information was hardly "mere" (i.e., only) information. New knowledge was in constant interface with its justifications, as the emerging data on haplo transplants for sickle cell disease had posed uneasy co-existence with previously established (yet still heterogenous) transplant knowledge and practice. "Just" information also stirs questions of fairness in the availability of and access to new knowledge—positions that cannot be extricated from conjoined hemispheres of obligation and responsibility, from who ought to provide information to how should it be conveyed.

Byron Good summarized an essential observation from Favret-Saada's positionality as ethnographer, that "[o]ne could only talk about witchcraft from an engaged position—as one bewitched, as a suspected witch, or as one willing to serve as a unwitcher. To engage in talk was

to enter the struggle" (Good 2003[1994]:13). I pose an analogous truth for health care practitioners and researchers, as they provide information about treatment options to their patients: that the "engaged position" is unavoidable. To illustrate: near the end of my fieldwork in France, Docteur O had suggested that I meet a family for what would likely be their last visit clinic visit to Hôpital B before moving to the U.S. Over the course of observing Docteur O's approach to outpatient sickle cell management, I knew that she was unlikely to have had a prior conversation about transplant with the family of this school-aged child. Their transfer through the father's work for a multi-national software company would relocate them in proximity to a pediatric sickle cell program where the hematologist also spoke French, and I mentioned this to them. "*Que practique*!" [How convenient!] had been the mother's appreciative reply. As their departure date approached (shortly after my return to the U.S.), Docteur O asked me for the center's contact information to refer for the patient's family, which I provided.

Scarcely nine months after my return to the U.S., I received an e-mail from the same U.S.-based pediatric oncologist. In passing, she mentioned the "good news": the younger sibling of the patient I had recommended to their center was a perfect HLA match, and they had referred the family to University Hospital for transplant. A few months later, the same family was discussed during candidate rounds at University Hospital. The attending who presented the case to the transplant team phrased her surprise in nearly identical language to what the patient's hematologist in the U.S. had written to me in her e-mail: "I can't *believe* this family had never heard of transplant, especially since they are from *France*."

This series of events foregrounds the power of information, or at least the guise of its potential, where the forging of biosocial links between a child with sickle cell disease, her sibling donor, and the technology of hematopoietic stem cell transplantation seem to have sliced through

space and time. This form of knowledge transfer, however crucial, remains but one of the practices in the process of treatment intensification. As in the case of Docteur Eugenie's clinic patient, a family's knowledge of and proclivity towards the possibility of an intervention like transplant are necessary but insufficient practices for ensuring its own utilization. When I had the opportunity to greet Docteur O's patient for a second time, a little over a year after meeting her in France, she was receiving her post-transplant care at University Hospital; by then, I also had learned not to attribute these opportune encounters to serendipity alone.

In addition to the transience of the family's stay in the U.S. and their shift to a foreign health care system, the decision to transplant their daughter proceeded despite the lack of systematic provisions to cryopreserve her ovary. Premature ovarian failure is a common complication of the chemotherapy and radiation required for transplant. In an attempt to preserve fertility for pre-pubertal girls and adolescents, the surgical removal and freezing of ovarian tissue is available through the private sector in the U.S., but often at prohibitive cost. While the storage of ovarian or testicular tissue (or of oocytes or sperm in adolescents and adults) does not guarantee future fertility, it affords a partial safeguard against the unpredictability of this post-transplant complication.[90] University Hospital's transplant specialists informed the family that the French health system covered this procedure, including the necessary cryopreservation, for children undergoing transplant. Nonetheless, her parents opted to forego pursuing this option in France and proceeded with transplant in the U.S.

Deming's theory of process control reminds how the patient's capacity to utilize complex treatment options requires not only the material infrastructure of health care systems and institutions, but also the (re)assurances between patients and health care providers reproduce even ancillary practices that maintain the process of treatment intensification. Regardless of a

positive reception from families at the outset of entertaining a transplant, a procedure that entails myriad and intricate steps, contingencies, and risks can as readily stall out without even mundane forms of support, when momentum pauses or begins to falter. This situation was reiterated in the case of a family I had met on two occasions the outpatient clinic at Hôpital B, where I had the opportunity to interview the parents during the second visit.

Prior to the follow up appointment, their sickle cell provider suggested that I attend the consultation, mentioning that the mother had become "*très demandeuse*" [very demanding].[91] Since learning that their newborn, whose cord blood was collected at birth, was HLA-matched with their son with sickle cell disease, she had requested an appointment earlier than their scheduled interval follow up to discuss next steps. As they settled into the examination room, the mother and I recognized each other from their previous visit. This time, Juneau's father was also present. The visit, in some ways, was more of a formality, or at least a gateway to the next step: a referral to consult with the transplant team.

After the appointment with their sickle cell provider, I had an opportunity to interview Juneau's parents together. Juneau's father was born and raised in France, but his parents met abroad, while his father visited relatives in West Africa. During our interview, Juneau's father recounted obtaining a degree in accounting, but paused momentarily before mentioning his current occupation. Juneau's mother directed a questioning look towards her husband and answered for him, "*Un facteur*" [A mailman]. Juneau's mother did not receive formal schooling while growing up in Ivory Coast. She had met Juneau's father when she was an older adolescent, and the couple eventually settled in metropolitan Paris to have their family. Their older son had tested negative for sickle cell disease; Juneau was their second child. Although a great grandparent was known to have had sickle cell disease, for unclear reasons, Juneau did not

undergo newborn screening and was diagnosed only after manifesting symptoms of the disease in infancy. Juneau's life with sickle cell disease became complicated early on. Numerous hospitalizations, of which four were due to acute chest syndrome, led to a year of exchange transfusions to stabilize his condition. Now four, he finally enjoyed his longest period out of the hospital, maintained on a stable dose of hydroxycarbamide [hydroxyurea].

Juneau's mother was the first member of the family to learn about transplants for sickle cell disease, though not from a health care provider, but rather when the procedure was mentioned on a television program. During her most recent pregnancy, she had asked her obstetrician about the possibility of collecting blood from the umbilical cord for future donation. As a result of this advocacy, the cord blood was arranged to be recovered at delivery and prepared for HLA testing and storage. Both parents were delighted that their daughter was a match. Although Juneau's overall condition had improved considerably, hydroxyurea had not been a panacea, as two of his episodes of acute chest occurred while on treatment. His mother voiced their vigilance against provoking complications, the constant reminders that Juneau's disease also prevented him from participating in activities of childhood, even just to play in the snow. His father reiterated that they wanted Juneau to lead a normal life, like his brother and sister. Hearing these sentiments, I was reminded of the phrase Nina's mother had used. As I repeated those words aloud, Juneau's parents' faces broke into smiles. "*Sans limitations,*" they repeated, nodding together.

The following month, Juneau's physician at Hôpital B's sickle cell center presented his patient's case to the national teleconference. The argument for transplant was persuasive: Juneau's sickle cell had been severe, he had a fully matched donor, his family was supportive. By all expectations, his transplant seemed imminent. Some six months later, near the close of a

subsequent teleconference, I was surprised to learn that Juneau had not yet undergone his transplant. The update was brief, mentioning only that Juneau's parents had completed their consultation with the transplant service and were scheduled to consult a fertility specialist, but due to reservations on the part of the parents, the transplant, for now, was on hold.

Another 18 months had passed, when I ran into Docteur Eugenie at the 2015 ASH annual meeting. She expressed her dismay, as Marine Le Pen's National Front party had just captured the popular vote during the first round of French regional elections. The runoff vote (that eventually thwarted the ultra-right party from gaining power) was days away; the referendum approving Brexit, and the election of Trump as president of the U.S., would soon follow. I asked Docteur Eugenie how Juneau was doing. He continued to attend their sickle cell center, and his transplant still was not imminent. She was vague as to the reason for the delay, perhaps demurring because she did not provide the direct care to Juneau, who was followed by one of her colleagues. She did mention that his overall condition remained precarious. Their clinical team did not seem to object to proceeding; rather, the family was hesitating, possibly due to the risk of post-transplant infertility.

I could not help but wonder: had Juneau's family received their care at Hôpital Y and been followed by positive deviants like Lena and Docteur Dani, would their son have been transplanted by now? If concerns for Juneau's future fertility had been the primary impediment, a referral to a fertility specialist was standard procedure at either center; in terms of bare content, the information provided about possible options, such as testicular tissue preservation, likely would have been similar. Unlike ovarian tissue, the utility of preserving prepubertal testicular tissue is still experimental, but still covered by the French health system. Had Docteur Dani spoken with Juneau's family, however, she likely also would have reassured them that their male

transplant patients underwent normal puberty and were not encountering issues with infertility after transplant (unlike their female counterparts, most of whom required hormone replacement to induce puberty and/or maintain their menstrual cycle). Certain other practical issues come to the fore, as Juneau gets older. Hematopoietic cells need to be dosed by the recipient's weight, and as Juneau grew, it would be harder to match this dose to the stem cells available in preserved umbilical cord blood, likely requiring a supplemental bone marrow harvest from his younger sister. Though he was still young, delaying the transplant also meant accumulating end organ damage from sickle cell disease, which accentuates the risks posed by chemotherapy.

In the course of this fieldwork, I encountered a range of practices that health care providers employed to produce new knowledge about their patient cohort and implement novel treatment strategies. These varied in their capacity to exert process control on an institutional scale (i.e., "Control the steps of the process and the final product will largely take care of itself" [Young 2011:118]). This included the practice of providing information to patients and families about options for treatment intensification, as well conveying this expertise across a range of clinical and professional settings. During our interview, Holly reiterated the centrality of trust, particularly when the patient-provider dynamic entailed offering unfamiliar treatment options and modifying previously established modes of care: "You really have to know your patients. You have to be inside of their heads, inside of their souls… . And they have to believe in you, … that you're not going to leave them ... that you will stick with them no matter what. Once you get the trust, you've got a chance. Without the trust, nothing's going to happen."

This chapter makes the case that whereas health care provider obligations to inform patients of their treatment options is commonly apprehended as ethical duty or compassionate performance, entrusting knowledge to patients and families is an inherently political act that

shifts power dynamics within the clinical encounter. The act of informing patients and their families of their options to intensify treatment needs to be conceived as such to begin to uncouple treatment innovation from the reproduction of social inequalities. Placing the onus on patients to perform their own advocacy (as had Nina's well-resourced family), while possible, can only work to a point (as Juneau's family experienced). Analogous to Deming's example of industrial process control (as described by Young 2011:118): "No amount of educating the consumer [patient] will fix the process. No amount of teaching—or of blaming—the worker [practitioner] will materially change the group behavior." Likewise, to mitigate the outcome gaps that are produced when introducing new knowledge to stratified social systems, clinical practices and health policy must reckon with their incumbent and embedded power relationships. In an effort to redress this limitation, the next chapter proposes a constructivist approach to demonstrate the role of trust, hope, and beliefs in scientific innovation and their affective appeal in persuading clinical practice change.

# 4

## Transplant Candidates, Treatment Collectives: Embracing the Problem of Belief

> The tracing of the social and psychological role of religion is thus not so much a matter of finding correlations between specific ritual acts and specific secular social ties,—though these correlations do, of course, exist …. More, it is a matter of understanding how it is that men's notions, however implicit, of the "really real" and the dispositions these notions induce in them, color their sense of the reasonable, the practical, the human, and the moral.
>
> Clifford Geertz (2000[1973]:124)

> Belief is good for religion, not for science.
>
> Docteur Eugenie (personal communication, 2013)

Up to this point, I have offered an ethnography of scientific and clinical knowledge production as multi-sited enactments in the care and practice for sickle cell disease. In the preceding chapter, I examined the practices and processes within health care institutions that recruited patients to treatment intensification options, such as hydroxyurea and hematopoietic cell transplantation. The politics of providing (just) information were among the contingencies for how knowledge was transferred among practitioners and families and whether novel clinical practices became embedded as treatment intensification processes within health care institutions**.** In retrospect, Deming's theory of process control recasts the case of newborn screening and comprehensive care for sickle cell disease as an example of a health policy process that reproduced gains in childhood survival on a national scale (see Chapter 2).

Many of the case examples of practices that had successfully supported treatment intensification within institutions also negotiated the structural constraints and social stratifications that pervade health care systems. Some of these strategies alleviated material and interpersonal barriers to circumvent some of the effects of disparate power dynamics that hindered knowledge transfers. The human capital and unconventional expertise of health care practitioners such as Holly at University Hospital and Lena at Hôpital Y proved essential conduits for support and reassurance. Without them, certain patients may have missed a discussion about transplant, foregone a referral to the transplant service, or deferred proceeding with this high-risk intervention.

Even for the families who had benefitted from Holly and Lena's involvement, the path to treatment intensification was rarely a linear sequence, nor reducible to an unfettered flow of informational exchanges. Relationships between families and health care providers produced malleable dynamics that tolerated multiple ways to practice medicine, allowing for even contradictory practices to be construed as acceptable, and even "good," care. Often families who received (at times markedly) different management for their sickle cell disease still endorsed satisfaction with their respective institutions and providers, particularly when they perceived a sense of collaboration with their health care team. I also met families who had utilized care across multiple centers, for example when patients changed health care institutions for their long-term follow-up. These participants took note of the differences in their children's disease management, and their comparative experiences were instructive, including families I met in France who had attended both Hôpital Y and Hôpital B.

The outsized effects of patient-provider interactions and their inherent power dynamics were not lost on the health care providers, as evident in the following exchange. In 2015, after months of

in-person and e-mail communications to secure an interview, I was tailing Dr. Michael DeBaun yet again, this time at the annual symposium of the Foundation for Sickle Cell Disease Research. At one of the educational sessions, DeBaun was among three physician-scientists presenting on, and ultimately debating, the relative merits of hematopoietic cell transplants then available for sickle cell disease. Even though DeBaun had been a co-author on the haploidentical transplant trial, he guarded against offering transplants of any kind to the pediatric population, and these objections were also pronounced at this forum.[92]

When the session opened to the audience for questions, Elliott Vichinsky commented to the presenters, repeating a position he had taken publicly at prior conferences: that in his experience, patients wanted to be informed of all the available treatment options—and wanted their physicians to communicate these to them—in order to arrive at a decision independently. To paraphrase Vichinsky, his patients were asking to "'just give me the information, Doc, and I can decide for myself.'" The implication of Vichinsky's position was that health care providers should not withhold information about treatment options from their patients. While health care providers may share their reservations, their own ambivalence should not preclude them from discussing these options at all.

Afterwards, conference attendees tarried on the mezzanine of the convention center, while serving themselves coffee and tea. I spoke with a pediatric hematologist who was struck by how differently the presenters had extrapolated the transplant studies to their clinical recommendations, differences that pervaded their respective interpretations of the same trials. During the pause between sessions, I also approached Dr. Vichinsky, who was, by then, familiar with this research. Eventually DeBaun joined our conversation, that was intermittently interrupted as colleagues stopped to greet them. Now face-to-face, Vichinsky posed his question to DeBaun directly, if hypothetically: "If there's a trial you don't agree with—ethical, but you don't agree with it—would

you promote it?" Dr. DeBaun's pause was measured, before answering, "If I think it would advance the science, I would." Vichinsky couched his response with care, noting that "[the sickle cell] population is so grateful to have a provider that really cares for them, it gives the provider tremendous power—"

"It is my *greatest gift*," DeBaun responded, embracing Vichinsky's observation fully. Like many physicians, DeBaun regularly culled anecdotes from his own clinical experience and had a knack for presenting these histories as deft parables. DeBaun related the case of a mother whose formal education was modest, but who had impressed him with how perceptively she read him as a clinician. He recounted offering her the option for her child to participate in a research study. She had listened politely as he described the risks and benefits, in what he considered to be a dispassionate manner. After he finished, she roundly rejected participation; astonished, he asked why she had declined the study so unequivocally. DeBaun laughed as he recalled her response, which reflected her (accurate) perception of her son's provider attitude toward the study: that if Dr. DeBaun had thought it was a good idea for her child to participate, he would have told her to just do it already. As this example illustrates, the health care provider's reported attitudes towards a particular therapy were insufficient to predict how these positions eventually translated as clinical practice. This was particularly true for interventions that were contested and heterogeneous, as often was the case in transplant for sickle cell disease.

