

The Genome on the Horizon:
Practical Reasoning in the Age of Personalized Medicine

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DEDICATION

To my wife, Becky, and my son, Kevin.

ACKNOWLEDGEMENTS

This dissertation, at its heart, is about the indispensable role communal effort plays in the realization of health and wellness. One lesson I have taken from writing it, however, is that the completion of a doctoral thesis requires the same type of support. In my effort to bring this work to completion, I have benefitted from the support and guidance of a great number of people, each of whom has contributed in his or her own unique way.

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This dissertation marks the conclusion of a long educational story. Along the way my parents have been unfailing in their support and love. During these busy years they have, together with my parents-in-law, shown their love by supporting my family. I could not have completed this project without the support of all four.

This dissertation is dedicated to my wife, Becky, and my son, Kevin. Despite the sacrifices they have made so I could pursue this degree, they have never once expressed regret. They have encouraged and inspired me all along the way, and still come running when I walk in the door.

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LIST OF ABBREVIATIONS

| | |
|---------|---|
| ACMG | American College of Medical Genetics and Genomics |
| CSER | Clinical Sequencing Exploratory Research Consortium |
| CYP2C19 | The gene encoding the enzyme cytochrome P450 2C19 |
| EHR | Electronic Health Record |
| eMERGE | Electronic Medical Records and Genomics Network |
| GWAS | Genome-Wide Association Study |
| HFE | The gene encoding the human hemochromatosis protein |
| IOM | Institute of Medicine |
| IT | Information Technologies |
| NHGRI | National Human Genome Research Institute |
| NIH | National Institutes of Health |
| OR | Odds Ratio |
| PCHR | Personally Controlled Health Record |
| PREDICT | Pharmacogenomic Resource for Enhanced Decisions in Care & Treatment |
| SNP | Single Nucleotide Polymorphism |

PREFACE

In 1952, psychiatrist Leslie Osborn published a book entitled *Psychiatry and Medicine: An Introduction to Personalized Medicine* (Osborn 1952). In this text, Osborn developed the idea that physicians of all disciplines should “personalize” their medical care by attending more carefully to the unique circumstances of their individual patients. Drawing attention to the way psychiatric and psychological factors contribute to this uniqueness, Osborn argued for a more humane medical practice that would take patients’ individual stories more seriously.

More than six decades on, personalized medicine has become one of the most influential and controversial topics in contemporary medicine. In the last decade alone, over 15,000 articles in medical journals have referenced this term (2015d). Osborn might be surprised, however, to learn of the vision for medicine that now carries this name. In contemporary usage, *personalized medicine* refers to the hope that *omics*-based laboratory technologies, including whole genome sequencing, will be used to tailor medical care to the individual needs of patients. This vision eschews Osborn’s earlier hope that medical providers would take a more personal approach to medical care. In fact, the contemporary interpretation of personalized medicine tends to de-emphasize the role of healthcare providers altogether.

From a certain perspective, personalized medicine in the modern sense appears, paradoxically, to be *less* personal than the approach to medicine it proposes to disrupt. A central element of the contemporary vision for personalized medicine is the use of patient-centered information technologies like online patient portals to return results from genomic sequencing and other *omics*-based laboratory tests directly to patients without the intervention of a healthcare provider. While these results can be said to be “personal” in the sense that they reflect

the distinctive genetic variants of individual patients, the proposed mode of delivery would remove any “personal” touch. The explanatory materials provided with these results would be generated by algorithm, not by a medical provider known to the patient, and the responsibility for settling on a course of action would fall, at least to some extent, on the patient alone.

The modern use of the term “personalized medicine,” then, reflects an important tension. In an earlier time, *personalization* described the human effort taken to tailor a service or product to an individual’s unique needs (1989). This craftsmanship was perceived to generate products and services of particularly high quality. When Osborn applied this concept to medicine, she clearly intended to highlight the value of careful human effort in medical practice.

The modern usage of *personalization* retains part of this earlier connotation. “Personalized” products and services are still assumed to be superior to their “one-size-fits-all” counterparts. This word can now also be used, however, to describe customization applied through a computer algorithm. Wikipedia, reflecting contemporary interpretations of this term, limits the definition of personalization to the use of “technology to accommodate the differences between individuals” (2013a). Human effort is no longer required for a product or service to be “personalized.”

In some ways, it is apt that the personalized medicine movement has adopted a name that reflects this type of ambiguity. This movement is an important locus of debate that reflects larger questions about the future of medicine. Should sophisticated technologies like *omics*-based laboratory tests, open data networks, and predictive analytics play a larger role in medical practice? To what extent could these technologies replace the “personalization” that was formerly carried out by human providers? If computer algorithms can personalize laboratory interpretations and clinical recommendations in ways unattainable by the human mind, what

value do healthcare providers still add? Do healthcare providers merely bring a caring smile and a reassuring touch to medical care, or do they contribute something more substantive?

This dissertation is intended to address this tension at more than one level. On the surface, it is a dissertation about personalized medicine and its place in the future of healthcare. I will argue that imprudent applications of *omics*-based technologies could create harms that outweigh their benefits. If this vision is to bring about positive change in healthcare, it needs to account not only for scientific knowledge rooted in *omics*, but also more traditional forms of medical science that provide mechanistic and empirical bases for medical decisions. These types of scientific knowledge play an indispensable role in ensuring the prudence of a course of action settled upon in clinical decision-making. This movement therefore requires a more robust account of the way different types of scientific knowledge can be applied to the circumstances of individual patients.

At a more fundamental level, however, I am deeply concerned about the larger trends reflected in the personalized medicine movement. An online patient portal designed to return genomic results directly to patients is just one example of a health information technology that would eliminate healthcare providers as mediators between patients and complicated medical information. I find this problematic not because it threatens my job security, but because it is based on a serious misunderstanding of the type of expertise that healthcare providers contribute to clinical decision-making. In this dissertation, I will utilize personalized medicine as a case study to demonstrate that healthcare providers are not important just because they have received extensive education about complicated scientific concepts, but because they know how to negotiate different varieties of scientific knowledge and apply them to complicated medical

decisions. Once the role of healthcare providers is understood in this light, it will become clearer that we should approach patient-centered information technologies with caution.

As a dissertation in a program focused on “Ethics and Society,” therefore, this project is likely to seem somewhat unconventional. The vision for personalized medicine involves a wide range of ideas about how healthcare might be altered, and thus poses a number of challenges that might be examined from the perspective of moral philosophy or bioethics. In fact, over the past seven years I have had the opportunity to explore many of these issues as an active member of a community of scholars focused on elucidating the ethical, legal, and social implications of genomic science – the so-called “ELSI” community. In this dissertation, however, I am concerned not only with the specific technologies and practices proposed by the personalized medicine movement, but also with larger contemporary trends in medicine that transcend one specific vision.

For this reason, my critique is rooted in epistemology as much as it is moral philosophy. Building on the pragmatist perspective of Jeffrey Stout, the philosophy of science of Thomas Kuhn, and the practical philosophy of Alasdair MacIntyre and Hans Georg Gadamer, I aim to develop a hermeneutic account of clinical practical reasoning that demonstrates how healthcare providers are able to draw on a range of traditions when developing a clinical course of action. I believe such an account is a necessary prerequisite for the prudent integration of personalized medicine into clinical care. But more importantly, such an account of practical reasoning provides a compelling justification for retaining a central role for healthcare providers in decision-making related to health and wellness.

Paradoxically, perhaps, my examination of these larger issues will depend on a detailed account of personalized medicine in its particularity. Even though this dissertation is focused on

practices such as the return of genomic results through online patient portals that have been widely discussed in the medical literature, the motivations and assumptions that underlie these proposals tend to remain implicit. It is precisely for this reason that personalized medicine is such a useful case study. The extensive discourse on personalized medicine offers a unique opportunity to unpack the implicit assumptions about patients and providers that are driving larger trends in clinical care.

CHAPTER 1

PERSONALIZED MEDICINE AS VISION

At the ceremony to announce the completion of the Human Genome Project in June of 2000, President Clinton predicted that, “Genome science will have a real impact on all our lives — and even more, on the lives of our children. It will revolutionize the diagnosis, prevention, and treatment of most, if not all, human diseases” (2000a). At the same ceremony, Prime Minister Tony Blair made a similar assessment of this scientific achievement, declaring it to be a “revolution in medical science whose implications far surpass even the discovery of antibiotics” (2000b).

In the fifteen years that have passed since that ceremony, the hope that genome science could transform medical care has developed significantly. What was once a relatively vague hope that knowledge about the human genome could transform medicine, is now a mature vision of the specific opportunities that this science offers to improve human health. The defining feature of this vision is the idea that laboratory technologies like those used to complete the Human Genome Project could now be used to tailor medical care to the individual needs of patients. *Personalized medicine* is the name now given to this vision. This name derives from the idea that the unique features found in each patient's genome could be used to tailor medical care to each individual patient's genetic makeup.

Despite the hope expressed by President Clinton and Prime Minister Blair, the “reference genome” completed by the Human Genome Project has not yet led to a new “era” of personalized medicine. President Clinton warned as much when he admitted that the next generation, more than the current generation, would be the primary beneficiaries of this effort.

The Human Genome Project was intended to be the first step in an interdisciplinary scientific effort with the ultimate goal of improving human health.

This long, progressive path was recently demonstrated in compelling fashion by Eric Green, the current director of the National Human Genome Research Institute (NHGRI). In an article titled “Charting a course for genomic medicine: from base pairs to bedside,” he argued that the effort to improve health through genome science would continue until well after 2020 (Green and Guyer 2011). On this account, the initial stages would involve work to understand the structure and biology of genomes, as well as the genetic basis for disease. As this work bore fruit, it would become possible to develop new approaches to medical care, and ultimately to improve the overall effectiveness of healthcare (Green and Guyer 2011, 206).

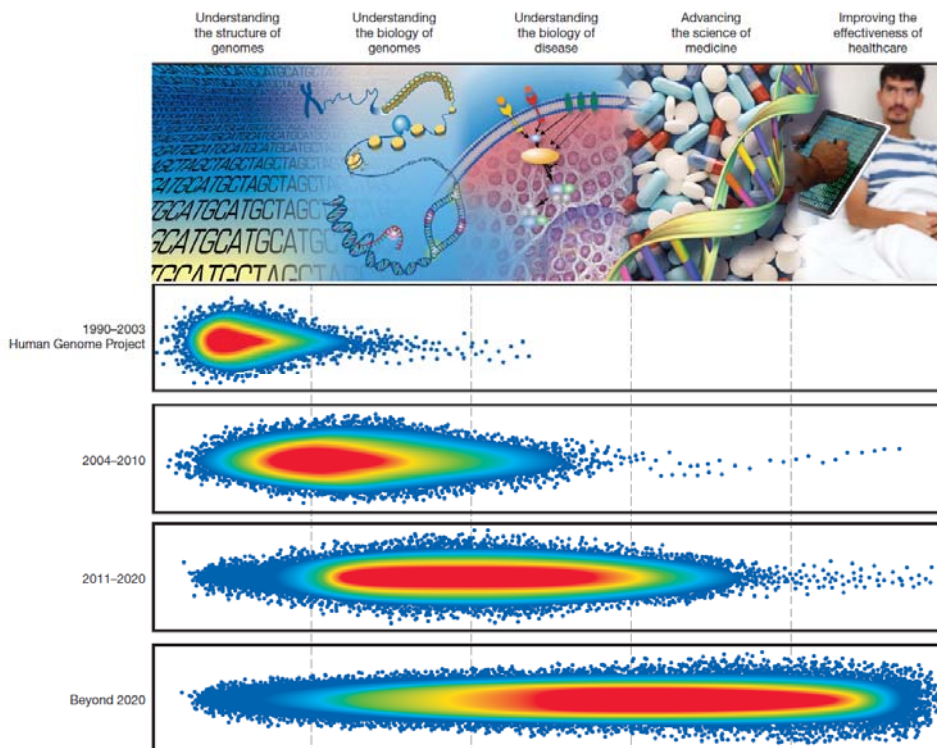


Figure 1: The anticipated progression “from base pairs to bedside” schematized as density plots (Green and Guyer 2011).

