INTEGRATING SOCIAL CONTEXT INTO PERSONALIZED MEDICINE

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ABSTRACT

Personalized medicine is the idea that every patient can be treated in a unique manner, tailored specifically to his or her individual needs. Traditionally the field of personalized medicine has focused on using genetic information to determine medical treatment. However, humans are not only the sum of their genetic parts. All people exist within the context of their environment, their experiences, and their relationships. While the connection between this greater context and medical treatment may not be immediately obvious, it exists. If we are to truly tailor medical care, it must occur in a holistic manner, combining both genetics and social context. A thorough understanding of the way that they interact, as well as the individual limitations of both, is the best way to offer individualized care to all patients.

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CHAPTER 1: INTRODUCTION

The goal of a physician is to promote health while diagnosing and treating disease. In order to do that, he or she must take the time to listen and get to know every individual patient. A thorough social history is a part of any good history and physical exam. Physicians ask patients where they live, what they do for work, how far they went in school, if they feel safe at home, if they have reliable access to food, who helps them when they need it, along with many other questions to get to know them better. All of these questions provide context into the richness of those patients lives. However, the ability to use that social context to differentially determine the best treatment for disease is often limited. The tools of modern medicine for holistically assessing a patient and predicting the best individual treatment are lacking.

First of all, the ability to understand a given patient as a unique individual is incomplete. Physicians ask so many questions in order to understand their patients as individuals. And then they proceed to make treatment decisions based on clinical evidence. However, most clinical evidence is performed in a manner that intentionally excludes outside social factors. So even though physicians collect a rich social history, the studies that provide the evidence to inform treatment plans were never designed to take social factors into account. It is impossible to know if a given patient, with all of the rich context of his or her life, will align with the "average" recommendations of a study or clinical guideline.

While lacking in clinical trials and guidelines, there is a wide body of literature on the way social factors influence risk for disease. That literature is especially useful for

selecting subgroups of individuals who are at increased risk for various diseases and intervening through prevention and screening. However, that information is less useful to a doctor who has a patient in his or her office who is already ill. And it is often unclear if (and how) social factors influence response to medical treatment. The lack of attention to the way social factors influence response to treatment leaves doctors without high quality evidence when integrating real world social factors into their treatment decisions.

In this paper, I define two determinants of individual health, "biology" (e.g. genetics and natural processes of disease) and "biography" (e.g. experiences, environment and relationships). While personalized medicine often focuses on biology, I argue that incorporating biography into the clinical decision making process is important for making individualized treatment decisions. As we develop a better understanding of how biology and biography each influence treatment response, we move closer to understanding the way they work in concert to influence health risk and treatment response in at the individual level.

CHAPTER 2: HISTORY OF PERSONALIZED MEDICINE

Understanding the building blocks of life has captured human curiosity spanning across centuries and cultures. From the elements of earth, water, air and fire to the DNA double helix, we are in a constant evolution in our understanding of what makes up the human body. A major step forward in our modern understanding of human genetics began in the late 1980s when US Government agencies, including the Department of Enegery, National Institutes of Health (NIH) and the Congressional Office of Technology combined resources to initiate the Human Genome Project. For more than a decade afterwards, the Office of Human Genome Research, headed by James Watson at the NIH, worked diligently to map the entirety of the human genome in collaboration with both private industry and international partners (Dickson, 2000). In a momentous speech on June 26, 2000 President Bill Clinton announced,

> "Today, the world is joining us here in the East Room to behold a map of even greater significance. We are here to celebrate the completion of the first survey of the entire human genome. Without a doubt, this is the most important, most wondrous map ever produced by humankind (Clinton, 2000)."

He noted the grand potential of this discovery for one day curing diseases such as Alzhemier's, Parkinson's, diabetes and cancer at the genetic level.

Public availability for accessing one's genetic makeup is more widely available than ever before. Commercially available testing kits from companies like "23andMe" and "Ancestry.com" offer genetic screening for major disease markers, while more intensive screening can reveal one's full genetic code. Given the fact that genetic

mapping is available with a small amount of saliva and the swipe of a credit card, the question becomes what to do with all of this information. While the cures mentioned by President Clinton have not yet come to pass, the integration of genetics into the practice of modern medicine is a rapidly advancing field.

Results from these genetic tests are already used clinically, guiding individual treatment decisions. For example, physicians can test for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) tumor markers in the breast tumor cancer cells, which each allow targeted hormonal treatment (Weigel & Dowsett, 2010). Additionally, genetic variation in the VKORC1 and CYP2C9 genes, which are responsibe for Warfarin metabolism, influence clinical decisions regarding the proper loading dose of the commonly used anti-coagulant. Those with genetic variants encoding high enzymatic activity experience faster degradation of the drug and therefore need a higher starting dose. Without increased dosing, these patients would be at risk for clotting. Conversely, those with genetic variants encoding low enzymatic activity experience slow drug degradation and therefore need a lower starting dose. Without dosing alterations, these patients would be at risk for bleeding (Dean, 2012).