In this chapter, I demonstrate how anticipation and expectations for the future, as matters of care, perform moral and political work in the production of scientific knowledge. I build upon my previous themes of anticipatory politics (Chapter 2) and institutional practices versus processes (Chapter 3) to articulate an iterative relationship between hope and belief (*croyance*) with medical knowledge and clinical practices in the validation of scientific truths. I explore the practice-based

and affective requirements for individuals and institutions to adopt a new treatment approach or explore a novel research design, as well the limits in refashioning these processes. Ultimately, I employ a multi-sited mapping of hope, where, I assert, constituent variables of belief, risk, and expectations for the future merit constructivist attention in their own right. I ask, how exactly is belief operating in clinical management when, for instance, the nurse practitioner Holly (re)iterates, "I *believe* in hydroxyurea, because I have seen it *change lives*"?[93]

In his epigraph from Chapter 2 (page 82), Michael DeBaun invokes hope in the anticipatory guidance he provides for his newly diagnosed patients with sickle cell disease: "I look the parents in the eye and say, 'Your child, as a result of medical advances, research that has been done by others prior to your child's birth has greatly increased the chances of your child reaching her 18th birthday, and I hope to be able to celebrate that day with you when it comes'" (DeBaun 2013). The circulation of affective economies can inform the motivations of researchers and health care practitioners to produce and disseminate new knowledge. As my preceding chapters also demonstrate, evidentiary assurances alone—scientific and otherwise—were insufficient to produce and institutionalize practice change.

Even when circumstances in one context appear to deem an intervention as clinically efficacious, practically viable, and ethically justified, these reasons do not necessarily ensure its adoption elsewhere. Alternatively, in low stakes settings, when the repercussions of accepting or rejecting treatment are few, the available scientific evidence need not be robust to encourage certain practices to spread. In these instances, interventions whose efficacy remain dubious but can be reframed as options that "may or may not help, but probably won't hurt" carry a potential to proliferate that is incommensurate with the convictions of those who had promoted them. A presentation of evidence and risk, absent of an account of their affective appeal and practical

consequences, ultimately serves as a poor predictor for whether new knowledge acquires scientific merit and social value over time. The construct of hope and belief offered in this chapter redresses the limitations posed by explanatory models, such as the health belief model, that prioritize cognitive reasoning but "does not consider the emotional component of behavior" (Champion and Skinner 2008:62). Rather, an acknowledgment of the relational properties of hope and belief also provides constructivist scaffolding for understanding how patients and health care providers knowingly, or even with partial or little knowledge, consent to risk.

In the course of this fieldwork, some participants identified belief as a "problem," or at the very least as problematic, as Docteur Eugenie's statement ("Belief is good for religion, not for science") suggests. A colleague posed his concern that the differences in treatment intensification practices across the regional sickle cell centers in France reflected their respective leaderships' degree of belief (*croyance*) in the utility of transplant, such that each took a position favoring transplant, hydroxyurea, or exchange transfusions to the relative exclusion of the others, and that this was "not rational" [*pas rationale*]. Byron Good carefully frames the problem of belief as an object of anthropological study, which historically has positioned the beliefs of its research subjects in subtle (and not-so-subtle) opposition with (Western) knowledge (Good 1994, 7). Good counters this disciplinary conceit when citing religious studies scholar Wilfred Cantrell Smith, who recognized the modern mistranslation of belief from its pre-Enlightenment usage in religious life:

> First, Smith finds that grammatically the object of the verb "to believe" shifted from a person (whom one trusted or had faith in), to a person and his word (his virtue accruing to the trustworthiness of his word), to a proposition. This latter shift began to occur by the end of the seventeenth century, with Locke for example, who characterized "belief" along with "assent" and "opinion" as "the admitting or receiving any proposition for true, upon arguments or

> proofs that are found to persuade us … without certain knowledge ….” [Good 2004[1994], 16 (Smith 1977:48)]

This also applies to the French word *croyance*, which is also derived from the Latin root for belief, *credere*. Good continues, again citing Smith:

> Credo, in the Latin, is literally, “I set my heart” (from Latin cordis or heart [as in cordial] and *-ido or *-dere, to put). Credo in unum Deum was incorrectly translated in the sixteenth century as “I believe in one God,” when it meant “I formally pledge my allegiance to God,” Whom we of course all acknowledge to be present in the world (Good 2004[1994]:17).

That is, whether one chooses to align oneself with—or be loyal to—another, including the Christian god, was the central question of pre-Enlightenment thinking. By contrast, a notion that beliefs denote the proof of a proposition based on persuasion arrived later.[94] This subtle yet significant shift is also salient for a critique of human agency that foregrounds rational intentions based upon an assumption that beliefs are primarily cognitively situated, as opposed to the alignment of affect, sentiment, and practices among individuals and groups. An examination of beliefs as they relate to hope and risk offers a potential workaround of this misattribution in causality, particularly where a cognitively-biased belief model has not aligned neatly with effecting the desired behavior or practice change.

In this chapter, I disentangle some of the structures of experimental practice (e.g., Kuhn 1996[1962]) that have produced transplant protocols and treatment strategies for sickle cell disease that are distinct to French and U.S. contexts. This includes elucidating how research environments, professional motivations, and institutional processes have an impact on what I refer to here as *treatment collectives* that expand and innovate, as well as uphold and conserve, existing experimental design and clinical care standards. In evoking Fleck’s *thought collectives*[95] (1979[1935])], or communities of collaborative *thought styles*, I elaborate examples of the single

center, multi-center, and transnational treatment collectives that made it possible to consider and adopt—but also postpone and dismiss—novel transplant protocols for sickle cell disease. Also using the analytic premise of anticipatory politics, I examine the production of treatment collectives by way of their practices and affective modes.

Whether in France or the U.S., participants' use of the term "belief" was regularly extended to scientific methods, material technologies, medical personnel, as well as to the otherworldly and unexplained. In applying anticipatory politics to beliefs, I take the step to approach its presence less as a problem, but rather as a premise for knowledge to become recognized and adopted by others. In analyzing belief as an affective economy, I draw from the enriched functionalism that Douglas articulates as her Durkheim-Fleck model. As Douglas observes, "[a] combined Durkheim-Fleck approach to epistemology prevents either science or religion to be accorded too much privilege" (1986:37):

> Durkheim evaded his own rules of method by making the sacred depend for its vitality on the emotional excitement of great gatherings. Fleck used the more coherent principle that trust and confidence are prerequisites of communication; he thereby avoided the inconsistency of suspending rationality in order to explain the origin of rational thought in effervescent emotions stirred up the by grand-scale public rituals. … (1986, 35).
>
> [For] Fleck… a scientific fact does not smack the researchers between the eyes and compel assent… .[96] (1986:37)

In this way, a constructivist representation of belief operates beyond a codified philosophical or religious system while also resisting its relegation to superstition or opinion. Just as Harding points out that "… Enlightenment assumptions constitute many everyday beliefs and practices and cultures" (2008:135), Fleck designates affect as an integral component of cognition:

> "[W]e must object that any thinking, to be emotionless, must be independent of momentary and personal mood, and flow from the average mood of the collective. The concept of completely

> emotionless thinking is meaningless. There is no emotionless state as such nor pure rationality as such. How could these states be established? … The power of establishing independent existences is conceded to it emotively. Such thinking is called rational." (Fleck 1979[1935]:49)

In positioning a constructivist understanding of knowledge, Fleck's thought collectives—in contrast to objectivity—provide the conditions and constraints for subsequent knowledge to develop (rather than progress). In this way, Douglas and Fleck's approach to knowledge production resonates with Geertz's insight that "men's [*sic*] notions, however implicit, of the 'really real' and the dispositions these notions induce in them, color their sense of the reasonable, the practical, the human, and the moral" (Geertz 2000[1973]:124).

This chapter also builds upon the analytics of hope and expectations for future cures already raised in the social study of science (e.g., Delvecchio Good 2001, Mattingly 2013), for example in the way that patient advocacy organizations have contributed materially to the political economic and intellectual investments underwriting their scientific research agenda (e.g., Rabinow 1999, Brown 2003, Novas 2006). These latter research concerns have responded to a proposition that "the confidence and hope expressed in scientific progress most prominently exists in situations of desperation or near-hopelessness" (Novas 2006:291). I argue that posing disproportionate attention to the "hyperbolic expectations" (Brown 2003:4) of these narrowly defined and highly speculative futures occurs at the expense of a critical accounting of anticipation and its co-production with care practices that are ongoing and otherwise routine. As this dissertation demonstrates, expectations for the future, including the future lives of children, circumscribe what becomes offered as treatment to families, as well as what patients seek from these care options.

When the researcher's positionality neglects attention to the expectations that become

enacted with the everyday, this ultimately works against Brown's own call for "reflexive engagement with expectations [that] … become[s] more sensitive to the many hidden futures that hype so often silences" (Brown 2003:18); it is precisely these "hidden futures" that become silenced when analytic consideration is relegated to abstract futures. Novas' political economy of hope results in a similarly aspirational proposal for a constructivist representation of hope: "[i]t is the relational qualities of hope that make it possible to consider studying it in a political economy context" [2006:291]). Yet in the political economic analysis he offers of advocacy organizations as they seek to alter research environments and hasten discovery for cures, Novas ultimately reverts hope to an object, the depository for distributed expectations and displaced biovalue.

By contrast, anticipatory politics locates abstract desires and expectations for the future to specific times and places. In so doing, anticipatory politics exchanges one form reductionism for another: as an alternative to materially narrating hope as political economy, anticipatory politics ontologizes hope through the composite lens of its practices and affects. Recalling the positionality that praxis and affect provides to the ethnographer (see Chapter 2), anticipatory politics grounds expectations for the future in the co-production of experimental science and clinical care practices. This approach holds the methodological advantage of representing the potentialities of hope, risk, and belief as phenomena that are continually co-constructed from daily life. This strategy also has been proposed by Mattingly in ethnographic work that reconfigures the tableau of care and clinical work to locate hope as it becomes produced through "moral laboratories" of quotidian practice (Mattingly 2013).

With attention to the everyday clinical practice of treatment intensification for sickle cell disease, I analytically position hope in relation to therapeutic interventions, such as hydroxyurea and bone marrow transplantation, that are no longer "coming down the pipeline." Both initially

were categorized as hyped technologies (e.g., Wailoo and Pemberton 2006), when their safety and effectiveness in clinical practice were still in question. Even as hydroxyurea and hematopoietic cell transplantation have become readily available in most high-income contexts, twenty years on, both technologies remain underutilized in the eyes of their supporters (e.g., Brandow and Panepinto 2010). Shedding light on why underutilization occurs for arguably effective therapies that also are readily available through the both the U.S. and French public health systems needs to take into account the role of affective conditions, such as hope and belief, as determinants for materializing treatment intensification practices.

This research implicates hope and belief for their part in the process of adopting experimental innovations and justifying practice change. In the pediatric population, transplants for sickle cell disease are no longer new, and the expectations for efficacy, morbidity, and mortality, when performed in children, have largely been established. Clinical trials have also expanded the indications for hydroxyurea and transplant to a broader patient population: in the case of hydroxyurea, from adults to children; in the case of transplant, from children to adults. For both of these examples, and reiterating the eventual adoption of newborn screening as national health policy, the pathway from published evidence to practice transformation has been far from direct. Shifting norms in clinical practice are also responding to a longer-term prognosis for sickle cell disease that included the incumbent uncertainties for adult survival and quality of life. The proliferation of treatment intensification practices is occurring alongside the desires of patients and expectations of caregivers and health care providers who attend to these futures.

**Treatment collectives**

In her analysis of Fleck's earlier work,[97] Löwy (1988) credits his dual training as a physician and microbiologist for providing the perspective to conceptualize an epistemology based upon thought styles and thought collectives. Because Fleck's own thought style was drawn from this liminal stance as clinician and researcher, his findings were initially excluded by his contemporaries in the history and philosophy of science[98]:

> Fleck's epistemology has its roots not in his philosophical training but rather in his scientific and medical practice. Taking his own clinical laboratory practice as a starting point for his epistemological reflections, Fleck did not ask what science *must be*, but attempted to investigate what science *actually is* and how historical processes and social institutions are related to the emergence of scientific 'facts.' (Löwy 1988:137)

As such, Fleck recognized the milieu of antecedent experience as the conscious and subconscious scaffolding for thought communities to apprehend and generate new knowledge, including in the sciences. Hence, no single disciplinary perspective or scientific approach can provide a holistic account of the individual disease experience.

In *Genesis and Development of a Scientific Fact*, Fleck cites a lengthy excerpt from the introduction to an immunology course given in 1910 by Julius Citron in Leipzig[99] (1979[1935]:55-59). Citron's lecture demonstrated that Western scientific thought communities construed from the complexity of bodily systems that "*[t]he dividing line between the physiological and the pathological event cannot be biologically drawn with any precision*" (1979[1935]:56). That is, given the multiplicity of arenas where humoral and cellular immunity were known to participate, even a century ago, any functional interpretation of these effects is necessarily socially informed. Since Fleck, others have applied constructivist positionalities to

implicate symbolic knowledge as more than a representational modality in service of a secular science (e.g., Canguilhem 1989[1943, 1966], Foucault 1994[1963]). Contemporary examples include Martin's work (e.g., 1991, 2001[1987], 2006) implicating the circulation of gendered metaphors that condition how scientific knowledge is observed, embodied, and practiced, as well as which populations and ailments are made visible, become valued, or remain marginalized.

Fleck's work also introduced the concept of the incommensurability (Löwy 1988:141-2) between thought styles, both as they shift and develop over time (rendering formerly held ideas and beliefs incompatible with newer ones), as well as between disciplines. As training across medical disciplines diverge, specialization leads to both a gain in knowledge through training, but also a loss of familiarity and practice in others (Löwy 1988:143). Because thought styles are produced from social worlds, experience is not simply additive, and as specialization increases distance from exchange with other thought collectives, expertise can contribute to the challenge of communication between disciplines.

The practice of comprehensive care and transplant medicine for sickle cell disease demanded both specialization and interdisciplinary coordination, and I encountered multiple examples of navigating incommensurability between specialties in an effort to provide this care. Among the challenges of meeting the needs of adult patients as they transition from pediatric care is the availability of providers with both expertise and the inclination to care for this group of high-risk patients, whose disease complications intensify with age. I spoke with multiple pediatric providers in the U.S. and France who offered the view that the task of providing comprehensive care to adults with sickle cell disease could be performed by a "good internist" or general practitioner, with training and experience in sickle cell medicine. One U.S.-based pediatric hematologist-oncologist offered the neologism "sickle cell-ologist" to describe a

primary care doctor who obtained such specialization without formal fellowship training in hematology.[100] Docteur Justine noted that internists "really have to know a lot [of medicine]." General practitioners of adult medicine regularly address diverse complications that become more prevalent with age, including high blood pressure, chronic kidney disease, lung and heart disease, arthritis, diabetes and other endocrine disorders. Internists regularly draw upon this broad base of clinical knowledge, arguably becoming better suited to provide comprehensive care than hematologists less acquainted with the prevalent health complications encountered by an adult population. Just as the practice of general internal medicine today rarely requires its practitioners to interpret a blood smear, the breadth of conditions that encompass adult primary care, without regular clinical exposure, can leave a sub-specialist adrift.