Consistent with this vision, recent work to bring about personalized medicine has involved the collaboration of scholars from across many fields. Scientists, clinicians,

informaticists, policy makers, ethicists, and social scientists have worked together in joint efforts like the Electronic Medical Records and Genomics (eMERGE) Network and the Clinical Sequencing Exploratory Research (CSER) Consortium. These groups, and many others in the U.S. and around the world, continue the work that was started in the Human Genome Project. Some continue to focus on the basic biology of the human genome, while others have begun to test real-world applications of genome science on a small scale.

This dissertation is intended to contribute, if only in a small way, to that ongoing effort. I believe that personalized medicine offers promising opportunities to improve human health and wellness. But there are many elements of contemporary medicine that are also important to this goal. The medicine of the future will need to involve a wide array of approaches, including those with high-tech and low-tech elements, as well as those involving both “science” and “art.” In order to find where personalized medicine will “fit” into this practice of the future, we will need to identify how patients, providers, and the healthcare system can best utilize the principles of personalized medicine to improve the effectiveness of healthcare.

As a primary care physician, I am especially interested in the role healthcare providers can play. My more fundamental aim, then, is to develop a robust account of medical practice as a whole. I will utilize this account to demonstrate how personalized medicine can be integrated with the other approaches to medical care that are already utilized widely. I will focus in particular on the way healthcare providers like physicians, nurse practitioners, and physician’s assistants draw on a number of different clinical resources when they work with patients to develop a personalized plan of care. Since the medicine of the future will not depend exclusively on whole genome sequences to guide clinical decisions, I believe it is crucial to develop an

account for how providers can utilize principles of personalized medicine alongside other factors that influence their decision-making.

Developing such an account will be a complex task. The vision for personalized medicine is not a well-defined program that comprehensively describes the medicine of the future. The scientists, clinicians, and entrepreneurs who work to make personalized medicine in reality are a diverse community. Within this community there are a range of ideas about what personalized medicine is, what contributions it might make to human health, and how best to work for its integration into routine healthcare.

It is most appropriate, then, to think of personalized medicine in its current form as both a vision and a movement. The vision for personalized medicine is comprised of a range of closely-related ideas about the future of medicine. The personalized medicine movement is a community of interested scholars who engage in discourse and debate about what this vision should be and how it may be brought into reality. Because the movement is dynamic, so too is the vision.

The ultimate aim of this dissertation is to augment the existing vision for personalized medicine by developing an account of the way it can be integrated into clinical care. My focus will be on the way healthcare providers make decisions - how they weigh a variety of factors and reasons in order to decide on a course of action. This could include the rationale that clinicians might use for deciding whether a particular laboratory test should be performed, for identifying results that might be relevant to a patient's health, or for deciding what to do about them.

Although the personalized medicine movement is actively exploring these types of clinical applications, it has not examined the underlying process of clinical decision-making in detail. Toward the end of this text I will have an opportunity to speculate about the reasons for this blind-spot. In order to develop an account of clinical decision-making that fits with the

vision for personalized medicine, however, we will first need to look for indirect evidence in the literature produced by participants in this movement. Within the debates and disagreements that have shaped the personalized medicine movement, we will find evidence for the rationale personalized medicine might present for justifying a clinical course of action. Taking these perspectives as a starting point, I will develop an account of clinical decision-making that is consistent with ongoing work in personalized medicine. As I have said, however, personalized medicine will not operate in a vacuum. For this reason, my analysis of clinical decision-making will necessarily involve an examination of existing perspectives that guide the way clinicians work with patients to decide on a clinical course of action. With this landscape clarified, we will then be able to develop a refined account of the vision for personalized medicine that could facilitate its incorporation in routine clinical care.

As a starting point, then, we will focus on the current vision for personalized medicine. As I have observed, the vision for personalized medicine is remarkably diverse and includes a range of ideas. A comprehensive account of the various perspectives on personalized medicine could probably comprise a whole book on its own. In the remainder of this chapter, I will focus rather narrowly on the clinical applications that are envisioned for personalized medicine.

This introductory discussion will center on three vignettes, a genre often used within the literature on personalized medicine. These vignettes will serve a number of purposes. First, they will help explain the clinical applications that are important to the vision for personalized medicine. Second, they will help communicate some of the excitement that often accompanies discussions about the potential for personalized medicine to transform healthcare. Third, and most importantly, they will provide an opportunity to draw out and define four key concepts that comprise the clinical vision for personalized medicine. These four concepts, all starting with the

letter “P,” were proposed by biologist Leroy Hood to be the key elements of the vision for personalized medicine. According to this account, *P4 medicine* is medical care that is predictive, personalized, preventive, and participatory (Hood and Friend 2011). Although few participants in the personalized medicine movement have adopted Hood’s proposed name for this vision, his account does capture a set of key ideas that are discussed broadly within this movement. These four concepts will recur throughout our exploration of personalized medicine, and will serve as the basis for my examination of clinical reasoning implicit in this movement.

Personalized and Predictive Medicine

Vignette 1: Choosing the Right Drug

At 83 years of age, Anneke started to experience chest and shoulder pain. Although she ignored it at first, attributing the pain to her age, she soon became more concerned. When she mentioned the pain to her cardiologist, Dr. Milne, he became concerned, too. Before she knew it, Anneke was undergoing a lab work-up as her cardiologist made arrangements for her to undergo a cardiac catheterization procedure. As a part of this work-up, Dr. Milne ordered a genetic test focused on a number of genes related to the way medications work. Given the stress of preparing to undergo a cardiac catheterization procedure, Anneke gave little thought to the test.

Once she awoke from the procedure, Anneke learned that her doctor had discovered a blockage in one of her coronary arteries. This blockage was restricting the flow of oxygen-rich blood to her heart muscle, and was likely the cause of her chest pain. Fortunately, Dr. Milne was able to place a tiny metallic stent in the vessel to open up the blockage. Anneke was spared a difficult coronary artery bypass procedure, and now had the chance to live for many more years free from further heart problems.

The only drawback, perhaps, was that having a stent created a need for Anneke to take a platelet-inhibiting medicine for the rest of her life. The medicine Dr. Milne usually used for this purpose was clopidogrel, a popular and relatively inexpensive medication. However, when he entered the hospital's electronic medical record to order the medication, he found that the results from the genetic test he had ordered before the catheterization procedure had become available. These results showed that both copies of the CYP2C19 gene Anneke had inherited from her parents had an uncommon alteration, or variant. This variation caused the enzyme made from this gene to be inactive in Anneke's body. Because of this, clopidogrel would not be converted to its active metabolite in her body. The message in the electronic medical record recommended to Dr. Milne that he could use the drug prasugrel instead. Prasugrel was newer and more expensive, but did not need to be activated by the body's enzymes. Following the recommendation of the electronic decision support tool, Dr. Milne prescribed the newer medication for Anneke. For her part, Anneke was very pleased to know that the medication her doctor chose for her would help prevent clots at the site of her stent.

Pharmacogenomics and Personalized Medicine

As this first vignette demonstrates, personalized medicine has, in some ways, already reached clinical practice. This is a fictionalized account of a real patient at Vanderbilt University Medical Center who underwent genomic testing through a clinical program named Pharmacogenomic Resource for Enhanced Decisions in Care & Treatment (PREDICT) (Whitney 2010). This program was instituted to explore whether genetic tests could be used to guide the selection and dosing of medications in routine clinical care settings.

The technology used to identify Anneke's variant in the CYP2C19 gene is known as a "SNP-chip" (pronounced *snip-chip*). A single nucleotide polymorphism (SNP) is a single site in

the human genome where the sequence of the genome is known to differ between persons. The SNP-chip technology used in Anneke's care was a laboratory testing platform that can identify variations in 184 SNPs across 34 genes. Since this technology can be used to simultaneously identify multiple variations across the genome, it is referred to as a *genomic* technology. The application of this technology to the selection and dosing of medications is referred to as *pharmacogenomics*. Similar applications of genetic technologies that only analyze one SNP or gene at a time are referred to as *pharmacogenetic* applications.

Many use “personalized medicine” as a synonym for “genomic medicine.” NHGRI, for example, defines personalized medicine as “an emerging practice of medicine that uses an individual’s genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease” (2013b). Other definitions broaden this slightly, but retain a focus on genomic information. For example, “Personalized medicine is a broad and rapidly advancing field of health care that is informed by each person’s unique clinical, genetic, genomic, and environmental information” (Ginsburg and Willard 2009).

This strong association between the vision for personalized medicine and genomics is reflected in the history of pharmacogenomics. The term “personalized medicine” was originally coined by investigators working on the use of genetic tests to guide pharmaceutical use. The original sense of this term referred not to a new way of practicing medicine, but to pharmaceuticals themselves. In the late 1990’s, for example, scientists and journalists wrote of “personalized *medicines*” (Langreth and Waldholz 1999, Marshall 1997). Other sources referred to “personalized therapy” (Mancinelli, Cronin, and Sadee 2000), “personal pills” (Stix 1998), and “personalized drug therapy” (Kalow 1999).

All of these sources evoked “personalization” in order to highlight that pharmacogenomics involves the use of genetic tests to “tailor” the selection of medications or medication doses for individual patients. It was in this sense that medical treatment was said to be *personalized*. It quickly became clear, however, that the same logic could be used to guide other dimensions of care. For example, genomic technologies might instead be used to guide the use of diagnostic tests, surgeries, or other medical interventions.

Not long after the term “personalized medicine” was coined, it came to be used to refer to these other clinical applications of genomic technologies, as well. By 2001, personalized medicine was already being spoken of as bringing a new “era” in medicine that would involve not only advances in pharmacogenomics, but also a “new generation of diagnostic, prognostic, and therapeutic modalities designed to improve patient care” (Subramanian et al. 2001). In the intervening years pharmacogenomics has remained an important part of personalized medicine, but the term “personalized medicine” is now used almost exclusively in this broader sense.

The vision for personalized medicine has also expanded to include non-genomic technologies that could be used to tailor medical treatment. In 1999, the clinical use of technologies that analyze gene expression, proteins, and small-molecule metabolites in large numbers had not received widespread attention. In the interim, however, these non-genomic technologies have become more widely available, and seem to provide a promising opportunity to personalize medical care. As a result, many now envision personalized medicine as an approach that could include the use of technologies that look at gene expression, proteins, or metabolites to tailor therapies and diagnostics.

This broader vision for personalized medicine is reflected in the definition proposed in a recent report from an Institute of Medicine (IOM) workshop. According to the participants at this

workshop, personalized medicine is “the use of information from genomes (from humans and other organisms) and their derivatives (RNA, proteins and metabolites) to guide medical decision-making” (Olson et al. 2012). This definition incorporates a range of technologies that support personalized medicine. For example, it suggests that the genomes of “other organisms” might be relevant to personalized medicine. This is a reference to the *microbiome* of patients. *Microbiome* refers to the collection of all microorganisms, particularly bacteria and yeast, that live in and on a human.

The suffix “-ome” and its adjectival form “-omic” imply that this field of study is focused on the full set of components that comprise a biological category. So while “microbiology” typically involves the study of a single organism in isolation, the study of the microbiome involves the study of the full set of microorganisms living in and on humans. Similarly, “genetics” implies a focus on individual genes, while “genomics” implies the study of the interaction of multiple genes, or even the entire set of genes in an organism (2011a). Proteomics is the study of “a set of all expressed proteins in a cell, tissue or organism at a certain point in time” (Pennington et al. 1997). Metabolomics is the study of “the quantitative complement of all of the low molecular weight molecules present in cells in a particular physiological or developmental state” (Goodacre 2005).