These advances in understanding the genetic basis of disease open exciting doors for both screening and treatment of disease. However, these advances have not arrived without producing concern about the potential for this information to be used in a negative way. As with any information that may be used to identify patients, there is a constant need to evolve our privacy policies and techniques. There is also a need to ensure that genetic information is not used as a method to discriminate against certain

individuals or groups of people. In that same speech by President Clinton, he mentions "we must guarantee that genetic information cannot be used to stigmatize or discriminate against any individual or group." Discrimination can be explicit in the form of using someone's genetic information to deny them a job, housing or other opportunity. However, discrimination can be in a more insidious form. Genetic determinism, or the belief that everything in one's life can be explained by underlying genetic causes, can be equally problematic, especially in the field of medicine. If clinicians only see patients as the sum of their chromosomes, the richness and context of that human life is lost. In order to avoid this pitfall, a thorough understanding of the way that social factors influence health is essential. Understanding the role of both genetics and social factors, with all of their strengths and weaknesses, is the best way to respect the power of both.

CHAPTER 3: HISTORY OF SOCIAL DETERMINANTS OF HEALTH

The impact of social factors on overall health is well established and it adds important context to the advances in modern genetics. In 1845 Frederick Engels published "The Condition of the Working Class in England" and argued that poor living conditions and low wages lead to worse health among urban workers compared to rural workers in industrialized England (Engels, 2003). In 1848 Rudolf Virchow published his report on a typhus outbreak in Upper Silesia, blaming social and economic disparities for impairing proper disease control (Virchow, 2006). American sociologists Kitagawa and Hauser expanded on these theories in 1973, publishing "Differential Mortality in the United States." They combined census data and death records for those persons, age 25 years and older, who died between May and August 1960. Research showed that socioeconomic status, determined by number of years of completed schooling, income, occupation, race and place of residence, inversely correlated to all-cause mortality in the US cohort (Kitagawa & Hauser, 1973). Shortly thereafter, the Whitehall I and II studies of civil servants in the UK in 1980 and 1991 showed a similarly inverse correlation between social class, as assessed by grade of employment, and mortality (Fuller, Shipley, Rose, Jarrett, & Keen, 1980; Marmot et al., 1991). These disparities in health, depending on social factors, are referenced commonly in the literature as the "social gradient in health," "SES gradient," and "social class gradient" (Kosteniuk & Dickinson, 2003; Sapolsky, 2005; STEIN, 1957).

Given the accumulating evidence and increasing interest in social factors influencing health, the World Health Organization defined the term "social determinants of health" (SDH) in the mid 1980s. Their current definition states,

> The social determinants of health are the conditions, in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms, social policies and political systems.

Until this definition, many people used the term socioeconomic status (SES) to represent a similar idea, although less encompassing. Since the 1980s, "SDH" has become more widespread but "SES" is still used commonly outside of social health research.

CHAPTER 4: SOCIAL DETERMINANTS OF DISEASE

SDH not only influence populations in respect to overall health and mortality, but they also influence the way that different populations of people experience specific diseases. For example, in the 1980s breast cancer mortality was nearly equal for white and black women in the United States. However, in the early 1990s, a significant mortality gap started to emerge (Chevarley & White, 1997). While incidence rates converge between races, black women are significantly more likely to die from the disease (Chevarley & White, 1997; DeSantis et al., 2016). Death files from the 50 largest US cities from 1990-2009 showed an excess of 1710 deaths per year (approximately 5 per day) of black women from breast cancer (Hunt, Whitman, & Hurlbert, 2014). Race is certainly not the only SDH that influences risk for disease. Studies looking at many factors, from educational attainment, to income, to marital status all address the way that different social factors influence disease prevalence among different populations of individuals. Knowing that these disparities exist, the next step is to try and understand why.

One way for social determinants to influence disease is when certain groups of individuals are exposed to risk factors at dissimilar rates from other people. For example, previous research has implicated adverse childhood events (ACEs) in a wide variety of negative adult outcomes. A retrospective cohort study examined the risk for autoimmune diseases in 15,357 adults who had previously enrolled in a study on ACEs between 1995 and 1997. Researchers combined previous survey data on ACEs, including childhood physical, emotional or sexual abuse, witnessing domestic violence, growing up with

household substance abuse, mental illness, parental divorce, and/or an incarcerated household member with medical records. After scoring ACEs on a scale from 0-8, researchers found that increased number of ACEs correlated with first hospitalization for autoimmune disease. They also found that those with more than 2 ACEs, compared to those without any, were at a 70% increased risk for Th1 disease, 80% increased risk for Th2 disease and 100% increased risk for rheumatic disease (Dube et al., 2009).