To implement a risky and complex treatment like transplant, let alone enable this practice to thrive, relied upon cooperation, or at least coordinated alignments, between otherwise incommensurable stakeholders and disciplines. As this research demonstrates, even the initial step to complete a consultation with the transplant service is hardly a cursory measure for many families. To proceed with treatment intensification relies upon the contingencies of patient-provider relationships, including how anticipatory care practices, beliefs towards available treatment options, and the expectations projected upon uncertain futures translate as advocacy for particular interventions. Here, I provide two examples of the unique treatment collectives that made novel approaches towards transplant practice and collaboration possible at the institutional and multi-institutional level.

The first example presents the unconventional practices that Hôpital Y adopted to redress the incommensurability between hematology and transplant medicine in assuming post-transplant follow up care at their sickle cell reference center. The second examines some of the

circumstances that enabled the haploidentical transplant to become the first non-myeloablative transplant protocol for sickle cell disease to be implemented in France. Until the haplo trial, nearly all of the French transplants performed for sickle cell disease utilized a myeloablative conditioning regimen, as defined by the selection of chemotherapeutic agents used to destroy the patient's bone marrow and make space for the infusion of donor cells to engraft and reconstitute the blood system. In addition, French transplants for sickle cell disease are exclusively performed using blood relatives as donors, and only until the more recent haploidentical transplant trials (see also Chapter 3), these relatives were limited to fully matched siblings.

When characterizing the French transplant standard for sickle cell disease as conservative, I refer to its lack of deviation from precedent. I should clarify that this consistency in selection of myeloablative agents began in 1992, after a collaborative review of transplant outcomes for the first 12 patients from the pilot phase of the trial. In response to the high rate of graft rejection with busulfan and cyclophosphamide alone, the working group recommended adding a third agent, rabbit anti-thymocyte globulin (ATG), to the conditioning regimen, which ultimately reduced rejection rates of over 20 percent to three percent (Bernaudin *et al.* 2007). Since 1992, however, the anomaly of adhering so singularly to one protocol for nearly all of the transplants conducted for sickle cell disease in France during the two decades that followed also skewed from customary transplant practice.

The norm in transplant medicine has been for centers to "tweak" conditioning regimens, as a U.S.-based transplant physician labeled the convention of starting from a previously implemented protocol and incrementally altering it. As an example, the publication that described the first 50 transplants for sickle cell disease in Belgium had aggregated its results across four centers that used five distinct conditioning regimens between 1986 and 1997

(Vermylen *et al.* 1998). While a center may appropriate a previously documented transplant strategy in an attempt to improve upon its safety and/or efficacy or broaden the pool of eligible patients, an attempt to modify rather than replicate a transplant protocol also carries the potential to make a unique, and therefore publishable, contribution to the field. A significant downside of proliferating experimental variation, however, is the ensuing reduction in statistical validity of study findings, as each additional trial duplicates recruitment from the potential pool of participants. Even well-established transplant centers draw from a relatively small cohort of eligible patients. The same U.S.-based transplant physician summarized the predicament thusly: "Everyone is doing something different, and [due to the small sample for each protocol,] we can't prove anything."

A range of intentions comprise the strategic justifications for tinkering with transplant protocols. These include improving upon the conditioning regimens' risk and efficacy and broaden their application in the patient population. Yet the very efforts to reduce procedure risk not only can occur at the expense of efficacy, but create complications of their own making. Using a less potent conditioning regimen in hopes of averting infertility and other end-organ damage not only contends with the likelihood of higher rates of graft rejection but also the unpredictability of GVHD. To date, the limitations of the unrelated donor trials for sickle cell disease include their inability to demonstrate a comparable efficacy and safety to related (including haplo) donor transplants. And in the case of the unrelated donor transplants that used a reduced intensity conditioning regimen, graft rejection was high, as well as mortality, where six of the seven deaths (out of 30 transplants) were due to chronic GVHD, a severe and long-lasting complication suffered by two thirds of patients (Shenoy *et al.* 2016, Roberts and de la Fuente 2016). For the over two hundred patients undertaking the French standard of busulfan and

cyclophosphamide, since tweaked with ATG over two decades ago, this transplant strategy has proved both successful and predictable over time. “Docteur Dani,” noted a French transplant physician, “is very attached to this protocol.” With the weight of epidemiologic evidence over time, it was hard to blame her for maintaining this attachment.

In reproducing 95 percent rates of survival and remission from sickle cell disease, while maintaining low complication rates using a myeloablative protocol, these findings also lent argument for limiting transplant donors to matched siblings. Certain institutions established processes that maximized identification of existing matched sibling donors and, in certain cases where these were absent, promoted their procreation. These practices included offering HLA testing for existing siblings, encouraging umbilical cord blood harvesting to expectant mothers, and referring families for pre-implantation genetic diagnosis (PGD) to conceive sibling donors (see also Introduction). Centers that practiced greater consistency in informing families of these options produced processes that initiated a potential conversation about treatment intensification or a potential referral for transplant.

In deviating from norms of transplant experimentation, this conservative strategy also made possible the “beauty” of the French cohort, as the aforementioned transplant physician had characterized the unusual existence of this sample. The sheer number of subjects continues to produce long-term data points, which have been used to analyze outcomes retrospectively. When I arrived in France, Docteur Dani had speculated that lower doses of ATG than the large one the protocol had initially adopted could produce comparable outcomes. By the following ASH meeting in the U.S., Docteur Dani presented the poster of the completed retrospective data analysis. On review of 236 patients, lower doses of ATG corresponded with higher rates of chronic GVHD,[101] reaffirming the existing standard and arguing against tweaking the

conditioning regimen further.

Rather than continue to tinker with the protocol, certain institutions enlisted strategies that stabilized the myeloablative standard for sickle cell disease and also accommodated its proliferation in France, including to adolescents (Bernaudin *et al.* 2010). For example, rather than risk compromising already high rates of engraftment by reducing the intensity of the conditioning regimen, Docteur Dani incorporated aforementioned methods of fertility preservation with existing underwriting from the French government. Yet even as the greater public health system facilitated experimental fertility methods for transplant candidates, the routinization of these processes still depended upon site-specific practices for their implementation. Lack of practice consistency across institutions yielded a lingering source of regret for at least one parent I met while her daughter received her post-transplant care at Hôpital Y. The mother lamented that the option for ovarian tissue harvesting, which she since learned was standard practice at Hôpital Y, had not been offered at their former sickle cell center prior to transplant.

Transplants with allogeneic donors are broadly dichotomized as related or unrelated, by virtue of a donor's biologic kinship to the recipient. Genetic relatedness between donor and recipient is among the major variables contributing to procedure risk, in addition to specificity of matching major and minor human leukocyte antigens. A hematopoietic stem cell donor who is immunologically matched and biologically related to the recipient is preferred over a similarly matched but unrelated donor, as the risk of graft rejection and GVHD increases with genetic difference between host and donor cells. While related donors are preferred in allogeneic transplant, certain conditions have allowed for the possibility of an unrelated transplant, provided that an immunologically similar donor can be identified.

Although unrelated transplants were not being performed for sickle cell disease there, its possibility was invoked by some of the families I interviewed in France: multiple parents voiced the need to increase participation from Black Africans who were underrepresented in existing blood and marrow banking systems. Despite more recent efforts to increase recruitment from racial and ethnic minorities, the composition of international marrow and cord blood banking systems are still disproportionately represented by Caucasian donors and White majority countries, including the U.S. and U.K. As HLA is transmitted by heredity, a patient's ancestry, race, and ethnicity has an impact upon the likelihood of identifying potential transplant donors. While a closely matched unrelated donor can be identified for nearly all White patients (and with all eight major antigens fully matched 75 percent of the time; Gragert *et al.*:344),[102] the paucity of samples collected from people of color significantly reduces these probabilities for those of Hispanic, Asian, and African descent and mixed ancestry. Population modeling of the existing registry in the U.S. placed the likelihood of identifying a well-matched unrelated donor lowest among Black patients, at under 20 percent (Gragert *et al.* 2014:344, National Marrow Donor Program 2018).

Haploidentical or "half-matched" transplants, which require only one rather than both HLA-bearing chromosomes to match the recipient, drastically expands the pool of potential donors to also include half-siblings, parents, children, and blood relatives more removed. This is contrast to matched related donation, which demands a full sibling[103] whose mendelian probability of inheriting the same HLA alleles is only 25 percent. For certain, usually malignant, conditions, it is possible to conduct an autologous transplant, where patients are the source of their own hematopoietic stem cells, which in turn undergo chemo- and/or radiotherapy prior to being reintroduced to the body. Hence the appeal of gene therapy, which also averts the problem

of locating a donor and of GVHD through genetic editing of the patient's own stem cells (e.g., Ribeil *et al.* 2017]). While autologous donation essentially eliminates the risk of GVHD and long-term immunosuppression, even gene therapy requires conditioning regimens to destroy the existing bone marrow, in order for the altered hematopoietic cells to engraft.

Transplants can also be differentiated by procurement method of donor stem cells, whether from bone marrow, peripheral blood, or umbilical cord blood. The source of donor cell collection has an impact upon the course of the transplant. Stem cells can be harvested from peripheral blood less invasively than bone marrow (which usually requires anesthesia in an operating room setting), but also is associated with increased GVHD compared with bone marrow and cord blood. Cord blood is collected non-invasively and associated with less GVHD when well-matched to the recipient, but also with delayed engraftment. In the case of the Sickle Cell Unrelated Donor Transplant Trial (or the SCURT trial), high rates of graft rejection led to premature closure of the cord blood arm of the study (Kamani *et al*. 2012).

As indicated above, transplants are also broadly designated as myeloabloative or non-myeloablative, based upon the relative potency of conditioning regimens. These are drawn from myriad combinations of chemotherapy agents, antibodies, immunosuppressants, and dosed radiation, with the short-term goal of making room in the marrow for the infused stem cells, while remaining mindful of the longer-term objective to attenuate undesired interactions between donor cells and the recipient's residual immune system. A subset of myeloablative transplants have been observed to result in stable mixed chimerism, an induced tolerance that maintains engraftment and disease remission, while both donor and host cells remain in circulation.

For certain non-malignant conditions, even partial participation from donor cells can relieve symptoms of an illness. A chimerism as low as 25 percent donor (as measured by the

presence of donor white blood cell precursors) can still produce remission from sickle cell disease symptoms, due to the competitive advantage of healthy donor red blood cells (Abraham *et al*. 2017). These phenomena provided plausible grounds for reducing the intensity of conditioning regimens, as a complete destruction of the recipient's bone marrow was not necessary for stable engraftment. And with less potent conditioning regimens, the pool of prospective transplant candidates (who would not tolerate a more aggressive protocol) could be broadened. Introducing mixed chimerism as an acceptable transplant outcome still contends with the shortcomings of reducing treatment intensity, including the increased risk of graft rejection and GVHD.

Graft-versus-host-disease (GVHD) is a significant complication and contributor to transplant-related mortality and unlike in cancer, non-malignant conditions do not benefit from its graft-versus-tumor effect.[104] At best, GVHD can be a worrying but relatively mild and transient complication; at worst it is emblematic of when a disease becomes substituted with another—one that, in the case of a chronic and/or severe GVHD, can precipitate a transplant-related death. As trials continue to experiment with potent immunosuppressive agents, such as monoclonal antibodies, in hopes of reducing the incidence and severity of GVHD, this objective is but one of multiple moving targets that can dog an incipient transplant regimen. The downside of increasing immunosuppression includes delaying the reconstitution of the immune system, causing yet another source of problematic and difficulty-to-treat infections that are potentially life-threatening and prolong recovery.

Some centers, including University Hospital, have further classified their conditioning regimens as "reduced toxicity" (e.g., Radhakrishnan *et al*. 2013), as opposed to myeloablative. This designation is based upon using more conventional chemotherapies, such as busulfan, at a

dose that is “moderately ablative” (e.g., Bhatia and Walters 2008:114). While busulfan is a familiar agent to transplant medicine, a physician at University Hospital reminded his team that its potency should not be regarded lightly, likening its toxicology to “liquid radiation.” Reduced toxicity transplants are also differentiated from reduced intensity transplants, that are intended to be non-myeloablative. While the benefits of reducing chemotherapy and radiation dosing reduces many of the more dramatic short-term side effects during the conditioning phase, the tradeoff for keeping one’s hair or experiencing less malaise, nausea, or painful mouth sores, can arrive at the cost of an increased risk of rejecting the graft and of GVHD. Hence, parsing what constitutes a reduction in toxicity and defining what makes a transplant less intense faces slippages in translating these terms to comparable outcome objectives.

As these examples demonstrate, hematopoietic cell transplantation can vary widely in practice, even in the treatment of a single disease process. The number of centers in the U.S. that are participating in transplant for sickle cell disease continues to expand. Those that are engaged in transplant research, however, have performed very different versions of transplant compared to the French standard. In addition to the haplo trial, these included experimental protocols that recruited unrelated donors and/or partially HLA-matched donors (e.g., Kamani *et al.* 2012, Shenoy *et al*. 2016), incorporated reduced toxicity (e.g., Radhakrishnan *et al*. 2013) and non-myeloablative conditioning regimens which were intended to be less toxic (Bolaños-Meade *et al.* 2012), while also prioritizing recruitment of adult patients (e.g., Hsieh *et al* 2009, Krisnamurti *et al*. 2015), who carried higher risks of transplant-related mortality and complications than children; or investigated alternate drugs and treatment strategies in an attempt to reduce the incidence and severity of GVHD. Rather than entertain participation in an unrelated donor trials, French experimental practice for sickle cell disease has focused its expansion to the haplo

protocol (de la Fuente *et al.* 2018) and gene therapy (Ribeil *et al*. 2017).

As indicated elsewhere, the transplant hospitalization is an intense, often month-long admission, that can readily become prolonged in the event of infections, GVHD, delayed engraftment, and the combination of these. Beforehand, patients undergo surgical placement of a central venous catheter to facilitate repeated blood draws and permit simultaneous infusions of chemotherapy, medications, blood products, and fluids. After chemotherapies and/or radiation are applied, patients spend the majority of days in physical isolation from visitors outside of immediate family due to profound immune compromise. Upon infusion of donor cells (i.e., "day zero" of transplant), the wait for first signs of engraftment begins, usually demonstrated by reaching and maintaining a minimum count of the neutrophil type white blood cells in the peripheral blood. During these initial weeks post-transplant, patients are still dependent upon transfusions of red blood cells and platelets. These other cells lines need to sufficiently repopulate before patients are stable for discharge and outpatient follow up. The gradual recovery of the fuller range of white blood cell lines continues after discharge, where patients continue to practice physical isolation at home.