To rephrase the IOM definition, then, personalized medicine is the application of *omics*-based science and technologies to clinical practice. This definition captures the broad scope of the current vision for personalized medicine, and is the definition I will use in this dissertation. Since genomic technologies are the only *omic* technologies currently being used in clinical settings, however, I will primarily focus on examples that involve clinical uses of technologies like SNP-chips and next-generation sequencers. When relevant differences exist, I will explicitly

discuss the implications of genomic technologies that are distinct from the other *omic* technologies.

Predictive Medicine

Having now identified the scope of personalized medicine in terms of the technologies that it might involve, we should turn to ideas about the advantages these technologies might provide. We have already seen, for example, that the application of these technologies is expected to support the *personalization* of medical care. The vision for personalized medicine involves – and, indeed, is defined by – the idea that *omic* technologies might allow patients and providers to more precisely “tailor” the way they select and utilize diagnostic and therapeutic options. However, personalization is not the only benefit envisioned for personalized medicine.

Vignette 1 demonstrates another common idea about the opportunities offered by personalized medicine. We saw in this story that most patients who have had a coronary artery stent procedure are treated with clopidogrel. This anti-platelet medication is necessary because some patients who have had a stent placed go on to develop a clot at the site of their stent. However, clopidogrel does not prevent clots in all patients. Specifically, patients with a particular variant in the CYP2C19 gene are not able to metabolize clopidogrel into its active form. We could predict, then, that patients with this variant are more likely to develop a clot at the site of their stent while taking clopidogrel. Knowing that Anneke had the problematic variant in CYP2C19 allowed Dr. Milne (with the help of an EHR tool) to *predict* that Anneke was at risk for developing a clot. Prediction, in this case, made personalization possible.

In this dissertation we will explore a number of ways the vision for personalized medicine includes medical prediction, and in particular predictions about which patients are likely to develop conditions. As an example, earlier in her medical course Anneke’s doctor might

have used genomics information to predict that she was at an elevated risk for coronary artery disease. In this scenario, he might have responded to this prediction by treating her cholesterol levels more aggressively, or referring her to Dr. Milne earlier. Similarly, Dr. Milne might have used Anneke's genetic information to determine that she was unlikely to develop restenosis at the site of her stent, and thus avoided treating her with an anti-platelet medication altogether (Leon et al. 2010, Räber et al. 2011).

Anneke's story, then, reflects Hood's second P-word, *predictive*. This concept will prove central to our examination of personalized medicine. We will explore in Chapters 3 and 4 how the applications of *omics*-based, predictive laboratory results envisioned for personalized medicine suggest a type of clinical decision-making that is distinctive to this vision. We will work toward this examination in the sections to follow by exploring how clinical prediction informs the role of the remaining "P" words – preventive and participatory – in the overall vision for personalized medicine.

Personalized and Preventive Medicine

Vignette 2: Diagnosing an Unexpected Condition

Despite his stressful career as a criminal defense attorney, Dennis had always been healthy and rarely needed to see a doctor. He followed a healthy "pescetarian" diet and exercised regularly. Still, when it came time to celebrate his fortieth birthday, he took this milestone as a reminder to monitor his health more closely. Since he had never had a primary care physician, he asked friends for recommendations. Eventually he settled on Dr. Thompsen, an internist who had a reputation for being up-to-date on the latest innovations in medicine.

When the time for his check-up came, Dennis was surprised when Dr. Thompsen recommended that he have his genome sequenced in addition to regular screening labs. Curious what this test might show, he agreed.

One week later, he received a call from Dr. Thompsen. She explained that his genome sequence had shown he likely had hemochromatosis, a medical condition that could cause his body, and in particular his liver, to become overloaded with iron. Luckily, early discovery of the condition would allow him to avoid problems in the future. The bad effects of hemochromatosis could easily be avoided by having his blood (and the iron it contains) drawn on a regular basis. This would provide a way for his body to remove excess iron, and allow him to avoid most of the problems associated with his condition.

Preventive Medicine

Unlike the story of Anneke, the second vignette is not a true story. But it could be soon. Genetic testing focused on the HFE gene is already used to confirm the diagnosis of hemochromatosis in patients who have high iron levels or other indications of this condition. However, this test has not yet been used as a screening test for patients who have no symptoms of this condition.

The reasons that have kept this test from being used as a screening test can help us understand the vision for personalized medicine. One reason is that it would not be cost effective to use a genetic test to screen asymptomatic patients for this condition (Beutler 2000). Most experts agree that early identification could reduce the long-term complications of hemochromatosis, which might then reduce the long-term costs associated with treating these complications. However, using a dedicated genetic test to screen for hemochromatosis would create a number of direct and indirect costs. From an economic point of view, these costs would

not be justified by the benefit that could be provided to the relatively small number of patients who might ultimately develop hemochromatosis.

Another reason that has kept a hemochromatosis-specific genetic test from being used for population screening is that this practice would generate a large number of positive results in patients who would never develop hemochromatosis. This disease is caused by a mutation in the HFE gene; people with hemochromatosis are homozygotes for this mutated version of the gene. This means that both copies of this gene – the copy they inherited from their mother and the copy they inherited from their father – are abnormal. However, this does not mean that every patient with two copies of a mutated HFE gene will develop hemochromatosis. In fact, only 10% of men who are homozygous for the mutated HFE gene develop hemochromatosis. In women, it is even rarer. Fewer than 1% of women who are homozygous for this mutation develop the condition (Fullerton et al. 2012). In the jargon of medical genetics, hemochromatosis is a recessive condition with incomplete penetrance, meaning that a person must have two copies of a mutated gene in order to develop the condition (recessive), but not everyone with this genotype will develop it (incomplete penetrance).

Unfortunately, there is currently no effective way to predict which patients with a positive genetic test will develop hemochromatosis. In order for a screening program to be successful, it would need to be combined with long-term monitoring of every patient who carries two copies of the mutated HFE gene; some of these will later develop the condition, but most will not. Preventive measures like drawing blood to reduce iron in the body might provide benefit for those who would later develop the condition. But for the majority of patients whose genetic test result will turn out to be a false alarm, the cost and risk associated with such measures would be unwarranted.

Despite these challenges, members of the personalized medicine movement see genomic technologies as an opportunity to improve the cost-benefit calculus of genetic screening.

Although hemochromatosis is rare, there are many other medical conditions that can have serious effects on health and develop as a result of genetic variations. While individually none of these are common enough to justify population screening using a focused genetic test, genomic technologies like SNP-chips and next-generation sequencers can make it possible to identify many different conditions using just one test. Because of this, genome-scale technologies have the potential to provide benefit to more patients than a test for only one condition.

The vision for personalized medicine, then, includes the use of these technologies to modify preventive care. In the vignette, Dr. Thompsen had found nothing in the history and physical exam she performed on Dennis that caused her to be suspicious for hemochromatosis. She suggested that Dennis undergo whole genome sequencing simply to identify his risk for conditions that he had not yet developed or that were not yet clinically manifest. In Dennis' case, his whole genome sequence unexpectedly revealed that he was at risk for developing hemochromatosis. If Dr. Thompsen were to perform this same test in her other patients she might discover patients who are at elevated risk for developing type 2 diabetes (2013), neurodegenerative disorders (Roberts and Uhlmann 2013), or even obesity (Rief et al. 2007). According to one estimate, each person carries about 100 genetic risks that could be discovered through the use of this type of laboratory test (Ormond et al. 2010).

According to the cost-benefit model envisioned for personalized medicine, performing genome-scale testing on every patient would deliver numerous useful results for every patient, and with the cost of only a single laboratory test. For this reason, low-cost whole genome sequencing is an important dimension of the personalized medicine vision. The ultimate goal is

to make this technology available to all patients for less than \$1000, a goal that seems close at hand (Herper 2014, Hayden 2014).

As we saw in the example of hemochromatosis, however, the identification of risk is just a first step. The work-up that is required to discriminate between true and false positives can be significant. According to the vision for personalized medicine, however, genomics could still decrease the overall expense of preventive healthcare. While current preventive care can be focused using factors like patients' medical and family histories, most preventive measures are performed in a "one-size-fits-all" fashion. The hope for personalized medicine is that such measures can be used more parsimoniously, focusing time and resources on the conditions that each patient is at highest risk to develop (Ginsburg and Willard 2009). In this way, genomic technologies are envisioned as tools that could help preventive efforts to become more personalized.

There is also a place for the other *omics*-based technologies in the preventive vision for personalized medicine. While genomic technologies identify constitutional risks that are relatively stable over time, technologies that examine patients' proteome, metabolome, or microbiome could be used to identify short-term changes that portend the development of disease. As an example, mass spectrometry technologies can be used to identify the "signatures" of various proteins in the blood. Since these patterns can reveal pathology developing in the tissues or organs of the body, it is hoped that they will provide a non-invasive method for identifying changes that predict the development of conditions like ovarian cancer or prostate cancer (Weston and Hood 2004, Petricoin et al. 2002). In this vision, patients and providers could then use this information to intervene before a disease has actually developed.

In this way, personalized medicine not only incorporates the idea of preventive medicine; it prioritizes it. There is a strong thread in the literature on personalized medicine, for example, that focuses on health and wellness rather than disease and treatment (Flores et al. 2013, Patel et al. 2013). In the next vignette, we will see that this focus on prevention and maintenance of health are also an important part of the final P-word we will consider: participatory.

Personalized and Participatory Medicine

Vignette 3: Empowering patient action through online patient portals

Like all children born after 2017, Eugenia’s genome had been sequenced when she was a child. Although her pediatrician and her parents had referred to it a number of times during her childhood, she had never been very interested in the information about her health it might hold. When she turned 18, she had the information transferred to her Personally Controlled Health Record (PCHR) and thought nothing more of it for five years.

By the time she was 23, she had fallen into unhealthy habits. Working as a system administrator for a large bank’s information technology (IT) department, she spent most of her long work day in front of a computer monitor. Even outside of work she exercised little, and tended to eat convenience foods that could be prepared quickly and easily in the microwave. She smoked, and had recently developed Type 2 diabetes.

One day, however, Eugenia had an epiphany.¹ She had been shaken up when her father experienced a “mini-stroke” earlier in the year, and was reminded again of her risk for this condition when a health screening at work had revealed her blood pressure was quite elevated.

¹ The hope that genetic information could bring about “mini-epiphanies” is drawn from (Christensen and Green 2013)

Remembering that her whole genome sequence was available online through her PCHR, she logged on and navigated to the summary of her risk for stroke. Based on a panel of twenty relevant genes, Eugenia's risk for having a stroke before age 65 was estimated to be 10%. Shocked by this estimate, she immediately followed the hyperlinks provided in her PCHR to resources on lowering her risk for having a stroke. Empowered by this information, she made a number of changes to her eating habits and began to exercise regularly. Taking control of her health, she felt confident she could prevent herself from suffering a stroke.

Participatory Medicine

Although the application of personalized medicine reflected in Eugenia's story is futuristic, the vision it presents for the active role of the patient is a “hot topic” in the present. In fact, it may seem odd in some ways to speak of participatory medicine as if it is merely one dimension of personalized medicine. In truth, an emphasis on the potential for patients to improve their health and prevent illness has become influential throughout healthcare in recent years.

Beyond the vision for personalized medicine, many other accounts of needed reforms in medicine emphasize an active role for patients. For example, there is an active community of scholars who have argued that many laudable goals, including improved adherence with treatment regimens for chronic disease, can best be achieved by inviting patients to take a more active role in exploring and selecting management strategies. This account of shared decision-making emphasizes that by encouraging the participation of patients in these types of decisions, patients are more likely to feel invested in the treatment approach selected (Lipstein, Dodds, and Britto 2014).

Similar ideas can be observed in discourses on the potential for information technologies to improve health. One vision for the future of medicine referred to as *healthcare 2.0* emphasizes the potential for technologies like PCHR or online patient portals to improve patient outcomes (Randeree 2009). In this vision, technologies that allow patients to access their own health information have an effect on patients that is similar to shared-decision making. When patients have the ability to monitor their own health information and perform research on their health problems, they begin to feel that they have the power to improve their health. Once they are *empowered* in this way, they begin to take responsibility for their health by, for example, making positive health behavior changes (Ball, Smith, and Bakalar 2007).