Another way for social determinants to influence disease is through unequal screening and detection. One possible explanation for the race differences mentioned above for breast cancer, black patients are diagnosed with a variety of solid tumor cancers at later stages than white patients. For 34 solid tumors, a study of surveillance, epidemiology and end results (SEER) data from 1992 to 2003 showed that Black patients were diagnosed at a later stage for 31 of the 34 tumor types. These disparities were still apparently in cancers with effective screening techniques, such as female breast, colorectal and cervical cancers. Black patients were significantly less likely to survive 5 years for 26 of the tumor sites, including esophageal cancer and colon cancer (Virnig, Baxter, Habermann, Feldman, & Bradley, 2009).

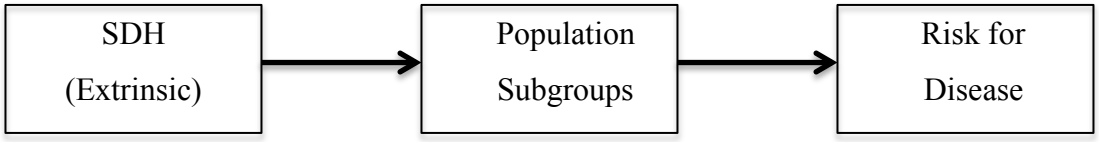
Furthermore, social determinants can directly influence disease pathogenesis causing different disease experiences in different groups. For example, a prospective cohort study of patients with Alzheimer's disease, age 65 or older, in New York showed more rapid disease progression in patients with a higher level of education. After recruiting subjects from community care registries and established aging studies, patients participated in an average of 3.7 neuropsychology visits over an average follow-up of 5.6 years. When controlling for baseline deficit, each additional year of education

corresponded with a 0.3% standard deviation lower cognitive performance each year of the study. The declines in cognitive function were especially pronounced in executive speed (0.6%) and memory (0.5%) (Scarmeas, Albert, Manly, & Stern, 2006).

Even the selection and implementation of medical treatment, which is meant to provide all patients with the best means to survive their disease, is impacted by social determinants. Shavers et al. describes three domains - structural barriers, physician judgment, and patient factors - where social determinants influence clinical care (Shavers & Brown, 2002). One illustrative example is race and cancer, where Black patients receive less aggressive care for many types of cancer. Using a SEER-Medicare linked database, one study identified 143,512 patients, ages 66-85 year old, with a primary diagnosis of colorectal, breast, lung or prostate cancer from 1992-2002. They showed that black patients were significantly less likely than white patients to receive surgical resection for early stage lung cancer (64.0% vs 78.5%), radiation after lumpectomy in breast cancer (77.8% vs 85.8%) adjuvant therapy for stage II colon cancer (52.1% vs 64.1%) and definitive therapy for early stage prostate cancer (72.4% vs 77.2%) (Gross, Smith, Wolf, & Andersen, 2008). Determining ways to ensure the proper delivery of treatment, regardless of race, is essential for closing the racial mortality gap in these cancers.

The above studies help to show that SDH influence overall health and risk for disease and they propose multiple mechanisms by which it occurs.

Figure 1. SDH and Population Risk for Disease



The field of public health focuses heavily on "upstream interventions" to reduce these risk factors and promote better screening, detection of disease and access to treatment. One disease has already occurred, the next question becomes whether social determinants continue to play a role by influencing differential patient responses to the same medical treatment. Rather than focusing on "upstream interventions" aimed at risk factors, clinical medicine can use information on differential treatment responses to design treatment plans that will be optimally tailored to a given patient and his or her unique needs.

CHAPTER 5: SOCIAL DETERMINANTS OF TREATMENT RESPONSE

Understanding the impact of SDH on response to medical treatments is important if physicians are to use social factors in the course of clinical decision making. Before looking into the literature on SDH and response to medical treatment, I would like to review the method used to produce the majority of medical research that drives treatment decisions. The gold standard for medical research, the randomized clinical trial (RCT), traditionally attempts to control all possible non-biological factors in order to isolate the chemical effect of a medication. However, averages from RCTs combine information from various individuals who may vary significantly from the average population effect. "Heterogeneity of treatment effects" occurs when individuals or subgroups within the same study have varying and opposing responses to the same treatment (Kravitz, Duan, & Braslow, 2004). These smaller differences are not always obvious when looking at the larger group data.