**The exception of French transplant exceptionalism**

All of the centers that I observed utilized a day hospital (e.g., Hôpital B and Hôpital Y) or infusion room (at University Hospital) which could provide the higher acuity care often needed during the more immediate period after discharge.[105] These clinical settings could still administer blood products and IV medications on an outpatient basis, while enforcing contact precautions in the case of immune suppression or infections. In absence of a transplant facility on site at Hôpital Y, Docteur Dani had cultivated relationships with the major regional transplant centers,

including (if to a lesser extent) with the transplant service at Hôpital B. In a departure from typical practice, however, Docteur Dani also trained herself, and subsequently her pediatric team, to replicate outpatient post-transplant care at the sickle cell reference center at Hôpital Y.[106]

In training its sickle cell service to provide the care usually carried out by transplant specialists, Hôpital Y created an exception to the incommensurability of practice delineations between pediatric hematology and transplant medicine. Likely also facilitating this blurring between specialty disciplines was that Hôpital Y was a community hospital and without its own transplant facility. Hence, for sickle cell providers to reassert patient care at this juncture did not encroach upon the expertise of an adjacent department, as would have occurred at Hôpital B or University Hospital. Transplant supervision at Hôpital B and University Hospital resembled the more typical practice configuration, where the transplant team assumes responsibility as the primary service caring for the patient, especially during the lengthy period of post-transplant recovery.[107]

While sickle cell providers may have occasion to encounter former patients after their transplant, these visits, for the most part, are out of courtesy and not for purposes of providing medical supervision or directing patient care. As explained by providers in the U.S. and France, because transplanted patients [*les après-greffés*] no longer have sickle cell disease, they also no longer require a sickle cell specialist.[108] During transplant and recovery, parents and caregivers often need to curtail or forego work altogether for several months or longer: first, to accompany children during the month-long inpatient stay, and subsequently to bring them to numerous follow-up appointments, when not otherwise homebound and restricted from everyday contacts. Adult caregivers are responsible for administering copious medications around the clock, including via their intravenous access and often, for young children, through a naso-gastric

feeding tube.

Unlike Hôpital B and University Hospital, where patients transferred from a sickle cell service to the transplant team, Docteur Dani had organized the day hospital and outpatient clinic at Hôpital Y to care for sickle cell patients after their transplant discharge. Hôpital Y also received a smaller but significant subset of transplanted patients who (like Nina) had received their sickle cell care from outside centers. Over time, the cohort of *ex-drépanocytaires* numbered well over one hundred. As care moved from the day hospital to the outpatient clinic, Docteur Dani continued meticulously to document the results from their diagnostic testing, bloodwork and laboratory markers, to her database in real time, simultaneously facilitating her own clinical research. By contrast, the sickle cell center at Hôpital B did not keep a formal record of their transplanted patients. On my behalf, Docteur Eugenie had arranged for an administrator from the transplant service to furnish a list. Fewer than three dozen names fit a single page, including the patients who were, by then, adults. As I began to meet patients from the list who were still followed as outpatients, I found that about half of the names had been referred from the sickle cell center at Hôpital B. The remaining patients on the list had been referred from outside centers, including Hôpital Y.

Similar to transplant care at other centers, patients at Hôpital Y paid at least weekly visits to the day hospital for the first three months after transplant. In absence of complications, these initial months of weekly visits gradually decreased in frequency to biweekly and monthly at the outpatient clinic. Members of the sickle cell team were trained to oversee the gradually withdrawal of multiple anti-infective medications and immunosuppressive drugs. Because Hôpital Y assumed their long-term transplant follow up, including patients' annual exams, Docteur Dani also learned to manage some of the lasting complications. This included

administering the hormonal contraceptive medications to induce puberty and maintain menses in patients with ovarian failure; elsewhere, this would have been supervised by pediatric endocrinologists.

The yearlong period of immunosuppression after transplant usually necessitates home-based or correspondence schooling. In another departure from typical practice, however, when children at Hôpital Y transferred care out of the day hospital to the outpatient setting, many also returned to school as soon as three months post-transplant. As I had been familiar with the typical transplant course in the U.S., where home quarantine under similar conditions was regularly nine months or a year at the least, I was surprised to see patients at Hôpital Y resume their scholastic re-entry so soon. Docteur Dani explained that this practice came about after observing that the majority of post-transplant infections in their cohort were due to pre-existing viruses that had been latent[109] and reactivated—iatrogenically due to their suppressed immune state—and not from infections acquired from the community. Provided an uneventful recovery, patients could return to school, Docteur Dani concluded, upon having their central venous catheter removed.[110] That children were beginning to exercise this degree of normalcy in their daily life so early in the post-transplant course was a noticeable difference in the families I met at Hôpital Y. The reduction in their caregivers' visible and expressed exhaustion with the demands of post-transplant care at three, six, nine months *après-greffé* made the ordeal seem a good deal more humane than I had experienced at other centers.[111]

At University Hospital, I also had the opportunity to meet and observe families as they underwent reduced intensity and reduced toxicity conditioning regimens, with a subset of these cases under trial with an unrelated donor protocol. These patients regularly contended with much longer recovery periods, often due to infectious complications and GVHD. Some had

experienced significantly prolonged hospitalizations, one approaching a year in duration. In nearly all, home-based quarantine continued for at least a year or more. Two particularly difficult hospitalizations for unrelated transplants involved patients who narrowly averted death. While they eventually recovered from refractory cases of GVHD with extracorporeal photopheresis, this complex from of immunotherapy entailed regularly removing and filtering whole blood, subsequently treating the circulating white blood cells with ultraviolet light, and reinfusing the treated blood into the patient. Completing therapy required maintaining a central line and transfers to an outside center with the equipment and expertise to perform this specialized treatment over the course of a second year of recovery.

In a contrasting example of the unpredictability of reduced intensity transplants, two children experienced uncomplicated hospitalizations while on non-myeloablative conditioning regimen and timely engraftment, only to reject their grafts shortly after discharge. Both families eventually underwent second transplants, which were ultimately successful, but used myeloablative conditioning regimens that produced the pain and discomfort of a higher dose chemotherapy. One of these mothers recalled questioning her son's relatively mild course during his first hospitalization, wondering aloud to the transplant team, "Are you sure you did enough to him [for the transplant to work]?" These outcomes led a member of the transplant team, who had advocated for reduced intensity and reduced toxicity regimens during the earlier stages of my data collection, to revise this assessment as my fieldwork came to a close. I asked whether it was the recently published negative findings from the SCURT trial that largely informed the shift in his perception, or their own institutional experience. Absolutely, it was their own experience, he replied, characterizing the aforementioned instances of arguably avoidable graft rejection as "tragic."

In France, the success of the myeloablative transplants using matched sibling ultimately provided its own argument against further innovating the protocol. While the post-transplant care model at Hôpital Y was unique, this form of knowledge transfer relied upon maintaining the conservative transplant strategy, in order to successfully shift these tasks to sickle cell providers. After observing a number of encounters with recently transplanted patients with Docteur Dani, I ventured to ask whether her patients with GVHD were being followed at the day hospital. She laughed, immediately recognizing my puzzlement with the absence of GVHD among her outpatients. "You don't see them, right?" she chuckled, adding, "We don't see much GVHD here."

When I conveyed Hôpital Y's approach to post-transplant care to Dr. S, a pediatric hematologist and oncologist at Community Hospital in the U.S., his own perplexity was directed elsewhere: "But how will they develop their GVHD treatment?" For the providers who cared for transplanted patients at Hôpital Y, their outpatient expertise had been broadened to include evaluating the recovery of blood cell lines and monitoring for insidious infections, including GVHD—but only to a point. In fact, Docteur Dani's adherence to the French standard had kept complications due to GVHD at a minimum, and this predictability over time made it possible for post-transplant care to be extended to non-transplant specialists. Treatment of refractory GVHD demands nuanced expertise in the management of immunosuppressant medications that would undermine the unique care model at Hôpital Y. To anticipate more frequent and extensive cases of GVHD requires collaboration from other specialists experienced with this complication, such as dermatologists and gastroenterologists to respectively biopsy the skin or intestines, and pathologists to provide diagnostic confirmation. Elsewhere, as Dr. S's question had implied, GVHD is part of the cost of doing the business of transplant medicine.[112] To concede this

complication to "the cost of doing transplant" at Hôpital Y would reintroduce incommensurability to their model of post-transplant care.

The particularities of French institutional experience also shaped what kinds of transplants eventually became available to the adult population. While the myeloablative protocol was being applied to a smaller number of adolescents and young adults in France, this conditioning regimen does not overcome the increased risk of procedure-related complications that are encountered with age and progression of sickle cell disease. Until recently, reluctance to entertain a reduced intensity conditioning regimen for sickle cell disease had excluded nearly all adults from transplant in France. With the exception of gene therapy, the haplo transplant became the first new protocol for sickle cell disease to be offered in France in over two decades, and the absence of GVHD with this low toxicity protocol became an important factor its adoption (e.g., Bolaños-Meade *et al.* 2012, Bernaudin and Kuentz 2012). I asked Docteur Dani the reason for adopting the haplo transplant protocol, despite its initially low engraftment rates.[113] She conceded that rejection with haplo was a problem, and while disappointing, this was more of a nuisance. By contrast, GVHD carried risks that were not only fatal at worst, but cannot be resolved by repeating a transplant.

Hence, the French experience with transplant points to the unique treatment collectives that worked against the tinkering otherwise assumed in transplant medicine. Upon realization of improved engraftment rates while also keeping GVHD at bay, unique treatment collectives in France incentivized continuation of the myeloablative protocol. Novelty was no longer being introduced to the conditioning regimen; however, novel practices had been enlisted to stabilize the selection of donors and normalize some of the long-term complications. While GVHD became an unsupportable outcome in the post-transplant care model implemented at Hôpital Y,

the finality of infertility was temporarily deferred, with the availability of gonadal cryopreservation.

Because donors had been limited to fully matched siblings, the practices that promoted the identification of related donors also produced secondary strategies to support the possibility of an eventual transplant. As exemplified in Chapter 3, these practices were also observed at centers in the U.S. whose institutional processes encouraged treatment intensification. Even when HLA testing of existing family members resulted in the absence of a match, this outcome derived additional forms of vigilance, for example in the anticipation of sibling births as an opportunity to harvest umbilical cord blood. At its extreme, the lack of a sibling match led to enlisting IVF with PGD for a minority of families to attempt to conceive a donor. Finally, the practice of exhaustive, real-time data collection and outcome analysis served as both a nidus for research productivity as well as a recursive inflection to stabilize ongoing institutional processes.

**Expectations: believing is seeing**

> Equal opportunity means something far more complicated for children than for adults. It cannot be assumed. It must be constructed piece by piece, by fostering human capabilities for emotional and cognitive achievement. These capabilities are complicated and expensive to develop, because they require care—personalized, customized, sustained, and committed attention.
>
> Nancy Folbre (2001:157)

Even as inter-institutional research priorities and national health policies have governed how scientific knowledge is produced, conveyed, and received in clinical practice, as crucial as are

the myriad practices reproduced in the everyday of clinical work, training, and caregiving. Practices can be reinforced when plausible hypotheses, or even intuition and common-sense, can serve to explain why the practice in question seems to "work." The personal experiences of managing a particular condition over time, whether prescribing medications or recommending interventions as they fall into and out of favor, have an impact on a practitioner's willingness to repeat them. These experiential ontologies also underpin more dramatic practice shifts, such as the *publicité vivante*[114] that Nina's mother noted her daughter's transplant provided for her pediatric hematologist, who had been initially reluctant to recommend the procedure, but subsequently changed her own referral practices upon witnessing the improvement in Nina's health afterwards. A form of "live advertising" appeared to perform similar work by way of the difficult outcomes the transplant team at University Hospital had experienced with reduced intensity conditioning regimens for their patients with sickle cell disease.

Docteur Dani pointed out that post-transplant interactions with sickle cell providers, facilitated by the unique care model at Hôpital Y, as an important source of buy-in for clinicians. The experience of seeing their own patients getting better from sickle cell disease in the setting of an uncomplicated transplant recovery sent a powerful message to providers and provided an ontologic basis to consider this form of treatment intensification for their other patients. A colleague of both Docteur Dani and Docteur Eugenie, who was also a collaborator on a number of multi-center trials, also mentioned an affective impact of having witnessed the aftereffects of transplant, diagnostically and clinically. As children returned for their follow-up testing without pain, their families content, and formerly elevated trans-cranial Doppler measurements no longer detecting an increased risk of stroke, one could not help but be impressed.

In addition to the specific conditions that eventually drew French participation in the

haplo trial, unique collaborations had emerged in the U.S., including a research partnership with Dr. DeBaun. As noted previously, DeBaun's support for transplanting children with sickle cell disease had been reluctant at best. At a Sickle Cell Disease Association of America convention in 2014, I had the opportunity meet Dr. P, a co-investigator on the haplo trials. He and DeBaun worked at different academic institutions, located in different states in the U.S.; how did they end up working together on the trial? "He won't want me to tell you this," Dr. P began, when asked, "but we ran into each other in the men's room…" and proceeded to explain that DeBaun had been visiting their institution, where a mutual colleague had introduced them. An adult provider, Dr. P had not specialized in sickle cell disease transplants prior to the haplo study. Moreover, his vision for the eventual utility of transplant included a range of non-malignant diseases historically dichotomized by systems-based specialties—for example, multiple sclerosis to neurology or Crohns disease to gastroenterology—whose treatment modalities are increasingly unified by modulating the immune system. Dr. P recalled discussing with DeBaun that the haplo approach[115] was "really the way to go" as far as transplant strategies for sickle cell disease. As our conversation drew to a close, he pointed out how the relationships between researchers and institutions were often more influential in producing clinical trials than the science alone.

When I asked DeBaun how he became involved in the haplo trial during our interview, he also pointed to importance of these relationships, emphasizing his existing collegial and professional network, built over a decades long research and clinical career:

> You know, I've been in this game for a while. … [P]eople know who I am, people who know me know what I stand for, … Fifteen years ago, I started with a consortium … of clinical sites, interviewing people, reviewing their data for protocols that we agreed to do together. ,,, [W]e had 14 sites in my original [silent stroke] study…. So it's a relationship, it's all about relationships, right? … I went to all the sites, did all the work myself, and learned

> a lot. And went to eat dinner with folks. And once you have a small group of people who believe in your vision, it's all about leadership and effectively delivering on the end product, in this case which is a manuscript, which they all shared in the success of. And then we went after the larger NIH trial. There were 25 sites, and I called every one of the investigators, talked to everyone on the phone, organized all the activities, treated them as well as I could … to listen to their inquiries and concerns and challenges. …So I speak with a loud voice, but it's really the voice of a lot of people that I work with. (DeBaun with Jae 11 April 2015)

DeBaun also invoked his presence on the haplo study as a check to the tendency for transplant research to prioritize engraftment as the primary measure of success. In his initial conversations with Dr. P, DeBaun stressed the importance of accounting for adverse events and long-term outcomes systematically and with rigor:

> I know how I remember it. I saw his data one day, and I said, "This, this is the solution to the problem." … [A]lmost … every individual with sickle cell has a donor, the benefit-risk ratio is pretty clear, very few deaths, 60 percent cure, the people who don't get cured go back to their baseline, with minimal toxicity compared to a myeloablative transplant. And it's really just a matter of going through the rigorous stats to improve the quality of this product. … [H]e was the transplanter, just focusing on engraftment. I'm the sickle cell guy saying, "Well, what about the end organ damage? What about the lungs, the kidneys, the brain?" And they didn't look at it in any systematic way … I'm like, "Come on, we gotta do this together. We gotta work this out. … We can't assume that putting in new stem cells will abate the progression of the disease." (DeBaun with Jae 11 April 2015).

Indeed, early reporting from the trial had emphasized the advantages of a very low mortality, the absence of GVHD, and the potential to significantly broaden the donor pool against its initially low engraftment rates (Bolaños-Meade *et al*. 2012). Over the course of attending these scientific meetings, it became apparent to me, that while DeBaun's estimation for the haplo transplant remained high, this esteem was directed towards its future potential. While haplo transplants

were still in trial phase, DeBaun's own recommendation for transplant was more as a salvage procedure for the patients, particularly adults, who were struggling to manage their disease on alternate therapy.