By examining these ideas contemporary with the personalized medicine movement, we can better understand the inclusion of “participatory” among the 4Ps of personalized medicine. Clearly, personalized medicine and healthcare 2.0 share very similar understandings of patient participation. As Eugenia’s story demonstrates, the vision for personalized medicine involves not only improvements in health brought about within the healthcare delivery system, but also those delivered directly to patients without the involvement of a healthcare provider. Both personalized medicine and healthcare 2.0 project that if patients are given online access to their health information, they will be able to find ways to improve their health outcomes on their own.

In contrast, the vision for shared decision-making interprets patient participation in the context of a provider-patient relationship. Given the emphasis on an active role for patients, it certainly rejects a paternalistic model in which healthcare decisions are dictated by providers. However, it also rejects what Cathy Charles calls the “informed model.” In this model, physicians merely inform patients of the medically reasonable options and leave patients to make decisions on their own (Charles, Gafni, and Whelan 1997). The shared decision-making model

emphasizes an interactive process through which patients and providers together decide on a course of action. This interpretation of patient participation is found in the vision for personalized medicine, as well. Shared decision-making has been proposed, for example, as a useful way to help patients identify their preferences about the types of genomic results they would like to receive (Berg, Khoury, and Evans 2011).

What the vision for shared decision-making, healthcare 2.0, and personalized medicine all share is an understanding of the connection between patient participation and patient empowerment. None of these three visions are content to argue for patient participation on the basis of a normative rationale, such as the right of patients to make autonomous decisions. Rather, they all argue that participation – whether it be involvement in shared decision-making or independent access to health information – leads to a change in the way patients regard to their own health. Through participation patients come to believe that they have the ability to improve their health (self-efficacy) and they thus choose to assume responsibility for their health. This is what all three movements mean when they speak of “empowerment.”

This interpretation of patient participation, and its link to patient empowerment, is of particular importance to this project. As I discussed briefly at the beginning of this chapter, my aim is to develop an account of healthcare decision-making in the context of medical practice that incorporates personalized medicine. We have seen in these vignettes, however, that the vision for personalized medicine incorporates at least two approaches to healthcare decision-making. The first is a shared decision-making model in which providers and patient use *omics*-based laboratory results to decide on a plan together. How can these decisions incorporate personalized medicine along with patient preferences and other frameworks for thinking about medical information, including evidence-based medicine? The second model is one in which

patients interact with health information without the involvement of a healthcare provider. How is decision-making in this context different from decisions that involve healthcare providers? Are recommendations delivered through online patient portals adequate? In order to answer these questions, we will first need to develop a thorough account of the way medical decision-making is conceived within the vision of personalized medicine. In Chapter 2 we take the initial steps toward developing such an account.

CHAPTER 2

PERSONALIZED MEDICINE AS MOVEMENT

The term *personalization* seems to imply a method for selecting a specific plan tailored to the circumstances and unique laboratory findings of individual patients. It seems odd, therefore, that the personalized medicine movement has not proposed a detailed account for the way medical care should be personalized in individual circumstances. In fact, an effort to develop such an account has not even received significant attention within the personalized medicine movement.

The reasons that underlie this dissonance are complex, and elucidating these reasons through an examination of the personalized medicine movement will be a major task for this project. We should start in this chapter, however, by simply considering the possibility that personalized medicine has not addressed this issue because it depends on existing accounts of clinical decision-making that are already influential within medicine. It is possible, for example, that the vision for personalized medicine is constructed around the rather detailed method for clinical decision-making that has developed in recent decades under the rubric of *evidence-based medicine*.

Evidence-based medicine is based on the idea that all decisions (that is, which investigations to perform, which diagnoses to give, which treatments to choose) should be guided by empirical research with human subjects. This research typically involves studying the statistical likelihood that a given intervention will lead to the desired outcomes in a large group of patients. Evidence-based medicine prescribes a method that physicians can use to examine this empirical evidence when deciding, for example, whether an antibiotic should be used in the

treatment of a particular child with an ear infection. Although the ideas behind this approach can be traced to the 19th century and beyond (Matthews 1995, 16), the method for making “evidence-based” clinical decisions has been formalized primarily in the past 20 years (Guyatt et al. 1992, 2420).

There is substantial evidence that many in the personalized medicine movement would accept the methods of evidence-based medicine for making personalized clinical decisions. For example, one account of personalized medicine proposes that the name “stratified medicine” should be used instead (Trusheim, Berndt, and Douglas 2007, 287). Rather than suggesting that clinical decisions should be made based on the factors that are unique to individuals, this account proposes that such decisions should be based on groups of patients that have been “stratified” into smaller groups that share a set of characteristics. This is evidence-based medicine, but based on comparing individual patients with small, homogenous sub-groups rather than the full study population from clinical trials. For example, the stratified medicine conception of medical decision-making would involve comparative effectiveness trials within groups of patients with the same set of genetic variants. “[I]n stratified medicine,” according to one account, “a patient can be found to be similar to a cohort that has historically exhibited a differential therapeutic response using a biomarker² that has been correlated to that differential response” (Trusheim, Berndt, and Douglas 2007, 287).

In addition to evidence-based medicine, clinical decision-making in the personalized medicine movement is sometimes understood in the framework of *experimental medicine*. In this approach, healthcare providers make clinical decisions using their understanding of the

² A biomarker is any substance that can be detected in a biosample such as blood or urine that can be useful for clinical care. Biomarkers in this context are typically genomic, epigenetic, or proteomic in nature (Langanke et al. 2011).

biochemical and physiological mechanisms of the body. This understanding is derived, as the name implies, from controlled laboratory experiments, often using non-human animals. Since clinicians typically utilize this scientific knowledge in the form of theories about how the body operates, it is sometimes called *theoretical medicine*.

Again, certain elements of the vision for personalized medicine seem to depend on this approach to clinical decision-making. As we will see in the next chapter, many view *omics*-based research such as Genome-Wide Association Studies (GWAS) merely as a useful source for new hypotheses about the way the body functions and diseases develop. From this perspective, clinical decisions would only be based on *omics* research in an indirect way. The proximal basis for clinical decisions would be the biological mechanisms that were elucidated through laboratory experiments based on insights from *omics*-based research.

My analysis of clinical decision-making in personalized medicine is based, however, on the observation that this movement involves a diverse set of perspectives on clinical decision-making. Some of these perspectives are based on evidence-based medicine and experimental medicine, but some fit into neither of these frameworks. In fact, I will argue that the personalized medicine movement is currently in the process of developing its own distinctive framework for clinical decisions. This novel framework is emerging within a discourse on the vision for personalized medicine, a discourse that involves negotiation around the nature of clinical decision-making.

Before we can uncover the distinctive framework for clinical decision-making that is emerging in the personalized medicine movement, and the process of development and negotiation that is taking place around it, we must first develop a better understanding of what we mean when we speak of a framework – or what I will later call a *tradition* – of clinical

decision-making. That science-based clinical decision-making typically falls under either the evidence-based medicine or experimental medicine framework is well-recognized in medical practice. But this casual way of speaking about different approaches to clinical decision-making is too imprecise for our purposes. We want to identify those perspectives on clinical decision-making that are distinctive to personalized medicine, how those perspectives conflict with evidence-based medicine and experimental medicine, and ultimately to identify solutions that will make it possible for personalized medicine to be successfully integrated into the practice of healthcare providers. In order to attain these goals, we will need to develop a substantive account of how a tradition of clinical decision-making develops, how it is utilized by clinicians, and why it matters which framework of clinical decision-making a clinician uses.

Developing such an account is the focus of this chapter. In the next section, we will begin this task by examining how paradigms of scientific research differ from one another. This examination will serve as a useful starting point for understanding the traditions of clinical decision-making that utilize this research.

Scientific Paradigms and Paradigm Shifts

We are on the leading edge of a true revolution in medicine, one that promises to transform the traditional “one size fits all” approach into a much more powerful strategy that considers each individual as unique and as having special characteristics that should guide an approach to staying healthy... If you are interested in living life to the fullest, it is time to harness your double helix for health and learn what this paradigm shift is all about (Collins 2010, xxiv-xxv).

NIH Director Francis Collins is not alone in his interpretation of the personalized medicine movement as a “paradigm shift” (Coughlin 2015, Bowdin et al. 2014, Deisboeck 2009). This claim is intended, of course, to signal that personalized medicine is fundamentally different from conventional medicine. Collins seems to indicate in this quote that personalized

medicine represents a paradigm shift because it offers individualized care rather than so-called “one-size-fits-all” care.

What is not so clear, however, is precisely which differences Collins and others have in mind when they speak of personalized medicine as a paradigm shift. It is likely that these commentators have evoked the image of a paradigm shift primarily as a rhetorical device to express their excitement for the potential this approach offers (Tutton 2012). In this way, the claim that personalized medicine represents a paradigm shift might be taken as similar to the claim that personalized medicine will bring about a new “era” or “age” of medicine (Khoury 2010, Hood and Flores 2012). It is intended “not only describe a future state but to bring it into being” (Tutton 2012). In other words, these terms are part of a larger effort to present the potential for this tradition in a way that will be convincing to others who might support and invest in bringing it about.

Despite the rhetorical register of these claims, it seems that the personalized medicine movement does, in some ways, represent a paradigm shift. In order to see how this is so, we should examine the philosophical basis for this term. The idea that scientific progress proceeds through a series of paradigm shifts was introduced in 1962 by physicist-turned-philosopher Thomas Kuhn (Kuhn 2012). Kuhn argued that scientific fields are marked by periods of stability interrupted by revolutions – paradigm shifts – that change the way scientists think about their subject and formulate their scientific investigations. During periods of stability, Kuhn argued, scientists do not call the basic assumptions of their field into question. Rather, they conduct what Kuhn called “normal science,” the work of refining or clarifying specific scientific questions of interest within the field.

A paradigm, according to Kuhn, is the framework of rules, assumptions, and interests that defines a scientific field during periods of stability. During this stage a single paradigm defines for a field which scientific questions are worth asking and which types of scientific evidence will be viewed as convincing. Typically, however, the rules or assumptions that comprise a scientific paradigm are not made explicit. They are simply the foundational understandings that scientists appropriate as a function of their being socialized into a specific field of study (Kuhn 2012).

Kuhn observed, however, that paradigms inevitably fall into crisis. Typically, “normal science” simply proceeds with no awareness that the prevailing paradigm does not adequately explain all of the relevant phenomenon. At some point, though, one or more participants in a paradigm will begin to recognize that their field has failed to address previously unrecognized problems. Kuhn provides numerous examples of this type of crisis from the history of science. Perhaps the most well-known of these is the shift that took place when physicists like Albert Einstein began to realize that Newton’s model of mechanics, despite their status as scientific “laws,” did not adequately explain many of the related phenomenon that had been observed over a long period of time. A paradigm shift is the transition that happens when such problems ultimately cause scientists to abandon their old assumptions in favor of a new set of assumptions that seem to address the crisis.

It is useful to think of personalized medicine in these terms. If personalized medicine represents a shift in the assumptions and interests of scientific research related to medicine, then this provides a partial explanation for the way this vision might also change clinical decision-making. This is because Kuhn’s account of scientific paradigms provides us with a way of thinking about the differences among different scientific frameworks and the relevance of these

difference to clinical practice. In order to see why this account is so helpful, let us briefly consider why Kuhn's account was, and in many ways still is, so controversial.

The Cartesian Either/Or

In conventional accounts of scientific progress, the scientific method is seen as an approach that allows for scientific knowledge to be built incrementally. Scientists develop scientific theories, which they are then able to formulate into specific hypotheses that can be tested using experiments. When the findings from a study are consistent with the hypothesis it was designed to test, then confidence in the underlying scientific theory is strengthened. Sometimes, however, the findings from a study prove that a hypothesis cannot be true. As a result, the theory must be revised or discarded altogether. This approach creates a way for scientists to use empirical observations to move ever closer to objective knowledge about the natural world.