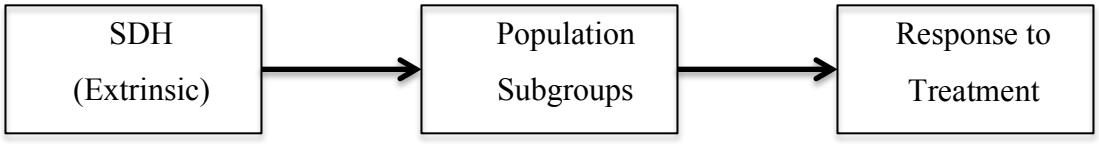
The role of social factors on treatment response is likely poorly understood at the point in time for several reasons. First, the current model of randomized clinical trials (RCT) intentionally excludes social factors and generally does not attempt to analyze them. Second, social factors likely influence the responses of individuals or smaller groups within a larger study. These subtle differences can be easily obscured when they are combined with the larger data set during analysis of averages. Assuming that population averages apply to all individuals within that larger group is clearly not accurate. And treating a patient on the assumption that they fall in line with the population average may not provide the best clinical care for that individual.

The Beta-Blocker Heart Attack Trial (BHAT) provides a real-world example of divergent sub-group effects in RCTs. In this study, researchers recruited 3837 patients, men and women ages 30 to 69, who had survived a previous myocardial infarction (MI). Study participants were randomly assigned to receive propranolol or placebo and monitored for at least 12 months regarding clinical severity, adherence, psychological and social variables, and mortality. While propranolol significantly reduced the risk of death overall across the 31 study sites, further analysis revealed that 10 of the 31 sites observed "divergent" patterns with a higher average mortality among the propranolol group. Further investigation revealed that propranolol was associated with improved mortality outcomes in the divergent centers among those also receiving aspirin and/or coronary surgery, but was associated with worsened mortality among those without these additional co-therapies. Researchers noted the need to further determine what factors in these ten sites made them diverge (Horwitz, Singer, Makuch, & Viscoli, 1996).

Improving understanding of variations within larger sample populations is gaining attention at the drug development level. The FDA's 2014 "Action Plan to Enhance the Collection and Availability of Subgroup Data" highlighted the need for better subgroup analyses and better information on individual response to medical treatment during new drug development. The FDA published its first subgroup information, from 5 new molecular entities (NME) in November of 2014, and now publishes public information on subgroups for all new NMEs and original biologics. The absence or presence of differential treatment effects based on sex, race and age subgroups is publically available via the FDA Drug Trials Snapshot website.

The need to understand differential responses to treatment is not limited to new therapies. It is important that we better understand the way that life experiences and social context impact the treatments that are already used daily.

Figure 2. SDH and Treatment Response



While this area of research is not yet robust, the results of already published papers show how much we potentially have to learn by focusing more energy on it.

Table 1. SDH and Differential treatment response

SDH	Treatment	Study Design	Differential Response
Gender	Aspirin	A retrospective study using data from 6 prospective randomized control trials of aspirin therapy in participants without cardiovascular disease. Researchers collected data on myocardial infarction (MI), stroke, and cardiovascular mortality outcomes for the 95,456 participants	Aspirin reduced the risk of composite cardiovascular events in both genders. However, women experienced a 17% reduction in stroke rates with no effect on MI while men experienced a 32% reduction in MI with no effect on stroke (Berger et al., 2006).
Socio-economic Deprivation	Colorectal cancer resection	A retrospective study on the relationship between mortality and socioeconomic deprivation among 2269 patients who	Following curative resection, the overall survival rate at 5 years was 47.0 per cent in deprived patients,