Provider expectations for the future lives of children held a complicated relationship with their appraisals of tolerable risk. Unpredictability pervaded patients' exposure to high stakes treatments such as transplant, as well as the uncertainty of disease-related complications due to sickle cell disease. These risk-benefit calibrations played no small part in how experimental and clinical practices were being extended to patients. Moreover, future expectations not only varied in interpretation between individual and health care providers, but across institutions and pediatric and adult patient contexts. For DeBaun, a historic mortality of one death for every 20 myeloablative transplants, using matched sibling donors, remained excessive, at least in children:

> I have 100 kids on hydroxyurea. They live a pretty good life. Most of them live a life in which they can't remember the last time they've had a pain episode. … How can I say this child, who wants to go out for varsity sports, should undergo a procedure where there's five percent risk of death in the next 12 months. It just doesn't make sense to me. (DeBaun with Jae 11 April 2015)

DeBaun, himself a former athlete and avid sports enthusiast, had been an early adopter of hydroxyurea for the pediatric population. While the availability of hydroxyurea did not deter Holly from recommending transplant to her patients, her own experience with this medication at University Hospital corroborated that of DeBaun:

> [H]ydroxyurea, in my opinion, has changed the face of sickle cell. It looks different. It smells different. It feels different. … Everything about that child is different because of hydroxyurea. … And for families, their lives changed. Parents don't miss work. So parents are now doing economically better because they're not missing work—they can hold onto a job. Kids can stay in school. I mean, everything is different. Parents say, "My child's normal." Isn't that

great to say that? “My child’s normal.”

Holly’s interview, however, also pointed to the challenges ahead, alongside the growing clinical exposure to hydroxyurea early in life. Children were entering adolescence largely naïve to the complications of sickle cell disease that they had been spared, as a result of taking hydroxyurea long-term:

> A kid doesn’t understand—kids [who] grow up with hydroxyurea at a young age and then become ... teens, unfortunately there’s a phase—I warn the parents: “This teen is going to stop taking this medicine. … When it happens, let it happen with me. … Let it happen before they go to [the] adult service. Because I will catch them. They will learn the lesson with me. Don’t you worry, Mom. I know you’re going to worry, I know you’re going to cry, I know you’re going to be upset, but let it happen with me, and it’s okay. Because once it happens, it won’t happen again.” Because … that child who became an adolescent does not understand sickle cell… [T]hey’ve been on hydroxyurea for ten years. “[W]hy do I need to take this medicine? I’m not sick.” Well, you stop taking that medicine for two months, and you will be sick. So, let it happen. It’s okay. It’s a great lesson. … [P]arents appreciate the forewarning of what’s going to happen. … [W]hen that teenager does stop the hydroxyurea and does get a crisis or does get acute chest [syndrome], the parents look at me and say, “You know, you said this was going to happen.” Yeah, I did say this was going to happen. It’s okay. Now let’s move on.

As more children are being recruited to hydroxyurea therapy early in life, it remains to be seen in what ways this practice leverages the bar for considering transplant. A transplant physician in the U.S. and a hematologist in France used identical language (“Look, this is a terrible disease…”) to preface the complex deliberations needed to justify transplant for the pediatric patient, given the unpredictability of an individual’s long-term prognosis with sickle cell disease. In using this turn of phrase, both providers were acknowledging the seriousness of a condition that could warrant a high-risk intervention like transplant, but also that in many of these cases, the potential for sickle

cell disease-related complications was not necessarily reflected by a child's current state of a health.

Prognostic uncertainty also placed difficult and contradictory expectations on individual patients, whose prospects for "living well" with sickle cell disease have been affected by the specificity of their personal and health-related challenges. I illustrate some of these tensions here, as they arose in fieldwork. A pediatric hematologist at University Hospital had returned from her clinical session and began to vent in the provider work room a comment from one of her adolescent patients. "She used to say she wanted to go to college. Now she is saying she wants to go to beauty [cosmetology] school," the doctor lamented. "It just sounds so ghetto." Her colleague standing adjacent frowned, unsure how to respond to this unguarded comment; ultimately, the remark went unchallenged, and the moment passed. I did not expect this fieldnote to become comparative until I found myself observing an uncanny mirroring of it, this time in a consultation room at Hôpital B. When asked about her plans for after *lycée*, an adolescent patient answered that she was going to vocational school… in cosmetology. "*C'est fantastique!*" [That's fantastic!] the provider not only exclaimed, but leaned forward, holding both arms outstretched. The exorbitance of her enthusiasm seemed to cow the patient, who shifted in her seat; inwardly, I also recoiled.

The disposition of the U.S. provider's perceived diminution, however off-putting, in her patient's ambition acquired an entirely different valence when held against her French counterpart's outburst upon learning of her own patient's intent to continue schooling at all. Encounters with low expectations for patients' life chances while living with sickle cell disease, and concomitant surprise when these expectations were exceeded, were regularly triangulated by

Dr. Carlton Haywood, Jr. from members of the health care community, including at the intersection of his professional and personal life:

> Even now, when I give talks at certain places that have a heavy medical school or clinician crowd, … I love … when the person who brought me to the institution[,]… they'll talk about my credentials and talk about my research with sickle cell disease, and … if my presenter hasn't said it [already], I always … find a way to build in and say, "In addition to being a researcher who studies sickle cell, I'm also living with it." And I can't tell you how many times I see surprised looks on people's faces when I say that. [I]'ve always just wondered … how much, if any of it, is … just seeing someone who's now—I'm near 40—with sickle cell disease and still trying to get around … . Is it just the shock of seeing … someone with sickle cell disease who has a PhD and who's presenting research? I haven't quite figured out what it is, but there is a look that I always get… . And after the session, the kind of things they say to me … with almost this air of incredulity. And it's for that, among other reasons, that I feel like, "Oh, well, I have sickle cell disease, so I guess you weren't expecting me to know anything, were you?" … [N]ot only do I see it in research, but … I see it in real life as well. (Haywood, Jr. with Jae, 11 April 2015)

Dr. Haywood, Jr. related similar accounts from professional colleagues with sickle cell disease, who were also met with astonishment when disclosing their disease to health care providers.

At the 2015 SCDAA Annual Convention, there was a distinctly different feel at the Lonzie Lee Jones Patient Symposium, where Kwame Ohene-Frempong and Kimberlin Wilson-George had shared the same stage three years prior. Subtitled, "Inspire 2 Dream,"[116] the invited guests were exceedingly accomplished, and they included a Division I collegiate athlete, a top attorney, and members of the entertainment industry. In a conspicuous moment during the question and answer period, an audience member identified herself as having Hb SS disease and asked the panelists to share their genotype; all but one were Hb SC.[117] In the conversation over convention hall breakfast fare the following morning, the topic of the prior day's symposium was

broached by some of the attendees who shared the table with me. Evera, who was in her forties and had Hb SS disease, had noted that the session had generated a heated discussion among her colleagues later that evening. “I understand what they were trying to do…,” she conceded in acknowledgement that the session was intended to be motivational; but the reactions it had produced were mixed. Not everyone with sickle cell disease was healthy enough, in spite of their best efforts, for those achievements to have been realistic. Evera referred specifically to her older brother, who had struggled with significant complications from his sickle cell disease since childhood.[118]

The selection of patient panelists did reflect a concerted effort on the part of the conference organizers to highlight individual accomplishment within the sickle cell community. Donnette, both a patient and advocate, who had founded a local community-based sickle cell organization, noted that the leadership at SCDAA was responding to the critique that the public face of sickle cell disease had been “too depressing,” In her own advocacy, Donnette has expressed frustration that sickle cell disease has not benefited from significant activism on the part of more Black athletes, artists, and celebrities.[119] Whether or not awareness-raising for sickle cell disease had been hampered by the trope of its suffering, Donnette supported the intentions behind a counter-narrative; after all, “You can’t just tell everyone they are going to die.”

Hence, the challenge of holding aspiration and pragmatism as twin aims during a chronic, unpredictable, and life-shortening illness: how to remain vigilant and ward against future risk, while instilling the resilience that ensues from choosing vulnerability, even hardship; to not only protect, but also nurture, those futures? Even after bracketing out the health politics of sickle cell disease (which can never truly be pushed aside), the balance still felt precarious. The following year, Donnette’s organization held one of their local forums on sickle cell disease. These events

were open to the public and provided participants a space to share personal experience and network, as well discuss clinical insights and research, and the invited presenters included local advocates as well as health care providers. During the financial planning session, the emcee, who also had sickle cell disease, stressed the importance of the topic by pointing out that their organization—"let's be honest"—has had to provide emergency funds for funeral expenses. At this, one of the attendees sitting at my table, who had introduced himself as having sickle cell disease and was in his thirties, drew in an audible breath, then suppressed his emotion in silence. Efforts to provide affective uplift were readily thwarted by the expediency of having to apply vigilance to foreshortened futures.

In an example from her own life with sickle cell disease, Halima's reflection illustrates the shift in risk tolerance that occurs from childhood to adulthood: "[A]s a kid, even though I knew that getting in the pool would maybe make me sick [due to a pain crisis], I got in the pool anyway, you know? If I got sick, I got sick, and if I didn't, I didn't. … But as I got older, the pool was off limits. You know I'm not even taking that chance … of getting sick…" (Heyward with Jae, 11 April 2014). The withholding of an activity like swimming eventually became a self-enforced limitation, and the risk of inciting a vaso-occlusive crisis (that ensues from the immersive cold exposure), tipped the balance towards withdrawing from an ordinary pleasure of childhood. The repercussions of restricting everyday enjoyments, like recreational water play, were recurring themes of growing up with sickle cell disease; reclaiming these quotidian pleasures also were powerful symbols of embodied recovery after transplant. In a photograph gifted to Dr. del Toro from the parents of a patient who had undergone a successful transplant, their school-aged son is shirtless, laughing, and soaking wet. His mother had explained the significance of the moment captured in his candid portrait: as he played with abandon in the

water park of an outdoor playground, their family had been released from the fear of provoking a pain crisis.[120]

When I first met Halima, it was during a Foundation for Sickle Cell Disease Research meeting (though I encountered her subsequently through her work with Community Hospital, where she held a grant-funded position for the community outreach arm of the pediatric sickle cell program). At the conference session, I was among the audience members to a panel of patient advocates, that included Halima. Among the comments that prompted me to recruit her to share her oral history was her depiction of having to grieve the life she might have led, had it not been for sickle cell disease. It was a moving testimony that I asked Halima to elaborate upon during our interview later that evening:

> [Y]ou know, it's just so funny how you could meet somebody that has sickle cell, and they're a doctor, they're a nurse, … and they've been sick. [I]t's not like they escaped being sick, but … they had support. They had parents, they had whoever who always told them, "You could still do it." Or if they were in the hospital, their parents would go to the school and bring [their homework] to them… . And that makes all the difference… . [N]ot to say that I haven't accomplished anything in my life, because that's not true. But, … you just have to grieve, that kind of mourn, the life you think you could have had, if you had only been healthy, or if your parents were only better parents. … Knowing everything that I know now, and knowing that I can do anything that I want to do—I may have to do it differently, I may have to take my time, I may have to do it slower, it may take me longer. But I can do it. And that's the difference in perception. And I had to come to it on my own, because I didn't have anybody to tell me that. … because I never really had anybody to believe in me (Heyward with Jae, 11 April 2014).

Halima's account illustrates Folbre's argument that "equal opportunity … for children … cannot be assumed. It must be constructed piece by piece…" (2001:157). I maintain here that beliefs and expectations compose essential pieces in the construction of children's futures. When

apprehended through a constructivist approach, beliefs can be located outside of cognition or abstract argument, where they are forming co-productive allegiances with affects and practices. Anticipation, understood as expectations informed by beliefs, becomes a reflection of the capacity to imagine what becomes possible for the future. Not merely ornamentation, expectations and beliefs help to construct the foundation and weight-bearing walls to support where those structures might lead. The articulation of these futures is reinforced or becomes recalibrated through the practice of everyday life.

In the course of this fieldwork, Halima experienced a rapid decline in her health. She required multiple hospitalizations for encephalopathy, episodes of confusion and frightening mental status changes that resulted from accumulating toxins due to a malfunctioning liver. Though she had been urged by her colleagues to ask her provider about the possibility of a bone marrow transplant, it seemed her hematologist was reluctant to refer her. Perhaps this hesitance was understandable; in no uncertain terms, Halima was a high-risk candidate for transplant. Moreover, she already had a transplanted kidney that had begun to show signs of declining function, placing this organ at further risk with a bone marrow transplant.

Two years later, I ran into Halima at a public forum held by a local sickle cell organization. She was in good spirits, and there was a rounded contour to her face suggesting that she was taking immunosuppressants. Indeed, much had happened in the intervening time: Halima had undergone an unrelated transplant, having found a 10/10 match—the best possible combination of major and minor HLA antigens—through the bone marrow registry. As she was ineligible for any available trial, her transplant physician tailored a reduced intensity conditioning regimen, using as little chemotherapy as possible, given her fragile condition. A year and a half later, Halima had beaten the odds, having survived a non-myeloablative

transplant using an unrelated donor. She noted that she had been "cured" of her sickle cell disease, qualifying that she was no longer producing sickle red blood cells. Halima also acknowledged that she still attended transplant clinic regularly, with an upcoming visit to evaluate a possible case of graft-versus-host disease affecting her skin. Though it was likely her renal graft would eventually fail, requiring dialysis, she was looking forward to her daughter's graduation from college in six months. Halima's bone marrow transplant had bought her additional time, but I noticed that she was no longer gripped by fear for the future, a dread that I, too, had felt the last time we had last met in the hospital. Halima spoke of that period of time leading up to her transplant, with humor, but absent of irony: "My days were *numbered*."

I offer this dissertation, which falls short of delivering an architecture, more as a bricolage of the temporal, affective, and practice-based constituents of hope, with anticipatory politics as its methodological and analytic guide. Like vigilance and care, beliefs are a resource; and as resources go, these are not unqualified goods. Beliefs, care, and vigilance are subject to the intemperance of their excesses, in addition to deprivations from their dearth. Moreover, and as exemplified above, certain deprivations that become reproduced by aversion to risk ambiguously assume modes of anticipatory self-care, while at the expense of limiting participation in the everyday. These tensions reflect underlying incommensurabilities—not only between scientific and clinical thought styles, but also of patients and their health care providers' expectations for the future. For those stakeholders who are deliberating a transplant (and more recently, gene therapy), considering this intervention acknowledges the contradiction between expectations to live a life in spite of the limitations posed by sickle cell disease and an improbability of living well with them.

## Conclusion

We have a lot of stories. What we need is data.

Lanetta Jordan, MD MPH, Opening Address, SCDAA Annual Convention 2012

Politics without hope is impossible …

Sara Ahmed (2015:184)

In this examination of the anticipatory politics of scientific innovation, I demonstrate how medical research, clinical practice, and public health policy are deployed and repackaged in an effort to contain risk and uncertainty through the production of practice standards in clinical care. As research methodology, anticipatory politics materially links affect and praxis to expectations and concerns for the future. This ethnography makes the case that recognizing the future-seeking and affective properties of scientific knowledge production can also identify the expectations that respond to and reshape the practice of sickle cell disease medicine in the present. These anticipatory concerns become embodied as belief and hope in the pursuit of new scientific knowledge and innovations in disease management and prevention.