When Thomas Kuhn trained as a theoretical physicist in the 1940s, this account of scientific objectivity was just as familiar as it is today. Kuhn reports that his confidence in this account was undermined when he was later involved in teaching a course on the history of science. As he studied the way scientific theory had changed over time, he came to recognize that the historical record of scientific discovery did not fit this story about scientific progress and its ability to generate objective theories (Kuhn 2012, xxxix). Whereas the conventional account claimed that discordant experimental findings and observations provided definitive rationale for disproving scientific theories, he observed long periods of time when scientists continued to accept a prevailing theory despite its manifest failure to explain the available data. According to Kuhn, this occurred because these scientists necessarily viewed the data through the lens of their

scientific paradigm. This framework tended to frame how available data was viewed, and defined which findings could be interpreted as problematic.

Kuhn's account of scientific revolutions, in effect, demonstrates that empirical observations do not lead to objective knowledge as had been claimed. Rather, scientific knowledge is generated within a social and historical context that shapes its theories and perceptions of its findings. It is not surprising, then, that Kuhn was seen as accusing science of irrationality (MacIntyre 1977, 467). For his part, Kuhn denied that his account portrayed scientists as operating irrationally. He claimed only that he was proposing an understanding of rationality different from that normally accepted within science (MacIntyre 1977, 467).

More than fifty years have passed since Kuhn referenced a "different" account of rationality, and yet this claim still strikes us as confusing. After all, rationality is understood by most, scientists and lay persons alike, to be the one and only standard we have available to justify and evaluate claims. When we do not make rational claims to support our conclusions, we are said to be acting or thinking "irrationally." When we do support our conclusions using rational claims, we expect these claims to be convincing – undeniable, even – to all.

However, this understanding of rationality is rooted in a history of its own. The account of rationality as a universal standard emerged during the Enlightenment. Its most famous proponent was René Descartes, who introduced the idea that "[e]ither there is some support for our being, a fixed foundation for our knowledge, or we cannot escape the forces of darkness that envelop us with madness, with intellectual and moral chaos" (Bernstein 1988, 18). For Descartes, we must either obtain certainty through objective means, or we must accept a form of relativism where each person's knowledge is treated as private and incontestable. Philosopher

Richard Bernstein calls this the “Cartesian either/or”: either we have objective knowledge, or we are left with sheer relativism.

But Bernstein and Kuhn agree that this Enlightenment view represents a false dichotomy, one that is all too easy to accept as true because we live in a world so heavily influenced by this perspective. For Kuhn, scientific claims can be rational even if they are not objective. Objective claims are those that would look the same to all scientists in all times. Rational claims, on the other hand, are those based on justifications that others can understand and evaluate. A scientific paradigm cannot provide the basis for objective claims, but it can provide the context within which the rationality of claims can be evaluated. In short, Kuhn did not reject the rationality of science, he rejected the Cartesian either/or (Bernstein 1988, 55-57).

On this account, we can say that a scientific paradigm is comprised, at least in part, by a *rational framework*. A rational framework is the shared understanding to which scientists can refer when they want to give an account for their conclusions or actions, and by which other scientists may judge these claims. The rational framework of a scientific paradigm allows scientists to justify why the data they gathered was meaningful, why the analytical methods they utilized were appropriate, and why the conclusions they drew from their analysis were sound.

This analysis helps us begin to add substance to the claim that personalized medicine represents a paradigm shift in science-based medicine. The vision for personalized medicine is based on emerging research using *omics*-based technologies. These new types of research studies represent not only new fields of scientific inquiry, but new rational frameworks – new sets of assumptions and ideas about which scientific questions are worth asking and which types of scientific evidence are viewed as convincing.

At the same time, though, Kuhn's account provides only part of the foundation we require to understand clinical decision-making in the vision for personalized medicine and its place in medical practice. Kuhn's account does not explain *how* clinicians can utilize scientific knowledge to make medical decisions. His account of scientific paradigms focuses exclusively on the development of scientific knowledge, and provides little help for understanding the application of this knowledge. In order to address this need, we will turn in the next section to the work of Alasdair MacIntyre, a philosopher whose work has been heavily influenced by Thomas Kuhn. MacIntyre is not primarily interested in the work of scientific communities or the application of science to clinical decisions. As a moral philosopher, his life's work has centered on the way moral and ethical decisions are made within intellectual and religious communities. However, we will find that his account of moral traditions is extraordinarily helpful for understanding the "traditions" of science-based clinical decision-making that inform most contemporary medical practice.

MacIntyre's Traditions

The problems that motivated MacIntyre's seminal work *After Virtue* were similar, in some respects, to the problems that prompted Kuhn's work. In the same way that post-Enlightenment scientists were focused on attaining objective theories, moral philosophers were focused on attaining objectivity on issues of morality and ethics. Without an objective method for making moral decisions, they feared, there could be no universally agreed-upon standard to judge persons' actions. This desire for objectivity drove a number of different approaches to moral philosophy and moral theology. Some argued that the only absolutely binding moral rules were those based in religious doctrine, while others argued that only philosophical justification could guarantee objectivity. Some religious and philosophical traditions held that actions should

be judged on the basis of duties (deontological ethics) while others insisted that it was the outcomes that mattered most (consequentialist ethics).

Although the “Cartesian anxiety” had been the same in both science and moral thought (Bernstein 1988, 16), the outcomes had been quite different. Scientists tended not to be troubled by the issue of objectivity, since most accepted that the scientific method provided a way to attain objective knowledge. Moral philosophy, however, had provided no such reassurance. When MacIntyre examined the important moral and ethical debates of our time, he found they all shared one disturbing feature: it appeared that there was no way to resolve them. The various approaches to moral thought provided a variety of languages with which arguments could be provided, but there was no way to ensure that they would be accepted as convincing by others. As a result, many had simply concluded that when a person makes a moral or ethical claim, these statements simply represent the individual’s own arbitrary opinions or preferences (MacIntyre 2007, 6-55). The Enlightenment aim to attain objectivity in moral matters had, in MacIntyre’s view, failed utterly.

Given this set of problems in moral thought, it is interesting how similar MacIntyre’s solution was to Kuhn’s. MacIntyre argued that prior to the Enlightenment, people had lived in coherent communities with others who shared the same understanding on moral matters. Each of these communities was like an individual scientific paradigm. Within a community, a person could be confident that the justification she could provide for her actions would be accepted by others as convincing. In other words, these communities shared a rational framework within which moral issues could be judged.

After the Enlightenment, however, the rational frameworks of individual communities were no longer considered adequate. The expectation was that there would only be one rational

framework. This applied to moral thought just as it did to science. And just as in science, every effort to identify a universal rational framework had failed. This was felt more severely in moral philosophy, however, because there were no longer insular communities that shared an account of rationality.

MacIntyre proposed that in order to respond to this crisis in moral thought, we should accept that a universal rational framework for moral claims could not be achieved. If we were to give up this “Cartesian anxiety,” we could then come to understand moral thought in terms of the traditions that had once provided a coherent moral framework for individual communities. Although we could never attain the unanimity on moral issues that was attainable in the ancient Greek *polis*, we could at least understand ourselves as making moral decisions within a specific framework of moral thought. This would provide us with a coherent language for talking about moral issues, and a framework for judging the morality of our actions and providing an account to others.

Importantly, a tradition would also provide us with a meaningful framework for debating moral issues. MacIntyre understood a moral tradition as a living community within which participants would have enough shared understanding to engage in meaningful moral discussion. He defined a tradition as “an argument extended through time” (MacIntyre 1988, 12). This means that the tradition itself is defined by the internal discourse that takes place around moral issues. Participants in a tradition might be able to identify, for example, that according to their shared standards a certain dimension of their rational system no longer worked well for addressing the problems they faced. This could create “an argument extended through time” around finding solutions for this problem. When solutions were proposed, their shared rational

framework would provide a means to evaluate them. Through this process, notions of rationality would be “advanced, modified, abandoned, or replaced” (MacIntyre 1988, 350).

Although different traditions are likely to come to different conclusions on moral matters, MacIntyre does not emphasize these external debates. Although it is tempting to view different traditions as competitors, it is extraordinarily difficult, in MacIntyre’s view, to compare them with one another. Just as there is no universal standard for judging moral claims, there is no universal set of criteria for judging rational frameworks. The set of standards one would need to compare different traditions and settle on a “best” rational framework can only be found internal to the traditions themselves. MacIntyre calls this the problem of incommensurability, and proposes a solution that recapitulates Kuhn’s account: we must be content to evaluate whether our own tradition seems to address the problems that seem important from our point-of-view as an insider. If it does not, we must work from the point-of-view it provides to find solutions. MacIntyre does not raise hope, as Kuhn does, that a “shift” might allow for an entire tradition to be replaced with a new and innovative perspective.

MacIntyre also identifies a related challenge that prevents useful comparisons among traditions: untranslatability. MacIntyre argues that because we necessarily interpret moral claims and moral language from within our own moral tradition, we are forced to interpret the claims and statements of those outside our tradition using our own rational framework. Because of this, when a member of one tradition gives an account of her actions or uses moral language, those outside that tradition cannot avoid misunderstanding. It is only within a tradition that such claims make sense and can be understood as the speaker intended.

Traditions of Practical Reasoning

It is clear from this discussion of MacIntyre's thought that he is not primarily interested in medical decision-making. His abiding interest has been in the way we justify our actions, and the types of actions that interest him are typically of a kind that require moral or ethical justification. Because of this, it may seem odd that I have spent so much space examining MacIntyre's thought. After all, our primary concern in this work is the way that medical providers make clinical decisions.

If we look closer, however, we can see that clinical decisions are remarkably similar to moral decisions. Healthcare providers do not want their clinical decisions to be arbitrary. They want the course of action they ultimately take to have a rational justification. They want to be able to provide a substantive account, both to themselves and to others, for why that course of action is "good." Moral or ethical justifications can certainly be relevant for medical decisions, but more frequently the focus is on a rational framework rooted in science.

For MacIntyre, the framework for deciding on a course of action is similar regardless of the nature of the rational framework. He places his concern with moral and ethical justifications within a larger framework of *practical reasoning*. Practical reasoning is the process by which humans decide what "on particular occasions it is best for them to do" (MacIntyre 1999, 67). This involves a special kind of rational process – the process of "making" a decision – which involves applying relevant knowledge. Practical reasoning is closely related to what St. Thomas Aquinas calls *conscientia*. This is not the same as conscience, a faculty of the human mind that warns us when we have broken a moral rule. In St. Thomas' framework, *conscientia* involves the judgments we make in particular situations; it is "the application of knowledge to activity" (Aquinas 1473, I-II, question 19).

It is possible, then, to expand MacIntyre's account of moral traditions so that we can instead think of them as traditions of practical reasoning. At the core of each tradition of practical reasoning is a rational system within which individuals make decisions in particular circumstances. Closely linked with this rational system is a body of knowledge that can be applied to decisions, and a language that allows one to provide an account of the reasons and knowledge that were utilized in making a decision.

We can think of a whole host of domains within which traditions of practical reasoning are important. In fact, virtually every human practice involves at least one such tradition, and many involve multiple traditions that compete with one another. Consider, for example, the profession of teaching. Practicing teachers can choose from a number of frameworks in thinking about how to approach a particular class session or an individual student. The Montessori and Waldorf traditions, for example, each provide a coherent framework for such decisions. When one of these models is adopted by individual teachers or schools, they tend to inform every decision that teachers make.

We can think of many other examples as well. Many parents adopt a specific model for deciding how to approach their child, including the "attachment parenting" or "slow parenting" models. Painters, too, tend to adopt a specific framework for reasoning about how they will apply paint to a canvas in order to create a specific work of art.

As we have seen, the practice of medicine has its own traditions of practical reasoning. In fact, medical practice has been a key case study for practical reasoning extending as far back as Aristotle (Gadamer 1996, 31). And just as in parenting and painting, medical practitioners have a range of traditions of practical reasoning from which to choose. The four humors, for example, once formed the basis for a tradition of practical reasoning that had its own rational system and

body of knowledge. Physicians utilized this tradition from the time of the ancient Greeks until into the 18th and 19th centuries (Nutton 1993).