		underwent resection for colorectal cancer in hospitals in central Scotland between 1991 and 1994	compared with 55.4 per cent in affluent patients (P = 0.05); the cancer-specific survival rate was 62.6 per cent in the deprived and 68.1 per cent in the affluent (P = 0.05) (Hole & McArdle, 2002).
Education	Breast Cancer Clinical Trial	A retrospective study using data from 10 trials conducted by the Cancer and Leukemia Group B to examine the effect of education on the survival of breast cancer patients treated in those clinical trials. They included 1020 patients with metastatic disease and 5146 patients with early stage disease.	Less educated women had worse survival in early stage disease. However, lack of high school education improved survival among black women but lack of a high school education decreased survival in white women with metastatic disease (Herndon, Kornblith, Holland, & Paskett, 2013).
Marital Status	Definite treatment for epithelial cancer (treatments with curative intent)	A retrospective study on effects of marital status on the diagnosis, treatment, and survival of patients with cancer. Researchers examined population-based data on 27,779 cancer cases.	Unmarried persons with cancer had decreased overall survival (relative hazard, 1.23; 95% confidence limits, 1.19 to 1.28). After adjustment for stage and treatment, unmarried persons still had poorer survival (Goodwin, Hunt, Key, & Samet, 1987).
Adverse Childhood Events (ACEs)	Behavioral and/or pharmaco-logical depression treatment	A prospective study of 681 patients, ages 18 to 75, with chronic forms of major depression. Participants were enrolled and randomly assigned to treatment with an antidepressant (nefazodone), Cognitive Behavioral Analysis System of Psychotherapy (CBASP), or the combination. They were	Overall, combination therapy was the most efficacious in the entire study population. However, for those with a history ACEs, psychotherapy alone was superior (48.3% remission) to antidepressant monotherapy (32.9% remission). Combination therapy (53.9% remission)

		also assessed for ACEs before starting therapy.	was only marginally superior to psychotherapy alone (Nemeroff et al., 2003).

These studies show that social determinants can, in fact, influence response to treatment. Intentionally pursuing further research on these differences may allow for the development of more effective treatment methods.

CHAPTER 6: FROM POPULATION TO INDIVIDUAL

As shown in Table 1, sub-group analyses can uncover patterns of divergent or differential effects within a larger population. But sub-group analyses still rely on population averages, even though smaller populations. To provide truly personalized care, using social determinants at an individual level, it is necessary to further refine the way we research them. Table 1 primarily includes traditional measures of SDH that appear throughout the population health literature. These measures focus heavily on institutional and environmental influences that are fixed and extrinsic to the individual. Measuring SDH using extrinsic variables is very useful for studying population trends, as researchers can collect these data easily and use them to describe large groups. For example, the table contains the measures of "race" and "gender" which are external social roles. But they do not necessarily indicate anything about the inherent biological traits of "genetic ancestry" or "sex." They also do not necessarily indicate anything about the way an individual experiences those social roles like "perceptions of discrimination" or "gender identity." Extrinsic measures of SDH are less successful at capturing individual variation, as the extrinsic focus obscures the role of the individual. Even when these measures are used to establish smaller sub-groups, they are still population measures that do not truly explain individual-level characteristics.

Table 2. Population Versus Individual Characteristics

Population (Extrinsic)	**Individual (Instrinsic)**
Biological Sex	Gender Identity
Race	Perceptions of Discrimination
Income	Financial Strain
Education	Self-efficacy
Address/Location	Feeling of control
Experiences of Violence	Cortisol Response
Marital Status	Feelings of Social Support

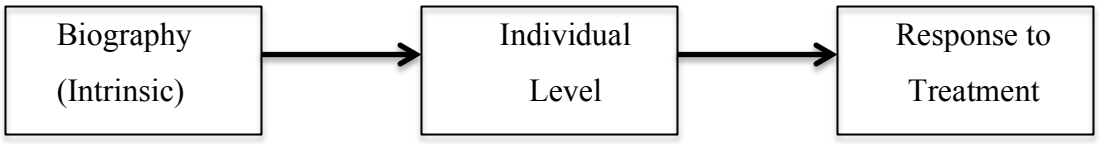
Because there are cases where individual and population data do not correlate at all, we must be cautious about using population data to draw individual conclusions. For example, higher income promotes improved health, which in turn promotes further income attainment, at the individual level. Despite the individual effects, research on that same data shows that income actually worsens health across a population when controlling for education (Deaton & Paxson, 2001). Recessions are also unexpectedly beneficial to health on a population level although they remove individual participants from the wage-earning labor pool, rising unemployment negatively correlates with mortality rates (Ruhm, 2009). These examples do not discount the value of population research, but they do caution against incorrectly using population trends to draw conclusions about an individual. This practice of obtaining population data and incorrectly applying it to an individual is known as "ecological fallacy" (Idrovo, 2011).

"Educational attainment" is a good illustration to further explore the potential for ecological fallacy between population and individual measures. A study of educational attainment and risk factors for coronary heart disease in middle-aged women examined the relationship between education (a population measure) and specific feelings and experiences (individual measures). The study enrolled 541 women, ages 42-50, in 1983 and followed them for 5 years to monitor coronary heart disease risk factors, such as blood pressure, cholesterol, glucose, BMI, smoking, exercise and psychological measures, in the peri-menopausal period. The study was unique in the way it separated the extrinsic measure of educational attainment from a wide variety of intrinsic, individual measures. The study showed that lower educational attainment correlated with increased feelings of anger, lower reported social support, lower self-esteem, more depressed affect, higher work related dissatisfaction and more pessimistic outlooks (Matthews, Kelsey, Meilahn, Kuller, & Wing, 1989). While they generally correlate, using a patient's educational attainment and making assumptions about feelings of anger, social support, self-esteem, depression, work satisfaction or pessimism is misguided. Asking specific questions about those intrinsic, individual characteristics and experiences is the only way to gain reliable information without the risk of incorrect assumptions. With these examples in mind it is possible to recognize and avoid the temptation of assuming individual characteristics based on group membership alone.