In this way, anticipatory politics attends to the contingencies of risk, belief, and hope as they became embodied and reproduced in the ethical and clinical justifications for pursuing experimental protocols, weighing the uncertainties of treatment intensification, and modifying standards of care. The comprehensive care processes that improved childhood survival for sickle cell disease, like newborn screening and preventive testing and transfusions for stroke, not only shifted expectations of that children will reach adulthood, but provided the rationale to elaborate

high-risk interventions like transplant to improve upon adult life expectancy and quality of life. This is not to say that the contingencies that comprise affective concerns, beliefs, and hopes go uncontested. This tension is evident in the argument posed by Dr. DeBaun and others, particularly as less toxic alternatives to the myeloablative transplant, such as hydroxyurea, gain traction in the pediatric population:

> I'm not denying [parents] that desire [to have a "normal" child]. But if you have that desire, I think it has to be balanced with the true knowledge of what you're trading off. You're trading off death—a five percent risk of death in 18 months in the best-case scenario, and chronic graft-versus-host disease. That's what you're trading off. … [I]n a situation where the parents are partly responsible for the disease [as] carriers of the [sickle] trait, they made a decision to have a child, and so … there's an inherent conflict ... . All of us …, if we were partly responsible for our child's suffering, would want to relieve their suffering. It's an innate parental feeling. And so there's conflict in saying, "I'll take that five percent risk of death for a cure." … [I]t's not just that five percent risk of death, it's the morbidity and the tradeoffs for that child at a point that we haven't perfected the strategy of how to do this. (DeBaun with Jae 11 April 2015)

Dr. Ohene-Frempong notes how perceptions of treatment-related risks become translated outside of high-income settings, particularly where sickle cell disease remains largely fatal in childhood:

> If I [proposed transplant to patients in] Ghana right now, and I say, "[Y]ou have [an] eighty-five percent chance of being cured and maybe five percent chance of dying and complications," I know there'll be a line from here to there, because they know that … people [with sickle cell disease] die young. And eighty-five percent chance of being cured of the disease, they will take it. So, in that frame, in that context, the same [outcome] may be interpreted quite differently. (Ohene-Frempong with Jae, 16 April 2013)

Like Lena and Holly (Chapter 3) and Vichinsky and DeBaun (Chapter 4), Ohene-Frempong points to the sway of provider-patient dynamics in influencing treatment choice, but he also

implicates his own specialty of pediatric hematology-oncology as a barrier to discussing transplant more often with patients and families:

> So I think that we could do more with transplant. We could do a lot more. If we—and I blame myself—I mean we, the pediatric hematologist—we're supposed to be the "brick wall" against transplant. But I think it's because we're not approaching it from a long-term perspective. We don't lose children [to sickle cell disease] anymore, so we don't want any child to die in our hands. [Even] if they … die when they're twenty-five, … we just don't want it to happen when they're three or four or five [years old]. But the idea that if we actually did give them the opportunity for being cured … [w]e don't have that perspective. Our job is to take you to twenty, and [then] let the others [in adult medicine] worry about it. So it's an opportunity … that I think has not been fully explored. I just wonder whether if we actually educated families very well, and they started demanding [transplant]…. But that's something… rare in sickle-cell disease: that families demand anything. They may demand better treatment in the emergency department, but this is a field where the health worker is way above the affected patient in terms of choices. Almost all the decisions are made by the health worker. And the parents, they're not informed well enough for them to say, "We want transplant program at our hospital." Or "We have heard about this treatment, and we want it done." It's almost all controlled by the health workers. (Ohene-Frempong with Jae, 16 April 2013)

Whether a transplant became imaginable, ethical, and possible depends upon alignments between lay and expert knowledges that also contend with the moral implications of informing families about complex and difficult treatment options. As this work demonstrates, health care institutions were instrumental in leveraging this knowledge. How patients, families, and health care providers received and provided information about available treatments also served as access points to their own utilization. Institutional processes that produced higher rates of transplant not only considered the more proximate acuity or uncertainty of a patient's prognosis at the given point in time, but operationalized adult caregivers' and health care providers'

concerns and aspirations for the future lives of their children. As a result, whether providers broached the subject of transplant, or when this form of treatment intensification was offered to, considered by, and acted upon by families, does not necessarily reflect the current severity of a child's state of health.

Health care providers' stated reasons for withholding discussions about treatment intensification options are often are presented on the grounds of protecting patients from potential harm. This rationale, however, also operates to shield providers from uncomfortable or ambiguous care responsibilities that came with introducing risky, novel, or unfamiliar treatment modalities to patients. Those institutions that brought treatment intensification to scale, including high-risk interventions like transplant, not only implemented practices to potentially democratize information exchange, but relied upon treatment collectives across providers, patients and families, and institutions that aligned respective affective concerns and beliefs with experimental knowledge and innovative care practices.

Though this work is comparative, the global flows of people and knowledge, and the respective networks of patients, professionals, and caregivers, produced field sites and participants whose lives and histories intersected both sides of the Atlantic. In the course of this fieldwork, the relatively small world of sickle cell disease and transplant medicine not only provided the potential for technologies to travel, but for patients and their families, such that these transnational movements could be mistaken for kismet. At the first Worldwide Initiative on the Social Studies of Hemoglobinopathies held in 2010 in in the U.K., Dr. Ohene-Frempong had been among the attendees. During one of the discussions, he noted having recently attended a sickle cell conference in Saudi Arabia, and how he had been struck by the representation among the health care providers. In attendance were orthopedic surgeons and other sub-specialists rarely

encountered at the research and advocacy meetings held in the U.S. and Europe. When he asked local attendees why they had come, one of these physicians explained that "everyone" in the medical community in Saudi Arabia has a family member, friend, or acquaintance who has sickle cell disease. Ohene-Frempong suggested that until comparable sentiments are kindled in the United States, advocacy for sickle cell disease will likely remain marginalized. Dr. Carlton Haywood, Jr. makes a similar appeal, not only for aligning expectations between patients and providers, but suggesting the impact of broadening sickle cell's stakeholders to "society as a whole":

> One of the things I want sickle cell providers and really the general public to try to understand is that we are just like everyone else. … I certainly understand there are challenges that go along with sickle [cell disease] … but, what I try to help health care providers know and understand is that … [w]e have the same kinds of hopes and dreams as everyone else. … We have the same desires, ambitions, and wants, … I'm really hoping that helps to encourage a stronger feeling of connectedness: my problems actually mattering to some other community. … [N]ot just saying, "Oh, well, look at the people with that"—quote unquote—"'black disease,'" [but] really feeling like society as a whole begins to see all of our stakes in improving conditions for sickle cell patients. (Haywood, Jr. with Jae, 11 April 2015)

**Epilogue**

> I really do hope that … in the next few years, I'll come to meetings like this, and we won't be talking about the same set of issues and problems all over again, as if … no progress has been made. … I hope that … when I come here next year and the year after … that we'll begin to really see lots of new initiatives, whether there are policies or availability of care or programs … that really inject some hope and life into the sickle-cell population as a whole… [S]o many things are … promoted as the next thing for us, and it seems like it always falls apart. So I'm hoping that that will begin to actually change in the near future.
>
> Carlton Haywood, Jr., PhD
> Fort Lauderdale, 11 April 2015

While much in the world of sickle cell disease advocacy has remained the same, since I began this fieldwork, new currents are shifting the scientific and policy discourse. One area gaining momentum comes from private sector investments that underwrite drug research and development and the biotech industry. Then-chief medical officer of SCDAA, Dr. Kim Whitley-Smith, announced at the 2015 national convention that, "Sickle cell disease is hot!" She was referring to recent uptick in research attention from pharmaceutical companies, who were beginning to conduct clinical trials for new agents, in hopes of bringing them to market.

In 2017, the FDA approved L-glutamine, branded Endari by its manufacturer Emmaeus Life Sciences, a small U.S. biotech company. Sickle cell disease falls under the FDA Orphan Drug Act. This expedited Endari's approval process, after demonstrating that trial participants experienced a reduction in painful episodes and hospitalizations compared to placebo. The medication is not without controversy and has not been approved in Europe, where regulators questioned whether the reported 25 percent decrease in hospitalizations was a statistically

significant decline. Endari is a pharmaceutical grade preparation of a commercially available supplement and works by adhering to hemoglobin and modifying its protein chain configuration, resulting in a more tightly bound oxygen molecule. By retaining more oxygen to hemoglobin, the drug purports to prevent the formation of HbS polymers and thereby reduce the distortion of red blood cells. Since hydroxuyurea was approved for adults in 1996, Endari is only the second medication to receive FDA approval for sickle cell disease. Though it is now available in the U.S. to adults and children aged five years and older, whether Endari makes a clinical impact remains to be seen. Initial sales for the $15,000-a-year drug were considered low, at 20 million dollars, in 2018.

The broader drug development landscape, however, also has pivoted: Pfizer, Novartis, and Global Blood Therapeutics all have compounds pending the last stage of clinical trials. A product from Novartis, called Voxelotor, is expected to be the next agent to gain approval in the U.S. Pfizer has promoted how their company hired ethnographers to improve the poor recruitment they experienced during their earlier trials. Bluebird bio's gene therapy for sickle cell disease, called Zynteglo, has just been approved in Europe for patients with beta thalassemia, who do not have a transplant donor. The treatment has been priced at 1.8 million dollars, and the company proposed a payment plan from governments and insurers for annual installments of 315,000 euros for five years, where the subsequent payments only would be made if the treatment is successful. With approval of the current drugs in development for sickle cell disease across Pharma, investors project annual sales at over one billion dollars in the U.S. and Europe.

In a rare example of recent bipartisan legislation, the Sickle Cell Treatment and Surveillance Act[121] was signed into law in December 2018. A twenty-first century updating of Nixon's Sickle Cell Disease Control Act, the measure renews federal funding for research and

clinical services, as well as data collection and epidemiologic surveillance. Among the Congresspeople introducing the bill was Representative Michael Burgess (R-Texas), who cited his own experience as a physician caring for hospitalized patients with sickle cell disease in his support of this legislation. In February of 2019, the California state legislature introduced a bill to improve adult services for sickle cell disease, citing adult mortality data in their state as unacceptably high. The bill proposes designating health care institutions to provide comprehensive care, telemedicine to improve access to sub-specialty consultations, and recruitment and training for health care providers. In addition to domestic legislation and the development of novel drugs intended for patients in high-income settings, positive findings from a recent study that had introduced hydroxyurea to children with sickle cell disease in sub-Saharan Africa were published in the *New England Journal of Medicine* (Tshilolo *et al*. 2019). The study demonstrated the feasibility of providing hydroxyurea to children in low-income settings, as well as clinical benefit to a significant portion of those on treatment. Participants aged one to 10 years were recruited in Angola, Congo, Kenya, and Uganda; while taking hydroxyurea, they experienced fewer pain crises and infections, reduced transfusion requirements, and decreased mortality.

In March 2019, the longstanding television news magazine, *60 Minutes*, aired a story on an ongoing gene therapy trial for adults with sickle cell disease at the NIH (60 Minutes 2019). The program divulged several details usually not made explicit in media portrayals of gene therapy. First, gene therapy makes use of modified HIV-1, usually referred to by its genus name *lentivirus* in scientific literature, to transfer the corrected genetic material into patients' stem cells. The modified virus retains the efficiency of HIV to insert genetic material into the host, making *lentivirus* the vehicle for gene therapy trials to date. Its origins, however, often goes

unmentioned, in part to avoid creating panic in the lay public. Thus, the technology of gene therapy has hinged upon the virulence of HIV as the means for introducing modified genes into blood-forming cells. The *60 Minutes* report also alluded to gene therapy's earliest forays that were marred by deaths and treatment-induced malignancies to explain why it has taken nearly two decades after the complete sequencing of the human genome in 2003 to beget examples of gene therapy's clinical promise.

In depicting Jennelle Stephenson's journey on the trial, the program also made explicit that gene therapy requires chemotherapy before re-introducing a patient's genetically modified stem cells. Like hematopoietic cell transplantation, the modified blood-forming cells need to engraft within the bone marrow. Because gene therapy uses the patient's own stem cells, however, GVHD is not an issue. Patients do still experience the complications of immune suppression and toxic effects from the conditioning regimen itself. The online supplement to the aired broadcast shares that Jennelle had decided to move forward with gene therapy, while understanding that chemotherapy would likely leave her infertile. Also absent from the program is mention that the *lentivirus* vector used for the NIH trial comes from bluebird bio®, the aforementioned biotech company that had performed the first gene therapy for sickle cell disease in France (Ribeil *et al*. 2017).

Now in her late twenties, Jennelle is a compelling protagonist. She had strived to complete college despite her illness, but maintaining employment afterwards proved difficult, when even climbing a flight of stairs could precipitate a pain crisis. By age 22, she realized that, for a person with sickle cell disease, she probably had reached her middle age. Shortly after airing footage depicting the ordeal of chemotherapy during her month-long hospitalization, the program revisits Jennelle fifteen months later. She is dressed for Jiu-Jitsu class; on camera, she

learns how to score—and receive—a throw, holding her opponents' body over her shoulder and heaving them to the ground. For Jennelle, who had previously longed to be able to run, her present reality is a "new life, indeed."

In summarizing the early results of the nine adults who had undergone the procedure, Francis Collins, director of the NIH, ventures so far as to say, "I believe that this looks like a cure." Collins, who formerly led the Human Genome Project, is also the lead singer and guitarist for a cover band comprised of NIH scientists. Among the members in the ARRA—short for Affordable Rock'n'Roll Act (so named because the musicians are unpaid, according to Dr. Collins, who posts photos from their performances on his social media account)—is hematologist and bassist, John Tisdale. Tisdale is also a research scientist and principal investigator for one of the first successful trials that transplanted adult patients with sickle cell disease using matched siblings and a reduced intensity (i.e., non-myeloablative) conditioning regimen (Hsieh *et al*. 2009). During his interview on *60 Minutes*, Tisdale explains that in 2016, he had "pitched" the idea of moving forward with a gene therapy trial to Collins, over pizza, after "setting up… before [a ARRA] gig."

Multiple elements in this media portrayal can be scrutinized through the lens of anticipatory politics. This includes the national commitments of a U.S. government research institution and the personal sentiments of the story's protagonists, Jennelle Stephenson and NIH researchers, Francis Collins and John Tisdale. Even as Jennelle explains the experience of daily "bone-crushing" pain due to sickle cell disease, she breaks down only upon recounting how she had not been believed by health care providers, during a pain crisis. Francis Collins recalls meeting a patient with sickle cell anemia for the first time during his first year of medical school, over 40 years ago. Despite a relatively low incidence of sickle cell disease in the U.S. at large,

medical training regularly places students and residents in inpatient contact with patients, whose complications can often require hospitalization.

When Dr. Lanetta Bronté (then Jordan) addressed 2012 Annual Convention as chief medical officer of the SCDAA, in her remarks, she implored, "We have a lot of *stories*; what we need is *data*." Dr. Bronté may have been appealing for "hard" evidence, or perhaps for a systematic data collection process, to build upon existing medical research and strengthen the case for policy improvements and advocacy for sickle cell disease. If the implication is that patients' stories, taken alone, are insufficient to effect needed action, accordingly, data rarely, if ever, can speak for themselves. Outcomes and findings are made meaningful by their commensurability, or at the very least, with the alignment of beliefs and practices, of affective and pragmatic concerns, of care across stakeholders. Ultimately, data becomes science, by means of the stories they tell. In the online supplement, the medical correspondent for *60 Minutes*," Jon LaPook, was asked about Francis Collins' use of the word "cure" at this stage of the gene therapy trial. "Oh, I would never have said the word 'cure,'" replied LaPook, also a gastroenterologist. "We're people of science, but you don't want to jinx it."[122]

# ENDNOTES

## Introduction

1 As an example, Brazilian researchers have taken the additional step of estimating admixture genetics in a cohort of patients with sickle cell disease in the state of Minas Gerais, citing a greater degree of ancestral mixing within Latin American populations when compared with African Americans (da Silva *et al.* 2011:4493). In their results, they point out that 13.8 percent of the study population "had predominant European ancestry" compared with the "only 11.05%" who had predominant African ancestry, which the authors defined as greater than 85 percent of the 54 genotyped SNPs/INDELs (single nucleotide proteins and single base insertion / deletions) previously validated as European and African (da Silva *et al.* 2011:4494).