In the introduction to this chapter I introduced two more current traditions of practical reasoning in medicine. Both of these – evidence-based medicine and experimental medicine – are widely utilized by healthcare providers in their efforts to decide on a course of action in the care of individual patients. Both involve a rational framework that allow providers to judge which course of action would be best, and both provide a language for giving an account of this judgment.

For this discussion, it is also important to observe that we can understand both traditions by combining Kuhn’s account of scientific paradigms with MacIntyre’s account of practical reasoning. Experimental medicine, for example, directs providers to make medical decisions based on scientific knowledge generated in the laboratory in the fields of biochemistry, biophysics, and microbiology. These fields focus on elucidating causal mechanisms that influence health and disease, and experimental medicine focuses on utilizing this understanding in clinical decisions.

We can think of experimental medicine, then, as a tradition of practical reasoning that is closely linked with a number of closely-related scientific paradigms. Just as these paradigms have their own historical and social context, experimental medicine has developed over time as an “argument extended through time.” Its roots can be traced to the work of Claude Bernard, a French physiologist of the 19th century. Bernard championed the application of vivisection and laboratory experiments to clinical care. Although Bernard was a student of Francois Magendie, the two disagreed about how experimental results should be applied to medicine. Magendie emphasized the utility of biological facts derived from experiments, while Bernard came to

believe that experiments were useful to medical practice because they could be used to develop theories about the mechanisms through which the body works (Conti 2001). It was through this and the debates that followed that this tradition developed. Now this and a great many other issues have been settled and have become the commitments shared by the adherents of this tradition. As we shall see later in our discussion on the tradition of personalized medicine, the commitments that come to be seen as important within a tradition can be influential in determining the course of a tradition

The history of evidence-based medicine also demonstrates the dynamics of a tradition of practical reasoning. At the same time that Bernard was making the case for the application of experimental science to medical practice, another French physician, Pierre Louis, introduced what he called *Médecine d'Observation*. Louis advocated for counting the number of times a particular intervention led to a particular outcome (Vandenbroucke 1996). This tradition, like experimental medicine, has been shaped in the intervening years by debates through which its rational framework has been refined. Now called evidence-based medicine, it is the dominant approach to practical reasoning taught in medical schools throughout the world, and is utilized widely by practicing physicians.

Evidence-based medicine is linked with its own set of scientific paradigms. The research that informs this approach to practical reasoning is performed in clinics rather than laboratories. Scientists perform studies like comparative effectiveness trials in order to observe which therapies more frequently bring about the clinical outcomes desired.

From this we can begin to see a two-way connection that links scientific paradigms in medical research with traditions of practical reasoning in medicine. Laboratory scientists in the tradition of Claude Bernard work on scientific questions with the explicit intention of developing

theories that can be applied to clinical practice. This work is then evaluated within the community of scientists on the basis of whether it did, in fact, prove useful to the practical reasoning of providers. The rational framework of the scientific paradigm is informed by clinical practice.

This connection may even inform which scientific studies are performed. When providers find they lack the knowledge they need to make effective decisions in specific circumstances, they are likely to feed this need back to scientists as a clinical problem that needs a scientific response. In fact, it is common for physician-scientists to report that their laboratory research is driven by their experiences with individual patients.

We can see a similar relationship between evidence-based medicine and clinical research. Comparative effectiveness trials are explicitly designed to compare the utility of two or more therapies, and are conducted to address real-world challenges faced by clinicians. A “good” result within this paradigm is therefore one that can be used by clinicians in their practical reasoning about the care of specific patients.

It is worth noting, in addition, that both traditions are shaped by values and commitments that have developed within the tradition and are influenced by historical and social contexts. Recall, for example, that when Pierre Louis first introduced the idea of *Médecine d’Observation*, he simply counted the number of times a particular intervention (like bloodletting) results in a particular outcome (like survival). In the contemporary version of this movement, this type of measure is considered inadequate. Now a controlled trial is considered the ideal method for evaluating the effectiveness of a therapy. In other words, the standards that are used to evaluate the usefulness of a study have changed over time. This change has resulted

from debates inside the tradition, but have also been heavily influenced by changes in the cultures of science and statistical analysis.

Paradigms and Traditions in Personalized Medicine

In summary, the rational framework, body of knowledge, and language that comprise a tradition of practical reasoning are closely linked with similar elements in one or more related scientific paradigms. Precisely how scientific findings are utilized by a tradition of practical reasoning is influenced by a number of factors, including the commitments or values that come to be accepted through the discourse that creates a tradition. These connections among scientific paradigms, traditions of practical reasoning, and commitments provide us an avenue for developing a more detailed picture of practical reasoning in the vision for personalized medicine. In the two chapters that follow, I will examine some of the scientific paradigms and commitments associated with the personalized medicine movement in order to develop such a picture.

In order to put that picture into the larger context of current medical practice, it will first be helpful to make a few additional observations about the evidence-based medicine and experimental medicine traditions. We have already seen that both of these traditions involve rational frameworks that are explicitly scientific. That is to say, the justifications that a provider uses in deciding on a course of action are framed in scientific terms. Non-scientific issues such as the preferences or social context of the patient are considered in the overall process of practical reasoning, but the rational framework used for deciding on a course of action is framed in the language of science.

Even though we have not yet developed a detailed picture of practical reasoning in the vision for personalized medicine, it already clear that this emerging tradition will also be framed

in scientific terms. In the next chapter we will examine two scientific paradigms that will be helpful in our examination of practical reasoning in the vision for personalized medicine. Although we will be able to see from our examination of these paradigms that practical reasoning in personalized medicine is likely to look quite different from that envisioned by the evidence-based medicine and experimental medicine traditions, these three accounts are at least similar in that they are framed in explicitly scientific terms.

Closely related to their scientific foundation, the evidence-based medicine and experimental medicine traditions both propose a methodical approach to practical reasoning. In the case of the experimental medicine tradition, practical reasoning is methodical in that it involves reasoning on the basis of mechanistic cause and effect. Generally speaking, the scientific theories generated through scientific research provide clinicians with the knowledge they need to predict in mechanistic terms how the body will respond to new stimuli. The method of practical reasoning in experimental medicine, then, involves making mechanistic predictions about how the body will respond to the available interventions, and proposing those interventions that are expected to set off a chain of physiological events that lead to the intended outcome. In some cases the theories utilized for this reasoning are quantitative, and thus inform mechanistic reasoning in a very detailed way. In other cases the theories provide more qualitative descriptions of the way the body works. In both cases, however, mechanistic cause and effect provides a justification for the course of action selected.

The methodical nature of evidence-based medicine is even more apparent. Numerous books and guidelines have been published instructing healthcare providers how to utilize evidence from clinical research in their clinical decision-making (Straus 2011). The Centre for Evidence-Based Medicine at the University of Oxford, for example, provides detailed online

instructions that providers can use to methodically make a clinical decision based on evidence from clinical research (2014a).

Since both of these approaches prescribe a method for making clinical decisions, “good medical practice” in both traditions hinges on the effort of healthcare providers. The assumption in both of these frameworks is that patients and providers want to attain health and wellness, but it is not manifest which course of action will be most likely to lead to that outcome. It is through the application of one of these methods that healthcare providers are able to identify the courses of action that are medically reasonable. This feature of current medical practice will prove especially important when we examine the personalized medicine vision for patient participation. We will consider what role provider practical reasoning is envisioned to play when patients are able to directly access their *omics*-based laboratory results through tools like online patient portals.

Implicit in this description of methodical practical reasoning is an orientation around attaining goals. Moral and ethical traditions are typically classified as either deontological or consequentialist. Within deontological approaches, practical reasoning is focused primarily on the application of rules or duties. Rules and duties can have many sources, depending on the tradition, but in general the process of practical reasoning is focused on identifying the rule or rules (duty or duties) that apply in a particular circumstance, and interpreting what specific actions they require of the practical reasoner. Consequentialist approaches do not depend primarily on rules or duties. Instead, practical reasoning is focused on identifying which actions are most likely to lead to the outcome desired.

In both the evidence-based medicine and the experimental medicine traditions, practical reasoning is consequentialist in orientation. There are no *a priori* rules about which courses of

action should be taken, and there are no courses of action that are inherently good. Rather, a course of action is determined by the healthcare provider to be suitable for a particular situation through a process of practical reasoning focused on determining whether it is likely to lead to a desired outcome. While the methods utilized in these two traditions are quite different, practical reasoning in both place consequences in a primary position.

There are a variety of ways to apply a consequentialist account of practical reasoning, so it will be helpful at this point to be even more precise in categorizing the evidence-based medicine and experimental medicine traditions. Both of these traditions are *teleological* in focus. They accept patient health and well-being as the primary purpose or end of medical practice, and orient all deliberation around this aim. Because of this, it is possible that any accepted standard of care or routine practice could be discarded in a particular circumstance if a provider utilized practical reasoning and determined that the routine course of action would not lead to the outcome desired.

As I examine the account of practical reasoning that is distinctive to personalized medicine in the chapters that follow, I will make a number observations that indicate that this emerging account of practical reasoning does not operate exclusively within a teleological framework. Like evidence-based medicine and experimental medicine, personalized medicine certainly desires to help patients attain and maintain health and wellness. In fact, the picture of “good” health accepted by personalized medicine is probably very similar to that of these two existing traditions of practical reasoning. Personalized medicine is different, however, because there are some practices that it does not subject to a teleological evaluation. Within this tradition, practices like the imperative to take action in response to genetic risk and open patient access to

laboratory results are viewed as inherently good; they would be recommended even if they would not lead to improved patient outcomes.

In this way, I will argue, practical reasoning within the personalized medicine tradition is not purely teleological; it does not select interventions exclusively because they lead to the *telos* of medicine: health and wellness. While this is certainly not inherently problematic, it is an important difference that separates personalized medicine and the existing traditions of science-based practical reasoning. Because of this, this difference is a challenge that we will need to address as we work to discover how personalized medicine can be integrated into clinical practice.

CHAPTER 3

SCIENTIFIC PARADIGMS IN PERSONALIZED MEDICINE

Before examining practical reasoning in the vision for personalized medicine, it will be helpful to first remind ourselves of the overall aims of this dissertation. My overall thesis is that the conception of clinical decision-making emerging within the personalized medicine movement poses a range of problems for the integration of personalized medicine into routine care. In the final chapters of this dissertation I will pose some solutions to these problems. My aim in identifying this set of problems and posing solutions is to ensure that the net effect of the integration of personalized medicine into clinical care is to improve patient health rather than to bring about unintended harms.

My aim in this chapter and the next is to highlight a few elements of the vision for personalized medicine that can provide insights about how practical reasoning would operate in this approach to medicine. In this chapter, I will examine two scientific paradigms that have proven influential in the personalized medicine movement. By examining the rational frameworks for these paradigms, and the claims that have been made about their utility in personalized medicine, I will begin to sketch a picture of practical reasoning for personalized medicine. I will start by examining the paradigm of genome-wide association studies. The foundational role this paradigm played in the development of the vision for personalized medicine makes it an important window into this movement.

Genome-Wide Association Studies

A genome-wide association study (GWAS) is a type of genetic study designed to identify statistically-significant associations between genetic variants and clinically important

characteristics like the risk for developing a disease or a having an adverse response to a therapy. In genetics, these clinical features are referred to a “phenotypes.” The goal of GWAS, then, is to identify genotype-phenotype associations.

In some respects, the paradigm of GWAS is similar to other types of genetic studies. Virtually all conventional genetic research is oriented toward identifying genotype-phenotype associations. The key difference between GWAS and conventional types of genetic studies is the type of hypothesis that can be tested. Family studies, for example, are based on the hypothesis that when a genetic condition is passed down within a family, the cause of that phenotype can be identified by looking for genetic variants that segregate with that disease, or, in other words, is only found in those family members who inherited the disease. This study design is manifestly based on the mechanistic understanding that heritable diseases are caused by genetic variants that are passed down within families.