CHAPTER 7: INDIVIDUAL TREATMENT RESPONSE

Rather than trying to assume individual-level information from traditional SDH measures, like educational attainment, we should define more specific metrics for future research and clinical decision-making. Individual experiences, perceptions and reactions to the environment are valuable measures and demand that researchers adopt a new way of thinking. This shift requires new vocabulary to accurately describe these individual-level measures. We use the term "biography" to mean personal experiences, psychosocial factors, and individual reactions to those experiences that influence health risk and treatment response in an individual.

Figure 3. Biography and Treatment Response



While these parameters may initially be more difficult to define in a research setting, there are studies already seeking to dig deeper into biography and response to medical treatment. Table 3 shows several of these studies addressing biographical characteristics and differential response to treatment.

Table 3. Biography and Individual Treatment Response

Biography	Treatment	Study Design	Results
Pain management style	Lumbar disc surgery	A prospective longitudinal study of 111 adults wih acute radicular pain and lumbar diss prolapse or protrustion. The study examined the predictive value of psychological, somatic and social variables for persistent post-surgical pain and diasbility enrollment following surgery.	"Psychological variables" accounted for 37% of the variance in persistent pain scores. Pain coping strategies, such as avoidance of activity, "toughing it out," and physical expressions of pain were all related to increased post-surgical pain (Hasenbring et al., 1994).
Depressive tendencies	Lumbar disc surgery	See above	Higher pre-surgery depression scores were related to increased post-surgical pain (Hasenbring et al., 1994).
Self-efficacy	Back pain treatment	A prospective study of 62 subjects, with chronic, intractible, benign back pain. The study examined the relationship between self-efficacy and and back pain treatment outcomes at 3-11 months post-discharge. The self-efficacy scale categories consisted of (1) walking distance, (2) lifting ability, (3) pain coping, (4) working ability, and (5) social and recreational engagement.	Higher self-efficacy correlated to increased sitting, standing tolerance and elevated self-improvement ratings after treament completion. Total scores on the UAB pain scale were 3.44 for low self-efficacy group and 2.02 for the high self-efficacy group (Kores et al., 1990).
Feelings of stress	Substance Abuse Treatment	A prospective study of 102 participants in a residential substance abuse program examined the relationship between HPA axis activity and retention in substance	Higher salivary cortisol response to same stressful stimuli correlates to reduced completion of substance abuse treatment (Hazard ratio, 0.26; $p < .05$; 95% confidence

		abuse programs. Participants completed computerized stress tasks, and HPA axis response to stress was measured using salivary cortisol levels	interval, 0.09–0.74) (Daughters et al., 2009).
Adherence	Beta blocker after MI	A retrospective study examining previously collected data on 2175 participants in the Beta Blocker Heart Attack Trial. The goal of the study was to determine the relationship between treatment adherence and mortality after a myocardial infarction.	Poor-adherers (those taking less than 75% of their medication) were 2.6 times more likely to die within 1 year than good adherers. regardless of whether they received the beta-blocker or the placebo. Poor adherers had an increased risk of death whether they were on propranolol (OR = 3.1) or placebo (OR = 2.5) (Horwitz et al., 1990).
Perceptions of discrimination	Weight loss intervention	A prospective study of 55 overweight adults examining the relationship between overt weight stigma, depression, binge eating, and weight loss during a 14-week behavioral weight loss program.	Patients who reported more events of weight related interpersonal discrimination lost less weight over the course of the 14 week intervention $t(45) = -1.85$, $p = .04$ (Wott & Carels, 2010).

With studies showing the influence of biography on treatment response, several propose various hypotheses for the differential treatment responses (Bachur, Singer, Hayes-Conroy, & Horwitz, 2018). For example, it is possible that socioeconomic deprivation interferes with the host response to tumors through poor nutrition or ongoing inflammation. Lacking a robust immune response, these patients are at risk for occult micro-metastases, which are not detected during initial screening (Hole & McArdle,

2002). Exposure to adverse childhood events (ACEs) may drive differences in the neurological effects of depression. The subgroup of patients with depression and ACEs may have reduced hippocampal volume, and therefore exhibit a different neurological presentation and treatment response (Nemeroff et al., 2003). Patient pain management style may influence muscle strength, therefore impacting pain following lumbar disc surgery. Avoiding post-surgical activity might decondition the trunk and weaken back muscles, causing increased pain during normal activities. And "toughing it out" may overdevelop those same back muscles, also causing pain (Hasenbring, Marienfeld, Kuhlendahl, & Soyka, 1994). Prior to addressing these differences to help maximize the benefits of a certain intervention, it is essential to understand the underlying reasons that they exist.