2 Including in my son's sixth grade science class this past year.

3 Carriers of the sickle trait produce sufficient amounts of normal hemoglobin and in most circumstances are protected from sickling of red blood cells. With increased attention to sudden deaths experienced in trait carriers with extreme physical exertion (e.g., military boot camp, American football training, high altitude skiing), additional scrutiny is more recently being paid to anecdotal reports from trait carriers of pain syndromes resembling that of sickle cell pain crises.

4 This was 2002-2003.

5 National Heart Lung and Blood Institute. 15 September 2017. Opioid Crisis Adds to Pain of Sickle Cell Patients. https://www.nhlbi.nih.gov/news/2017/opioid-crisis-adds-pain-sickle-cell-patients, accessed 4 August 2019.

6 In sickle cell disease, as with many other non-malignant conditions treated with hematopoietic cell transplantation, resultant mixed chimerism can still produce the desired post-transplant outcome (e.g., Liesveld and Rothberg 2008).

7 In the case of transplant for refractory cancers, most (often 50 percent) mortality after transplant is still due to the underlying malignancy.

8 Assuming both parents are sickle trait carriers, the probability of a birth unaffected by sickle cell disease is 75 percent. The likelihood of inheriting the same HLA chromosomes from each parent is 25 percent. The probability of both conditions being met is 18.75 percent.

9 By contrast, PGD is outlawed altogether in countries such as Germany and Ireland.

[10] Using similar distinctions between reproductive versus therapeutic intents, Aliyah's parents were able to obtain coverage through their private health insurers for portions of the reproductive technologies that went towards obtaining her transplant(s), including the PGD used to conceive her HLA-matched brother, who eventually served twice as her bone marrow donor.

[11] See also, https://www.health.ny.gov/regulations/task_force/, accessed 24 May 2018.

[12] *V Simpósio Brasileiro de Doença Falciforme e outras Hemoglobinopatias* [5th Brazilian Symposium of Sickle Cell Disease and Other Hemoglobinopathies], Belo Horizonte, Minas Gerais, 4-7 October 2009.

[13] The first French case of IVF with therapeutic intent occurred in 2011, with the birth of a HLA-matched sibling whose cord blood was used to transplant an older sibling with Beta thalassemia (Thibert 2016).

[14] This is a jointly held annual meeting of the Center for International Blood & Marrow Transplant Research (CIBMTR) and the American Society for Blood and Marrow Transplantation (ASBMT).

[15] Research interviews and oral histories were conducted in the same manner and used the same interview guide; research interviews have remained confidential, while oral histories will be available for public record.

## Chapter 1

[16] French term for sickle cell patients after transplant (also used: *les après-greffés* [the post-transplanted]).

[17] By comparison, the recessive genetic disease, cystic fibrosis, has an incidence of 29,000 in the U.S., and 6,000 in France. The inherited blood disorder, hemophilia, affects approximately 20,000 in the U.S. and 6,000 in France.

[18] Sickle cell disease has been depicted in similar terms in the U.K. (e.g., Anionwu and Atkin 2001).

[19] "From 1986 to 2013, 1000 patients received an HLA-identical sibling transplant for SCD at 106 centers in 23 countries worldwide. The median follow-up for surviving patients was 55 months (range, 3-325 months). Four hundred thirty-nine patients were transplanted in the United States, 513 in Europe, and 48 in non-European countries" (Gluckman et al. 2017:1550-1551).

[20] Researchers from the French University hospital system and bluebird bio®, a genetic biotechnology company cofounded by a French scientist, published their case report of a child with

sickle cell disease who became transfusion independent after gene therapy that introduced non-sickling beta globin to his blood-forming stem cells (Ribeil *et al.* 2017). See also Conclusion.

21 In the past decade, publicized episodes of exertional deaths among U.S. collegiate football athletes added attention to the risks posed to sickle cell trait bearers. In response, the American Society of Hematology opposed the resulting practice of athletic programs mandating sickle cell trait screening, in part due to the potential for discrimination this posed to athletes, and argued instead that all athletes should be adequately hydrated and universally protected from exertion-related illnesses, a life-threatening condition regardless of one's sickle cell trait status. From the American Society of Hematology: "Most people with sickle cell trait have no symptoms and will not have any health complications. Occasionally people with sickle cell trait can have blood in their urine. Under extreme conditions such as high altitude, severe dehydration, or very high intensity physical activity, red cells can become deformed or sickled. Complications include muscle breakdown (rhabdomyolysis), reduced blood supply to the spleen (ischemia/infarction), or increased pressure in the eye (glaucoma) following eye injuries. Finally, a very rare form of kidney cancer (renal medullary carcinoma) has been associated with sickle cell trait" (Sickle Cell Trait, American Society of Hematology, http://www.hematology.org/Patients/Anemia/Sickle-Cell-Trait.aspx, accessed 18 May 2018).

22 The longer overall life expectancy in Hb SC disease is among the reasons that clinical indications for transplant for Hb SC disease are not as clearly established than for Hb SS disease.

23 Since 2013, pharmaceutical interest in drug development and innovative therapeutics for sickle cell disease has increased; see also Conclusion.

24 In high-income countries, blood typing that includes matching for minor antigens can help reduce the risk of allo-immunization.

25 Plasmapheresis and exchange transfusions are both examples of therapeutic blood removal. Plasmapheresis involves the extracorporeal separation and removal of plasma from the blood, in order to reduce circulating antibodies, before re-introducing the treated blood to the body. Unlike simple transfusions, which increase the net volume of red blood cells (and iron) in the body, the exchange transfusion gradually removes the patient's blood, while replacing it with donor blood.

26 As a result, however, hydroxyurea dosing is limited by this propensity to suppress the immune system.

27 Despite the findings of the BABY HUG trial (e.g.,Wang *et al.* 2011) and subsequent expert consensus that hydroxyurea is safe and effective even in infants as young as nine months of age, its pediatric prescribing the U.S. is off-label. This is because hydroxyurea is an older drug and no longer

under patent, and the costly testing required for FDA approval, such as pharmacokinetics and bioavailability of different formulations of the medication, typically requires underwriting from larger commercial pharmaceutical companies (Green and Barral 2014:196).

28 For example, see Ware *et al.* 2016.

29 Rabinow continues: "Nature will be known and remade through technique and will finally become artificial, just as culture becomes natural. Were such a project to be brought to fruition, it would stand as the basis for overcoming the nature/culture split" (1996:99).

30 https://www.bmtinfonet.org/about-us, accessed 24 October 2017.

31 See also Chapter 4 for some of the varieties in transplant applications and as they pertain to sickle cell disease.

32 For example, the phenomenon of mixed chimerism makes it possible for individuals of a different ABO blood group from the recipient to donate stem cells.

33 Yet even here there are exceptions, as some patients have been reported to regain splenic function post-procedure, even after this immune system organ had been already impaired by infarctions due to red blood cell sickling (Ferster *et al.* 1993).

34 Excerpt from Smith-Thompson 2018, "A Family's Journey." Sickle Transplant Alliance for Research (https://curesicklenow.org/a-familys-journey/, accessed 22 December 2018)

35 See Loi Informatique Et Libertes Act N°78-17 of 6 January 1978 On Information Technology, Data Files And Civil Liberties (https://www.cnil.fr/sites/default/files/typo/document/Act78-17VA.pdf, accessed 22 December 2018).

36 In revision, the first article which once read that all citizens are equal before the law "regardless of origin, race or religion" now reads "regardless of gender, origin or religion."

37 The same is not necessarily true, however, for the patient's family members who are undocumented and unaffected by sickle cell disease.

38 Though one of my informants in France took issue with the term "*cent pour cent*" and pointed out she had been charged a 10 euro fee (akin to a copay in the U.S.) for her daughter's flu vaccine.

39 See French legal code L.313-11 Alinéa 7° du Code de l'Entrée et du Séjour des Etrangers et du Droit d'Asile, la délivrance d'une Carte de Séjour Temporaire portant la mention Vie Privée et Familiale avec Autorisation de Travail (https://www.legifrance.gouv.fr/affichCode.do;jsessionid=F9459325B9AE65279C913A6BBC9E082C.tplgfr31s_1?idSectionTA=LEGISCTA000006180199&cidTexte=LEGITEXT000006070158&dateTexte=20091125, accessed 4 June 2018).

[40] See also Ticktin 2006.

[41] "… *en effet, il s'agit d'une population déjà sélectionnée par le biais d'une consultation hospitalière, ou de prévention maternelle et infantile au terme de laquelle le praticien a pu soit orienter un diagnostic, soit avoir une suspicion sur la base de l'origine ethnique*" [indeed, it is a population that already has undergone selection bias through a hospital consultation, or preventive care, after which the practitioner could direct testing based on ethnicity] (Rochette and Charbit 1990:152).

[42] In both cases, the families had received their prenatal care in France. One child had even been followed by a geneticist who had diagnosed a rare (unrelated) syndrome that was detected prenatally.

[43] No longer confined to France, "the great replacement" has been adopted as a rallying cry across White supremacy movements worldwide (e.g., Charlton, Loretta, "What Is the Great Replacement?" *The New York Times* [6 August 2019], https://www.nytimes.com/2019/08/06/us/politics/grand-replacement-explainer.html, accessed 25 August 2019).

[44] For examples of a far right group's internet use of French government newborn screening data, see: *En 2025, la moitié des naissances en France ne seront pas d'origine européenne* [In 2025, half of births in France will not be of European origin] (2 September 2015) https://www.polemia.com/en-2025-la-moitie-des-naissances-en-france-ne-seront-pas-dorigine-europeenne/, accessed 11 December 2018. For a mainstream press rebuttal, see Léchenet and Laurent 2014.

[45] Also, *Drépanocytose : la carte du grand remplacement mise à jour – Chiffres 2016* [Sickle cell disease: Map of the Great Replacement updated — 2016] (13 November 2017) http://www.fdesouche.com/906357-drepanocytose-la-carte-du-grand-remplacement-mise-a-jour-chiffres-2016, accessed 11 December 2018.

## Chapter 2

[46] Kwaku Ohene-Frempong speaks further on this discovery in his oral history conducted on 16 April 2013, in Miami, Florida.

[47] Unlike pediatric acute lymphoblastic leukemia (ALL), AML still confers significant mortality to children due to relapse. High-risk AML patients require myeloablative doses of chemotherapy that are high enough to destroy the bone marrow. Due to this higher burden of treatment-related toxicity, AML patients are more persuasive candidates for bone marrow transplantation than ALL patients.

[48] Please refer also to Keith Wailoo's extensive work (1997, 2001; also Wailoo and Pemberton 2006) on the visibility of sickle cell disease and other conditions as a co-product of technical, historical and political contexts; Tapper's (1998) interpretive treatment of sickle cell disease as a racialized and ethnicized discursive category in the US; and Lainé's work (e.g., 2004) that provides an analogous account of the disease's scientific and clinical recognition as a barometer of acceptance and citizenship among immigrant populations affected by sickle cell disease in France.

[49] I borrow loosely and generously from Nussbaum (2013 [2010]) and Sen's (e.g., 1999) capabilities concept in their respective work in philosophy and economics.

[50] French analogues of anticipatory guidance include *les conseils préventifs*, literally "preventive advice."

[51] To wit, anticipatory guidance has been defined as: [t]he psychologic preparation of a person to help relieve the fear and anxiety of an event expected to be stressful. An example is the preparation of a child for surgery by explaining what will happen and what it will feel like and showing equipment or the area of the hospital where the child will be. It is also used to prepare parents for the normal growth and development of a child (Mosby's Medical Dictionary, 8th edition, 2009).

[52] As an example of primary prevention, the American Academy of Pediatrics added recommendations to counsel parents to prevent childhood obesity during the anticipatory guidance provided for well child care (Daniels and Hassink 2015). By extension of this example, secondary prevention includes measures to reduce the risk of complications due to overweight, such as weight loss programming or screening for high blood pressure or insulin resistance. Tertiary prevention addresses the presence of obesity-related complications, such as the treatment of hypertension or diabetes through medical management, in order to reduce morbidity and mortality from end-organ damage.

[53] My reference to Latour's blackbox specifically engages his "new definition" (Latour 1987:271), rather than the cybertechnical one; namely: "[t]he assembly of disorderly and unreliable allies is thus slowly turned into something that closely resembles an organised whole. When such a cohesion is obtained we at last have a black box" (Latour 1987:270, 130-131). To illustrate, Eyal probes the origins of the autism epidemic through a careful analysis of emerging caregiver networks, as mental retardation deinstitutionalized in the U.S. in the 1970s (Eyal 2013). By looking beyond the jurisdictional struggles of professionally-defined experts, Eyal makes the case for recognizing knowledge production as "inclusive of all who can make viable claims to expertise" (Eyal 2013:899). These new therapeutic alliances included parents and caregivers and engendered the conceptual,

material, and institutional shifts to broaden the parameters for what would count as autism. Including families and lay practitioners in his analysis makes it possible to penetrate the blackbox of the autism diagnostic category and its success in contributing to the much higher rates of autism reported today.

54 Using a different example in their paper, Adams, Murphy and Clarke propose that through the lens of anticipation, prevention is more accurately a state of "biopreparedness," composed of "new and better means of dealing with inevitable disasters rather than actually preventing them" (2009:257-258).

55 In a poignant example of "well baby" care becoming operationalized in a pediatric practice, Michael DeBaun provides an account of the extraordinary influence of his own pediatrician while growing up in St. Louis: "The most powerful person in my life was Helen Nash, my pediatrician. She was a dominant Black woman. Dominant. She had to be, to be a Black woman physician who practiced in the [19]50s. … which means she went to medical school in the 40s, and for her to be a Black woman and go to medical school [at that time] says something in and of itself. … She was such a powerful person, that she had great influence on the care for children in the city of St. Louis. She was the closest thing I would say to a real life hero that had a great impact in my life. … I felt the benefit of that when I applied for my residency to Wash[ington] U[niversity] from Stanford [Medical School]. She was still prominent; she was still the busiest practice in the city. She said [to the residency selection committee], '*You take my well baby, Michael"*' (DeBaun with Jae, 11 April 2015). Helen Nash's remarkable life is also documented in press accounts published shortly after her death in October 2012, at the age of 91 (e.g., Jordan 2012).

56 Some practitioners object to calling sickle cell disease incurable, as this does not account for the treatment potential of transplant.

57 Newborn screening for sickle cell disease in metropolitan France is targeted, rather than universal (see also Chapter 1).

58 Due to their abnormal shape, sickling red blood cells are preferentially collected in the spleen. Splenic filtering of sickled blood cells progressively damages the organ and impairs its immunologic capacity to thwart potentially dangerous infections caused by encapsulated bacteria, principally *streptococcus pneumoniae*.