Candidate gene studies are also based on mechanistic understandings of genetics. In these studies, scientists look for genetic variants that are more common in patients with a phenotype compared with a group of patients who do not have that phenotype. In many respects, then, this approach is similar to the GWAS paradigm. The key difference is that candidate gene studies are based on the hypothesis that genes linked with a phenotype through known or theorized biological mechanisms – “candidate genes” – are more likely to be those containing variants associated with that phenotype.

What is distinctive about the GWAS paradigm is that these studies are not based on a mechanism-based hypothesis. That is to say, scientists do not use existing theories of causation to focus on specific genes. Instead, they treat every available variant across the genome as if it is equally likely to be associated with the phenotype. They do this by repeating the same statistical

test thousands of times, interrogating whether each variant is found more frequently in those who have a phenotype in comparison with those who do not (McCarthy et al. 2008). Because of this design, GWAS are often described as being “agnostic;” they are designed to detect statistical associations between genotypes and phenotypes independent of any pre-existing assumptions about the mechanisms through which a phenotype develops (Bogardus 2009). The only assumption, perhaps, is that the etiology of the phenotype is at least partly genetic in nature.

Clinical Application of GWAS

There are two prevailing ideas within the personalized medicine movement for how GWAS results can be applied to medicine (MacArthur 2009). According to one perspective, GWAS are expected to be useful primarily because they serve as a starting point for understanding how diseases develop. When a new association between a genotype and a phenotype is discovered using this approach, this information might allow scientists to form new hypotheses about the biological pathways that contribute to the development of that disease. This can open up new opportunities for investigating disease mechanisms using more conventional laboratory research approaches. From this perspective, then, the findings from GWAS research are not directly relevant to patient care. They are simply a promising way to discover disease mechanisms that were not previously suspected, which might then be useful for experimental medicine approaches.

According to another perspective, however, GWAS studies *can* provide direct clinical utility even if they do not lead to new knowledge about disease mechanisms. This is because the findings from GWAS can be used to infer patients’ risk for developing the phenotypes being studied. GWAS are not just capable of demonstrating that patients with a particular genetic variant are at an increased risk for developing a phenotype. They can also be used to quantify

this risk in the form of an odds ratio (OR). An OR reflects the risk that a patient with a particular genetic variant will develop a disease in comparison with patients who do not have that genetic variant. This calculation can be made even if the mechanism linking the genotype and the phenotype is not known, and therefore reflects a probabilistic rather than mechanistic understanding of risk.

There are at least two common and closely-related applications envisioned for the probabilistic risk information generated through GWAS studies. Both are based on the idea that the genetic risk variants identified through GWAS studies can be detected in individual patients using genome-scale technologies like SNP-chips or whole genome sequencers. In the first application, the risk information generated through these technologies would be used by clinicians, and in particular primary care providers, to prioritize preventive health measures. The “prediction” that a patient is likely to develop a disease – that he or she is at risk – could allow physicians to alter their “one-size-fits-all” approach to preventive care. Patients predicted to be at risk for developing melanoma, for example, would receive more frequent or more careful skin exams. Patients identified to be at risk for arrhythmias might undergo periodic electrocardiography, a study not usually recommended for use in periodic health screening.

The second application would be quite similar, except that risk estimates would be delivered directly to patients through online patient portals. In this case, the recommendations would generally be developed ahead of time by experts in the field, and might not reflect the individualized opinion of a patient’s personal physician. The recommendations would typically advise patients to mitigate their risk by improving their health behaviors or monitoring elements of their health more carefully. This application was reflected in Chapter 1 in the vignette about Eugenia and her risk for developing a stroke.

Whether these risk estimates are utilized by providers or directly by patients, the common element is that both of these applications focus on probabilistic predictions based on genetic variation. In the next section, we will explore another prominent scientific paradigm – systems biology – which is also viewed as a promising approach for developing the predictive and preventive dimensions of personalized medicine.

Systems Biology

In one introduction to systems biology, this paradigm is described as

an approach that looks at biology as an information science, studies biological systems as a whole, and recognizes that biological information is captured, transmitted, modulated, and integrated by biological networks that pass this information to molecular machines for execution (Price et al. 2013, 131).

This definition makes it readily apparent that systems biology is heavily influenced by information technologies. This is certainly manifest in its first phrase, which describes systems biology as an “information science.” I am more interested, however, in the second half of the definition, which describes the functioning of biological systems using the language of computer science. In this framing, the sequence of DNA molecules is described as “biological information.” This information is conceived of passing through a number of biological processes that are framed as “networks.” Finally, this information is described as if it is a piece of computer code that is “executed” on a molecular “machine.”

In some ways, describing cellular biology using the language of computer science is a subtle move. There is no indication in this definition that indicates systems biology rejects the conventional understandings of biological mechanisms. The term “machine,” for example, is frequently used to describe a piece of computer hardware. But it is also the classic analogy used to describe the body in terms of mechanistic cause-and-effect. This type of machine operates

through a series of physical and/or chemical interactions between material objects – organs, tissues, cells, and biomolecules.

The framing of DNA as “information” is also ambiguous. The conventional framing used within molecular genetics does understand DNA molecules to contain information, but emphasizes that this information takes the material form of a polymer of nucleotides. This is subtly different from a framing that understands the sequence of nucleotides as a computer code that needs to be executed on a computer.³

The reframing of cellular processes using the language and models of computer science has the effect of eliding mechanistic cause and effect, not rejecting it. That is to say, the framing of DNA as computer software and cellular machinery as computer hardware depends on a mechanistic understanding of cellular processes. But at the same time it takes a “10,000 foot view” of the mechanisms, ignoring the specifics so that larger patterns can be discerned. Specifically, this paradigm views elements of cellular biology as nodes in a digital network. These nodes interact with one another and effect measurable change in one another. But the mechanisms by which these changes are effected is of no consequence; what matters are the patterns that these interactions create across the whole network.

What does this look like in practice? Systems biology focuses on quantifying as many dimensions of the human body as possible. This might include, for example, the full sequence of the human genome – the body’s “software” – as well as the concentrations of biomolecules like RNA, proteins, and metabolites – the “output” of the biological computer. Scientists then follow these measurements over time to observe how changes in one measurement effect changes in

³ I am indebted to Barry Barnes and John Dupré for drawing attention to this distinction between material and informational frames for genetics (Barnes and Dupré 2008).

other measurements. Put another way, systems biology involves the study of the way “perturbations” propagate across the biological network (Price et al. 2013).

The ultimate goal of this approach is to understand how this “biological computer” operates so that it can be reproduced *in silico*. We can think of this approach as being inspired by the work of Alan Turing (Westerhoff and Palsson 2004). The so-called Church-Turing Thesis states, effectively, that any function computable on one computer can be computed, or in other words simulated, on another computer (Karl 1997). Turing demonstrated this principle during World War II when he built a machine capable of simulating the encryption function of the German “Enigma Machine” (Hodges 2014, 226f). In the case of systems biology, the effort to frame molecular biology as a computer creates the potential that this “machine” could be simulated in a digital computer.

Systems medicine, then, is the clinical application of systems biology. It is based on the hope that an accurate and dependable simulation of human biology could predict how the body will respond to novel stimuli, such as how a treatment will affect the pathophysiology of an individual patient (Price et al. 2013, 131).

Of course, hypothesizing that human biology can be simulated is one thing; developing an accurate and dependable simulation is quite another. When Turing attempted to simulate the function of the Enigma Machine, he had the benefit of directly examining the working pieces of a device that had been stolen from the Germans. Although laboratory science has worked to “unlock” the mechanisms of human biology for decades, this approach is simply not as straightforward as opening the cover of a mechanical encryption device.

Systems biology instead depends on a more indirect method for developing computer algorithms that simulate “biological networks.” As I noted earlier, this process starts by

collecting large sets of data reflecting quantifiable characteristics of the body – the human genome, proteome, metabolome, etc. The next step is to develop algorithms or models that describe how these factors change in response to one another. Next, this algorithm is tested in another dataset to determine whether it successfully predicts the way “perturbations” are propagated through the network. If it is unsuccessful, the model is refined and tested iteratively “until the working models reflect the reality of the experimental data” (Price et al. 2013, 131).

Although the application of this approach to *omics*-based data is distinctive to the field of systems biology, this general approach to developing a predictive model reflects one of the most influential trends in contemporary science and culture: the *big data movement*. Big data refers to a digital-age take on quantitative analysis made possible by information technologies capable of collecting and storing extraordinarily large datasets, and analytical tools capable of using this data to iteratively build, test, and refine descriptive models intended for particular applications. When these models are intended to predict how a system will develop, change, or respond to new circumstances in the future, this approach is referred to as “predictive analytics.” We can think of systems biology, then, as the paradigm that seeks to apply the principles of big data and predictive analytics to *omics*-based laboratory data.

Prediction vs. Practical Reasoning

The GWAS and systems biology paradigms generate very different types of predictions about human health and disease. Predictions from GWAS research are based on genomic risk, and reflect the influence of one or a small number of genetic variants. Systems biology, on the other hand, generates rather sophisticated predictions based on a large set of biological data.

In the last chapter we saw that in both the evidence-based medicine and experimental medicine traditions, prediction provides a basis for practical reasoning. For evidence-based

medicine, predictions about how an individual patient will respond to interventions are based on comparisons of how effective these treatments were in controlled studies. Providers use the results of these studies to reason about how likely their own patients are to respond to these treatments. In experimental medicine, predictions are mechanistic. The provider reasons based on their understanding how the body functions in order to predict how the disease process will respond to different interventions.

For personalized medicine, however, predictions function somewhat differently. GWAS results provide predictions about how likely patients are to develop a disease or other phenotype based on genetic variants alone. The prediction that a patient is likely to develop a disease based on her genetic profile does not, in itself, help providers reason about how likely the patient is to respond to preventive or therapeutic interventions.⁴ It simply highlights that a patient is at an elevated risk to develop a disease. As we saw in the vignette about Dennis in Chapter 1, this type of predictive information is taken as a signal that the patient or provider should take some action to mitigate this risk.

In later chapters we will see that this link between prediction and action does not hinge on the efficacy of available interventions. In the vision for personalized medicine, this type of genetic prediction is treated as information that is “good to know;” it has inherent value. Similarly, having an opportunity to take action is seen as important, even if those actions are unlikely to improve outcomes. This perspective highlights an important distinction between the personalized medicine tradition and the evidence-based medicine tradition. For evidence-based medicine, the decision to receive a laboratory result or undertake a clinical intervention should

⁴ Some GWAS look for genetic variants that predict patients’ responses to medications or other interventions. This type of finding might support a different type of practical reasoning than the one developed here. Still, it is telling that despite its original focus on pharmacogenomics, personalized medicine has more recently highlighted the utility of genomic variants that predict disease rather than response to pharmaceuticals.

be based on the potential for outcomes to be improved. This creates a need to undertake practical reasoning before pursuing a lab result or starting an intervention. In this emerging picture of personalized medicine, practical reasoning does not play the same role, since both information and actions are viewed as valuable regardless of their impact on health-related outcomes.

The predictions provided by the systems biology paradigm are somewhat different, but still demonstrate a trend toward deemphasizing methodical, teleological practical reasoning. In a general sense, the predictions generated through systems biology should be applicable to clinical care in a way similar to experimental medicine: the algorithm developed to simulate the function of the body provides a framework for predicting how the body will respond to novel stimuli. Where these frameworks differ, however, is in the ability of providers to utilize the model to engage in practical reasoning. In the case of experimental medicine, practical reasoning is possible because the provider has knowledge about mechanistic causation and can use this knowledge to develop a rationale for choosing one therapeutic approach over another. The systems medicine model, however, is not mechanistic. In fact, the provider cannot even understand this model in terms of cause-and-effect. The predictions generated through systems biology algorithms emerge as if from a black box; they provide no causative rationale for the provider to select one intervention over another. Because of this, patient and providers are forced either to accept or reject these predictions with very little supportive information. There is no opportunity to engage in a methodical evaluation of the predictions provided by systems biology algorithms.