Many of these same studies go on to further propose ways to address these differential treatment responses via improved patient selection or targeted parallel interventions (Bachur et al., 2018). For example, measuring cortisol stress response prior to initiation of substance abuse treatment may assist in identifying those people at risk for dropping out of the program. Additional therapies such as alpha-2-adregeneric agonists or corticotropin releasing factor antagonists may help to reduce stress-induced rises in cortisol, and therefore improve treatment retention (Daughters, Richards, Gorka, & Sinha, 2009). Experiences of weight related stigma, often intended to motivate people into losing weight, actually decrease weight loss. So designing weight loss programs to appropriately approach weight-loss topics, without creating a discriminatory environment, is important to avoid these negative outcomes (Wott & Carels, 2010). Because higher self-efficacy is related to improved pain following rehabilitation, a

structured and behavior-oriented program that encourages patient participation may improve post-rehabilitation pain (Kores, Murphy, Rosenthal, Elias, & North, 1990). As research continues to explore these individual level differences in response to treatment, physicians will be better prepared to tailor and supplement interventions to meet the needs of specific individuals.

CHAPTER 8: COMBINING BIOLOGY AND BIOGRAPHY

The goal of understanding individual level variation is to allow for better screening of patients and selection of additional or alternative interventions to maximize treatment outcomes. In order to practically achieve that goal, there must be more research on the role of biography in treatment response. Additionally, it is important to better understand the way that biology and biography act in concert to affect treatment response.

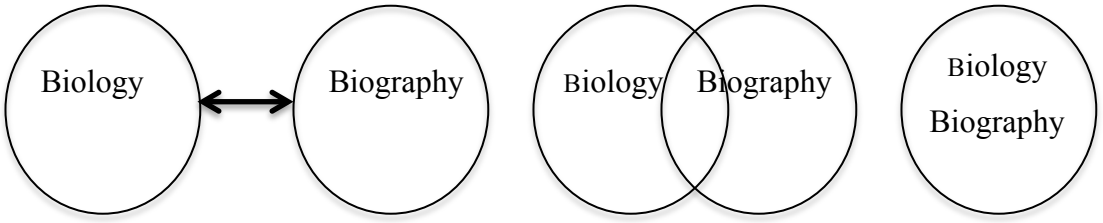
Research on the genetically homogenous Berbers of Southern Morocco highlights this confluence of biology and biography. In this study, researchers enrolled 284 adult men and women from several parts of the Souss region of Southern Morocco. Researchers selected participants, both Amazigh Berbers and Arabs, from two high-density cities and two rural areas. The Amazigh Berbers descend from the first modern humans of Northern African and many continue to live in traditional villages. The Arabs moved into Southern Morocco between the 7^{th} and 11^{th} centuries and occupy lowland villages. Both groups inhabit the cities. During the study, investigators collected peripheral blood samples from all participants and assessed for gene expression in peripheral white blood cells. Up to 1/3 of the "transcriptosome" from nomadic, mountain agrarian and coastal urban individuals was associated with different environment (diet, exposure to microbial organisms, and environmental stresses among other influences) in these genetically homogenous people (Idaghdour et al., 2010).

Although social determinants influence disease and treatment response, there is likely a point where biology overwhelms biography. Regardless of how social

determinants previously influenced health, disease risk, and treatment response a severe enough disease can eventually overwhelm the body. For example, while those with high levels of socioeconomic deprivation experienced increased mortality following curative colorectal surgery, researchers did not observe the same effect during palliative surgery (Hole & McArdle, 2002). Similarly, socioeconomic deprivation does not predict mortality following surgical removal of liver metastases in those with colorectal cancer (Neal et al., 2009). These examples show that once colorectal cancer reaches the point of metastasis or the point where curative surgery is not an option, socioeconomic deprivation is no longer a predictor of mortality. At that point, the biology of cancer is the primary factor. Knowing the limits of social determinants, in addition to knowing where they play an important role, is an essential piece in understanding how they affect response to treatment.