59 The Prophylactic Penicillin study used an intention to treat analysis: study subjects were randomized to intervention or placebo arms and analyzed as such regardless of whether the penicillin-assigned group complied with the prescribed dose of medication or not. The research design included an assessment of medication compliance using pill bottle counts and urine testing for

the presence of the study drug. Because compliance assessments were not reported for the majority of study encounters, these findings were not analyzed; however, there was enough evidence of episodic rather than consistent used of penicillin for the study authors to suggest that having penicillin readily available in the home made it possible for *the family* to administer antibiotic medication more promptly (Gaston *et al.* 1985:1598). The implications of this study finding to subsequent efforts to replicate its results in future trials is discussed in Elliott Vichinsky's oral history conducted on 15 April 2013, in Miami, Florida.

60 By "doing great," she elaborated that her son had "only been hospitalized nine times in seven years."

61 "Medical home" is a term introduced by the American Academy of Pediatrics and further developed conceptually by pediatrician Calvin Sia in the 1980s as a physician-led strategy for providing family-centered health care that is comprehensive and coordinated across the preventive and acute care spectrum of institutions, health care providers, and care practices, as well as continuous over time. In contemporary health policy contexts, the Patient-Centered Medical Home has since been elaborated and promoted by primary care organizations such as the American Academy of Family Physicians and is the subject of numerous demonstration projects to improve health outcomes and decrease health care costs.

62 My thanks to Gil Eyal for phrasing this phenomenon in this way.

63 The data contributing to adult mortality observed in Lanzkron *et al*. (2013), is limited by the lack of national registry data for individuals currently living with sickle cell disease in the U.S.; thus, it is not possible to extrapolate life expectancy or survival from these data. In sickle cell disease, it is possible to equate life expectancy with survival, as the disease both begins and can be diagnosed at birth. This is in contrast to certain cancers, for example, where survival statistics are also artifacts of the time of diagnosis. When the lead-time to diagnosis increases in absence of a treatment that modifies disease progression, an increase in survival time may be observed without a change in mortality. A more recent analysis of CDC registry data (Registry and Surveillance System for Hemoglobinopathies, RuSH: https://www.cdc.gov/ncbddd/hemoglobinopathies/rush.html, accessed 1 June 2019) collected in Georgia and California from 2004-2008 detected higher than expected death rates among individuals with sickle cell disease, as the existing death certificate data did not identify persons as having sickle cell disease in half of registry-identified deaths (Paulukonis *et al.* 2016). During this period, "the average age of death was about 43 years for females and 41 years for males. About 1 in 6 deaths occurred in those under 25 years of age and nearly half of all deaths occurred in

those over 44 years of age" (https://www.cdc.gov/ncbddd/sicklecell/features/keyfindings-scd-death-rate-estimates-ca-ga.html, accessed 1 June 2019).

64 I revisit Halima's story with more detail in Chapter 4.

65 See also Rouse (2009) for specific attention to adolescents and young adults with sickle cell disease as they engage the health care system during this transition.

66 Despite the clinical consensus around the importance of cerebrovascular screening, this form of anticipatory care is not practiced equally across centers. For example, the recruitment of patients to chronic transfusion programs can vary widely, and this was also a contentious practice difference observed between Hôpital Y and Hôpital B.

67 Roth *et al*. 2012 elicited this perception among two thirds parents surveyed at a single sickle cell center.

68 A more recent iteration of TAP is the U(ndetectable) = U(ntransmissable) campaign, which was recently, if belatedly, endorsed by the CDC (Centers for Disease Control, HIV/AIDS, Dear Colleague Letter [27 September 2017], https://www.cdc.gov/hiv/library/dcl/dcl/092717.html (accessed 18 May 2018)

69 "Implementation science is the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services"; see also Bauer *et al*. 2015.

70 The most common usage of a "process," as defined by the Oxford English Dictionary.

71 Depending on the management theorist cited, the principles of a process can vary (e.g., Brown and Duguid 2017[2002]).

72 See Chapter 2 for detailed discussion of adult mortality in sickle cell disease, including footnote 46.

73 While this chapter does include examples of knowledge transfers that are occurring among clinicians and researchers, practices among these groups are also examined in the context of experimental clinical research design in Chapter 4.

74 Section II of the National Society of Genetic Counselors code of ethics states: "The counselor-client relationship is based on values of care and respect for the client's autonomy, individuality, welfare, and freedom. The primary concern of genetic counselors is the interests of their clients." These concerns are outlined as guidelines for practitioners to: "3. Respect their clients' beliefs, inclinations, circumstances, feelings, family relationships and cultural traditions; and 4. Enable their clients to make informed decisions, free of coercion, by providing or illuminating the necessary facts,

and clarifying the alternatives and anticipated consequences."

[75] *Le mélange équimolaire oxygène-protoxyde d'azote 50% / 50%* (a gas mixture of equal parts nitrous oxide and oxygen).

[76] See also Chapter 4.

[77] Please refer to Chapter 2 for discussion of anticipatory guidance in clinical care work.

[78] One U.S. center calculated the median cost of the transplant year for their pediatric sickle cell patients as: "$413,070 (range, $155,265 to $1,554,690) inpatient and $17,791 (range, $5175 to $88,526) outpatient" (Arnold *et al.* 2015).

[79] See also Chapter 1 for brief discussion of genetic variants for sickle cell disease.

[80] Evidence for malignancies that can be attributed to hydroxyurea, while still cited as a hypothetical risk, still remain unfounded.

[81] My usage of "doctor shopping" in this fieldwork example does not include the (overwhelmingly) negative perception of this term when it refers to patients' attempts to procure controlled substances from multiple health care providers.

[82] In both the U.S. and France, a family's immigration status became a central concern when this posed bureaucratic and logistical challenges to providing payment for hospital services, obtaining housing, and ensuring adult supervision is available during recovery.

[83] Additional English translations for *au pays* include "in the homeland."

[84] Although adolescents with chronic diseases in France tended to transition to the adult service by age 16, the sickle cell patients at Hôpital Y who had been transplanted tended to remain patients through their teenage years. In part, this was due to Hôpital Y's expertise in post-transplant care, for what is still a niche population; however, this also facilitated the extraction of data points for long-term follow up after transplant, for the center's ongoing research and outcomes analysis.

[85] Nina's mother actually first heard about transplant from a friend outside of the health professions, who mentioned seeing a television program mention bone marrow transplant for sickle cell disease while Nina was still an infant. Not until years later, however, did they begin to discuss this possibility with Nina's doctors.

[86] In fact, Lena was from French Guiana.

[87] In the U.S., this documentation is also used to justify reimbursement from public and private health insurers.

88 At Community Hospital, Dr. S even garnered grant funding to publish a patient diary that in many ways resembled the ubiquitous Carnet de Santé, the personal child health record, which are distributed for all children after having their birth registered in France.

89 At the time of my fieldwork at Hôpital Y, patients received simple transfusions at the day hospital; by contrast, exchange transfusions, were available at Hôpital B.

90 In France, where cryopreservation of gonadal tissues is provided for children undergoing transplant, cases of *ex-drepanocytaires* who have become pregnant or restored gonadotrophic hormone levels by re-implanting ovarian tissue have been published (**add citation**).

91 Another colleague at Hôpital B's sickle cell center used the term "*très demandeuse*" to describe a parent after the family left the consultation room and cited the mother's requests for a referral to a sickle cell support group and for social work assistance, neither of which the provider was knowledgeable. I suspected the use of this term in both instances spoke more to the respective providers' sense of proficiency or customary practice than an excessive demand on the part of the family member.

92 DeBaun's reluctance toward transplant was also in spite of being the lead researcher of the silent stroke trials that concluded that chronic transfusion programs were insufficient to prevent silent strokes. Although children were eligible for and were recruited to the haplo transplant series, because the trial used a reduced intensity rather than myeloablative conditioning regimen, for many providers, the haplo protocol was particularly promising for adults whose disease severity often precluded them from the toxicity of myeloablative regimens.

93 See Chapter 3, page 101.

94 Good continues: "Today, it is a mistranslation, suggesting that the Credo consists of propositions the veracity of which we assert. This is historically inaccurate and profoundly misrepresents the traditional ritual acclamation. Equally important, for the comparativist, the misplaced focus on beliefs as the primary dimension of religious life has led to mistranslations and misunderstandings of other religious traditions, and in Smith's view, to the great failure to explore the faith of others in their historical and communal contexts, even to make faith a central category in comparative research" (Good 2004[1994], 17).

95 Fleck's explicit definition of thought collectives are: "*a community of persons mutually exchanging ideas or maintaining intellectual interaction… providing[ing] the special 'carrier' for the historical development of any field of thought, as well as for the given stock of knowledge and level of culture. This we have designated thought style.* The thought collective thus supplies the

missing component." In his example, Fleck poses "the statement, 'Someone recognizes, something,' demands some such supplement as, "on the basis of a certain fund of knowledge,' or, better, 'as a member of a certain cultural environment,' and, best, 'in a particular thought styles, in a particular thought collective" (1979[1935]:39).

96 Douglas continues: "…It took four centuries before scientific advances in other fields were important enough to establish a definitive distinction between different diseases originally clumped together as venereal" (1986:37).

97 That is, prior to *Genesis and Development of a Scientific Fact* (1979[1935]).

98 These largely remained unrecognized until *Genesis and Development of a Scientific Fact* (1979[1935]) was cited by Kuhn (1996[1962]).

99 Coincidentally, also the year of Herrick's published case report that first described the elongated blood cells that were visible microscopically, during the patient's still unnamed sickle cell crisis.

100 Indeed, one of the providers at Hôpital Y hypothesized that the sickle cell providers at Hôpital B were not as comfortable promoting transplants, because some of these were general pediatricians without training in hematology. I did not find this to be the case during my period of fieldwork, and the sub-speciality trained providers at Hôpital B were equally unlikely to promote transplant to their outpatients.

101 Bernaudin *et al.* 2013.

102 Compared to those of White European descent, where population modeling produced a 75% likelihood of identifying a fully matched (8/8 HLA) donor, the same study's probabilities of similarly matched donors was "only 46% for white patients of Middle Eastern or North African descent. The likelihood of finding an 8/8 HLA-matched adult donor for other groups is lower and varies with racial and ethnic background. For black Americans of all ethnic backgrounds, the probabilities are 16 to 19%; for Hispanics, Asians, Pacific Islanders, and Native Americans, they range between 27% and 52% (Gragert *et al.* 2014:344). Also notable is that donor availability was included in the statistical model, based upon historic percentages by race. Only in White populations did confirmatory testing and overall donor availability exceed 50 percent (Gragert *et al.* 2014:343).

103 Nonetheless, often parents are tested, as it is still possible, though rare, for a parent to have the same HLA as the child.

104 A benefit of GVHD unique to malignant conditions is that the activation of donated white blood cells against the host also can reduce the risk of relapse, through its graft-versus-cancer effect.

105 Community Hospital in the U.S. did not have an infusion room and utilized the inpatient ward to conduct blood transfusions for their pediatric patients.

106 Near the end of my fieldwork in France, I met Docteur Dani's husband, a retired adult transplant physician. The picture behind Docteur Dani's formidable interest in transplant medicine, and how this had been facilitated without formal fellowship training, became that much clearer.

107 For the subset of transplanted sickle cell patients who are now aging into adulthood, their transition from pediatric to adult services, both in the U.S. and France, remains uncertain and poorly documented.

108 In a related example, two of the patients I met at University Hospital experienced rejection of their initial graft. Both had been referred for transplant from outside centers, where they received chronic transfusions for their sickle cell disease; both planned to repeat the procedure, but needed a year or more of respite before attempting a second transplant. While awaiting his second transplant, one of the patients resumed transfusions through the sickle cell program at University Hospital rather than his former center, though only after negotiation with University Hospital's hematology service.

109 Depending on prior exposure history, donor or recipient may harbor latent infections, such as to cytomegalovirus (CMV) and Epstein Barr virus (EBV), that can reactivate with transplant immunosuppression.

110 The central line served both as a means for accessing the blood stream for diagnostic testing and the applications of medications, but as a foreign body in direct communication with the blood stream, the catheter is itself a potential source of infection. A family I met who received post-transplant care at Hôpital Y underwent even earlier removal of the central catheter, due to the team's concern for infection risk in their temporary housing situation, akin to the shelter system in the U.S.

111 This may also contribute to the quality of life measures observed in the DREPAGREFFE trial, which compared transplanted patients prospectively with those receiving the transfusion-based standard of care for stroke prevention. At one-year post-transplant, quality of life assessment measures were significantly higher for caregivers at one year post-transplant; by three years post-transplant, patients' self-reported assessment were significantly higher than controls (Bernaudin *et al.* 2019).

112 And again, in oncology, GVHD can assume the role of a necessary evil, in the interest of preventing a cancer-related relapse.

113 Since the first published haplo transplants for sickle cell disease, which reported a 50 percent rejection rate (Bolaños-Meade *et al*. 2012), a modification that added an additional chemotherapy drug, thiotepa, to the conditioning regimen. The updated conditioning appeared to significantly

improve engraftment to greater than 90 percent for a subsequent series of patients, which included French participants (de la Fuente *et al.* 2018).

114 See also Chapter 3, page 121.

115 In addition to vastly increasing the potential donor pool by using related half-matched donors, the protocol also utilized a non-myeloablative conditioning to reduce procedure-related toxicity as well as high dose cyclophosphamide administered post-transplant, which had dramatically reduced the incidence of GVHD.

116 A video recording of the 2014 Lonzie Lee Jones Patient Symposium is available online: https://www.youtube.com/watch?v=S-FqV1cpJkg, accessed 21 May 2019.

117 The epidemiologically milder genotype.

118 Evera shared in our interview the following her that her brother had died in the month after she returned home from the convention, after experiencing a precipitous decline in his health, at age 54 (Ivy with Jae, 30 April 2016).

119 In 2017, the sudden death at age 42 of rap artist, Albert "Prodigy" Johnson, of Mobb Deep, due to complications of sickle cell disease renewed attention to his autobiography, *My Infamous Life* (2011); the impact of his illness on his life and music was featured on a multi-episode podcast, "The Realness" (WNYC, https://www.wnycstudios.org/shows/realness, accessed 30 May 2019). Comedian Nore Davis has included details from his life with sickle cell anemia for his recorded stand-up performances (e.g., "Away Game" [2014]).

120 As another example, Toni related how much her daughter with sickle cell disease loved swimming, the beach, and all forms of water play; however, Aliyah's first severe pain crisis occurred at age four and began shortly after entering a swimming pool, while their family was on vacation within the U.S. Her mother related how the pain quickly escalated, becoming so severe that she was hospitalized, out-of-state, for the entirety of their stay (Thompson-Smith with Jae, 20 May 2017). Aliyah's first transplant attempt was not part of a study protocol but used a published reduced intensity conditioning regimen, a request from her parents that was accommodated by her transplant team, but resulted in graft rejection. On the second attempt, Aliyah's matched sibling remained the donor, but her physicians reverted to Vermylen *et al.*'s (1998) fully myeloablative protocol. After Aliyah was deemed cured of sickle cell disease following her second transplant, she selected a water theme park as their family's Make-A-Wish Foundation destination.

[121] The Sickle Cell Disease and Other Heritable Blood Disorder Research, Surveillance, Prevention, and Treatment Act of 2018 (S. 2465) was signed into law in the U.S. on 18 December 2018. (https://burgess.house.gov/blog/?postid=398890&rel=0, accessed 1 June 2019).

[122] *60 Minutes*. "More on the Trial Aiming to Cure Sickle Cell." CBS Interactive, Inc. (10 March 2019). https://www.cbsnews.com/news/more-on-the-trial-aiming-to-cure-sickle-cell-60-minutes/, accessed 29 August 2019.

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