Conversely, is there also a point where biography overwhelms biology? The exact relationship between biology and biography is not yet clear. It is possible that they both function individually with occasional influence on one another. Or perhaps they function individually but have a reliable overlap during some standard set of conditions. Or it is also possible they nearly always function in relationship with one another, to the point that it becomes difficult to distinguish between the two.

Figure 4. Combining Biology and Biography



Defining this relationship will require researchers and clinicians to acknowledge the importance of these questions and to proactively seek to understand them.

CHAPTER 9: BIOETHICAL IMPLICATIONS

Throughout this paper, I have discussed the need to consider "biology" and "biography" together in order to succeffuly treat a given patient as a unique individual. As with any new advances in medicine, it is important to consider the possible implications of these advances and to openly discuss where they may lead. I would like to focus on the bioethical principle of justice to explain the benefits in adopting a new paradigm and how it can ultimately allow for more equitable care.

As mentioned previously, RCTs and evidence based medicine use large population-level studies to determine the best treatments for all individuals. However, clinicians have long acknowledged that blanket guidelines are not always useful or appropriate for all patients. Even if the reason is unclear, some patients obviously respond better than others to the same treatment plans. While this type of care delivery promotes equality, it does not promote equity. True equity means that every patient receives what he or she individually needs, not that every patient receives the same thing. Personalized medicine, made possible by rapid advancements in modern genetic research, in some ways is a reaction to evidence based medicine. It seeks to uncover sublety, diversify treatment options, and bring an element of medical fairness to how each person is treated. However, the genetic aspects of personalized medicine are only part of the equation.

As mentioned in Chapter 2, personalized medicine has also previously been criticized for the potential for "genetic determinism." The idea that people will be seen only as chromosomes is relevant to the bioethical principle of justice. People deserve to

been seen in their true complexity and treated in a way that acknowledges it. I would argue that it is not enough to consider patient's social environment only when it seems to be an impediment or obvious hurdle to their standard medical care. There is a lack of understanding on the way that biology and biography interact. In order for that understanding to advance, research must proactively attempt to do so, and not only when treatments are failing. Just and equitable delivery of care involves many facets, such as allocation of resources, targeted interventions, and access to care. Even with a very limited preliminary understanding of social determinants of treatment response, studies show that patient's biography plays a role in their response to medical care. Furthering that knowledge and incorporating it into care will provide for even more equitable care delivery.

Recent advancements in medical data will greatly assist in the ability to collect and store these types of measures. The implementation of electronic medical records greatly assists in the ability to collect and record both biological and social data (Diez Roux, Katz, Crews, Ross, & Adler, 2015; Matthews, Adler, Forrest, & Stead, 2016). Based on the IOM consensus meeting, there are even proposals for including standard SDH factors in every digital medical record (Adler & Stead, 2015). While the ideal method of collecting biographical data is yet to be determined, electronic records will be the basis for collecting specifically selected metrics depending on the medical condition. It is important to remember that these biographical characteristics are highly dynamic. Experiences, attitudes and perceptions change and improved methods of data collection will assist researchers to adjust data in real time as research and clinical care progress.

Alongside better data collection, researchers must also pursue study designs that better facilitate understanding the combined effects of multiple variables on treatment response. Instead of retrospectively identifying subgroups from a larger pool, prospective study designs of specific groups of patients will be useful. Prospective studies pose logistical challenges for recruitment, so improved utilization of sub-group analyses and meta-analyses is also important. Most subgroup analyses currently control for a single variable of interest, isolating its role on treatment outcomes. However, many factors simultaneously contribute to disease risk and treatment response. Instead of controlling for single variables, we must begin to look at effect modifiers and interaction effects among multiple variables.

Some studies have already begun to create patient profiles that will serve as a model for understanding the relationship between biology and biography in specific medical conditions, such as Lupus Erythematosus (Wivel, Lapane, Kleoudis, Singer, & Horwitz, 2017). Creating further databases of patient profiles is a model that can be applied to other medical conditions as research into biology and biography advances (Horwitz, Hayes-Conroy, & Singer, 2017). The task of understanding individual patients using a holistic approach requires that we redefine the way that we view patients and collect and analyze data. This research should emphasize the individual, collecting data on *both* biology and biography.

In order to accomplish this shift in research, researchers and clinicians must integrate methods and knowledge across multiple research fields. Physicians, scientists, economists, sociologists, psychologists, geographers, social workers, bioethicists, statisticians and other academic fields are all currently working to understand the social

health gradient. Additionally, researching individual treatment response does not discount the need to continue studying population measures. Medical treatment alone will not solve the social health gradient and upstream interventions at the population level are essential. Each field must begin to build on each other's strengths and ideas so that physicians are able to care for every individual patient in the best possible manner.

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