We have seen, then, that the GWAS and systems biology paradigms seem to produce scientific results that are incompatible with a methodical approach to practical reasoning. The GWAS paradigm seems only to produce predictive results that are “good to know,” and therefore

do not require a methodical approach to practical reasoning. The systems medicine paradigm, on the other hand, produces information that directly predicts response to therapeutic interventions, but without providing an opportunity to “look under the hood” in an attempt to determine whether the prediction is meaningful. In this way, systems biology-based predictions seem to eliminate the possibility for a critical and expert evaluation of recommended interventions. The patient is just as capable of interpreting its straightforward output as a trained provider. This observation may explain, at least in part, why the personalized medicine movement has tended to neglect the topic of provider practical reasoning.

This may also explain, at least in part, the enthusiasm within the personalized medicine movement for what I will call “the independent patient action model.” In this element of personalized medicine, information technologies are utilized to provide patients with direct access to laboratory reports and automated recommendations. Patients are then expected to take action to improve their health independent from the assistance of a healthcare provider. In Chapter 4, I will examine some of the commitments that have developed within the personalized medicine movement as a result of its social and historical context. Through this exploration we develop a fuller understanding of the enthusiasm within this movement for the independent patient action model. This understanding will, in turn, help us complete our picture of practical reasoning within the personalized medicine movement.

CHAPTER 4

FREEDOM OF CHOICE

In Chapter 2 I introduced the idea that science-based approaches to clinical practical reasoning are closely linked with one or more scientific paradigms. The most obvious connection is that each scientific paradigm generates a body of knowledge that clinicians then use for clinical decision-making. But this relationship involves a number of points of communication. These scientific paradigms are oriented explicitly toward generating data that has utility for clinical application, so studies are evaluated on this basis. Planned studies are evaluated on the basis of their potential to provide information that addresses current challenges in clinical decision-making, and past studies are evaluated on the basis of their actual utility in clinical settings.

Inherent in both Kuhn's account of paradigms and MacIntyre's account of traditions, however, is that developments in both of these areas reflect the social and historical contexts which shape them over time. This is part of what MacIntyre had in mind when he defined traditions as "arguments extended through time." Since a tradition is shaped by debates among its participants, it reflects the social process through which it is created. This means not only that a tradition is shaped by the internal dynamics of its participants, but also by the values and commitments its participants bring into those debates.

Kuhn acknowledges this phenomenon in his own way. As MacIntyre himself observes, Kuhn's analysis does not attend carefully to changes that occur within paradigms over time (MacIntyre 1977, 466). Kuhn does not, therefore, highlight mechanisms by which paradigms are influenced by outside commitments or values. It is clear from his analysis, however, that such

commitments are important to paradigm shifts. He observes, for example, that new paradigms are frequently proposed by scientists who are very young or very new to a field. It is these scientists, he observes, who are the least committed to an old paradigm and thus capable of thinking of new ways of approaching problems (Kuhn 2012, 90). The implication is that the inspiration for a new paradigm comes from “outside.” The new scientist is shaped by historical and social factors, and these experiences allow him or her to propose new ideas.

I am interested at this point, then, in the non-scientific values and commitments that have shaped the personalized medicine movement, including its understanding of provider practical reasoning. In the first half of this chapter, I will explore how personalized medicine is being shaped by its roots in the clinical practices of medical geneticists and genetic counselors. Even though the personalized medicine movement extends far beyond traditional medical genetics clinics, the professional values of these professionals continue to be an important source of inspiration for this movement. In the second half of this chapter, I will turn to an examination of the values of the digital age. Like the professional values of medical geneticists and genetic counselors, the cultural values of the digital age have played an important part in the development of the vision for personalized medicine, including its understanding of provider practical reasoning.

Clinical Genetics and the Freedom of Choice

Throughout the 1970s, sociologist Charles Bosk observed the counseling sessions that physicians with expertise in genetics provided for patients seeking help with genetic testing. In these sessions, Bosk observed providers as they helped patients with such issues as deciding whether to obtain genetic testing and deciding how to apply genetic test results to their individual circumstances. When discussing these issues, Bosk found, the counselors focused primarily on

their role as effective communicators of scientific information. While they did demonstrate a willingness to discuss the medical options available to families, including controversial options like therapeutic abortion, they shied away from recommending a particular course of action. Instead, they treated such decisions as the private business of families, and explicitly avoided advising families on the best course of action. As the director of this clinic put it to Bosk, “Our job here is not to convince parents to do one thing or another. We provide information” (Bosk 1992, 123).

At about the same time that Bosk was performing his groundbreaking ethnography, genetic counselors had started to develop a professional identity separate from medical geneticists (Heimler 1997). This identity is rooted in person-centered therapy, the counseling approach developed by psychologist Carl Rogers, which is still regarded as the professional norm within this field (Mahowald, Verp, and Anderson 1998). In this approach, counseling focuses on helping clients with their development toward self-understanding and self-efficacy. In order to attain this goal, the counselor focuses on providing the client with empathy and other types of support. When these needs of the client are met, the client comes to understand her own purposes and values and realizes that she has the power to make decisions on her own (Rogers 1951). The implication of this theory is that clients, both in psychology and in genetics clinics, do not need a counselor to help them decide on a course of action. They simply need support so they can decide for themselves.

In addition to psychological support, genetic counselors also often understand patients as needing information. After all, decisions based on genetic test results typically involve such complex concepts as probability and risk. The “teaching model” of genetic counseling builds on Rogerian theory in that it specifies that patients generally have what they need to make good

decisions for themselves. In addition to psychological support, they can benefit from unbiased information focused on clarifying complex ideas and dispelling misconceptions (Kessler 1997).

While Rogers' theory has clearly been influential for genetic counselors, it is not obvious why this is so. After all, Rogers was a psychologist, not a genetic counselor, and he demonstrated no particular interest in genetics (Resta 1997). A number of reasons have been proposed for this connection. It is apparent from Bosk's ethnography, for example, that the controversy over abortion has been influential in the development of the professional identities of both medical geneticists and genetic counselors. Bosk's counselors seem to have adopted a nondirective approach in part to shield themselves – both in the public eye and in their own self-understanding – from an appearance of complicity with the pregnancy terminations that some of their clients ultimately sought. The earlier history of eugenics also seems to have provided some motivation for the culture of non-directiveness among genetic counselors and medical geneticists (Resta 1997). Regardless of the source, however, it is clear that both medical geneticists and genetic counselors have long been reticent to dictate a course of action for patients, either when it comes to deciding whether to order a genetic test or deciding how to respond to genetic test results.

This professional value is particularly striking in comparison with the practices of other physicians. Clinicians in the evidence-based medicine tradition typically argue that a diagnostic test should only be performed if it will alter the course of treatment. This practice is based, at least in part, on the concern that false positive results are more common when a test has been ordered without good reason, since the proportion of false positive to true positives will be higher (Jackson 2008). Medical geneticists typically interpret this axiom broadly, however. In addition to accepting that an alteration in therapy could justify performing a genetic test, geneticist also allow that other possible actions could justify such testing. The decision to

become pregnant or to terminate a pregnancy, although not typically considered a “course of treatment,” are considered relevant motivations for ordering a genetic test. Genetic tests are also often ordered to provide a diagnosis for an unexplained medical conditions. Although a genetic diagnosis may sometimes provide new options for treatment, more often it simply provides information to a patient or family that has been searching for an explanation. In genetics, this desire for explanatory information is considered a legitimate justification for performing a genetic test.

In fact, the decision to perform a genetic test is often framed in terms of a patient’s “right to choose.” It is probably not a coincidence that this idea is also used widely in the discourse on elective abortion, given the historical association between prenatal genetic testing and therapeutic abortions. But this framing extends beyond the issue of abortion. The idea that a patient has the right to choose a diagnostic or therapeutic course of action is closely tied to the patients’ rights movement. In this movement, the patient’s right to choose is seen as a remedy for physician paternalism, in which the physician determines the selection of diagnostic tests and medical interventions. And in the current environment, patient autonomy has convincingly won out over physician paternalism. In current medical practice, the patient is expected to make the final decision about a medical course of action. Typically, these choices are constrained by the options deemed by the physician to be “medically reasonable,” but even this limitation has weakened in recent years (Bishop et al. 2010).

Controversy remains, however, around the proper role for healthcare providers in helping patients settle on a particular course of action. Many believe that it is the provider’s responsibility to help patients identify the course of action that is most promising. The provider might, for example, answer a patient’s question about what the provider would do if she were in

the patient's situation. The provider might even use techniques referred to as "nudges" – subtle techniques for motivating patients to take positive action or to adhere to a selected plan of care (Aggarwal, Davies, and Sullivan 2014). Others, however, believe that even these approaches are too directive. They argue that providers should not answer questions about what they would do in the patient's situation. From this perspective, answering such a question is still a form of paternalism, since it substitutes the provider's values for the patient's values.

This spectrum of perspectives on the issues of patient choice and provider paternalism can help us understand the overall professional culture of genetic counselors and medical geneticists. Although members of these professions can likely be found at every location along this continuum, this distribution is clearly asymmetric. Medical geneticists and genetic counselors disproportionately fall at the extreme end of the spectrum in favor of patient choice.

Patient Autonomy and the Personalized Medicine Movement

The influence of the professional values of medical geneticists and genetic counselors is manifest within the personalized medicine movement. Even though one of the distinguishing features of this movement has been its diversity, medical geneticists and genetic counselors have certainly been among its earliest and most influential leaders. Again, not all of these have been fundamentalist supporters of patient autonomy, but many have certainly brought their profession's distinctive perspectives on these issues into the movement.

This trend is especially apparent in recent debates around the criteria that should be used for selecting genetic test results to be returned to patients or research subjects. As we have seen, many medical providers would argue that laboratory tests should only be performed if they are intended to address a patient's medical situation, and if these results are expected to alter the course of treatment. This practice is intended to decrease the number of false positives and avoid

follow-up investigations that could be harmful, and is closely linked with the evidence-based medicine tradition. From this perspective, a genomic result should only be returned to a patient, research subject, or ordering physician if there is sufficient evidence that returning such a result will not cause harm and will improve health outcomes.

It is clear, however, that this perspective has very little support within the personalized medicine movement. Rather than evidence of benefit, this community has settled instead on the criteria that results should be returned if they are “actionable.” This term was borrowed from law, where it is used to refer to events that “give cause for legal action” (Nelson, Keating, and Cambrosio 2013). In the personalized medicine movement, an actionable genomic result is one that can be used by patients, research subjects, or healthcare providers to take some action. The types of actions that are considered relevant in this definition are a matter of some debate (Garrett 2014). The potential to perform preventive or therapeutic medical interventions are, of course, universally agreed to be relevant to the decision to return a genomic result. In addition, many non-medical actions like reproductive decision-making are also considered to be relevant justifications for returning genomic results. Even the “personal meaning” that a genetic result holds for a patient or research subject has been accepted as an important reason to return a result (Ravitsky and Wilfond 2006, Wolf et al. 2012). These criteria seem to reflect the influence of medical geneticists, since they are virtually identical to the professional standards medical geneticists tend to use when ordering a genetic test. They do not reflect the more stringent criteria utilized by most other medical professionals.

The actionability standard is also of interest because it emphasizes the potential to act – to do something (Garrett 2014). This emphasis is in some ways reminiscent of the Rogerian strain in genetic counseling, which emphasizes support of clients’ ability to act rather than the

outcomes of those actions. In the next section, however, we will explore another set of commitments that seems to provide a more direct basis for this emphasis on action. The cultural values of the digital age, like the professional values of medical geneticists and genetic counselors, will provide us with one final window into the role of providers in the personalized medicine movement.

Autonomy in the Digital Age

The principle of patient autonomy emphasizes that patients have a right to self-determination. As we have seen, this principle has been accepted by most healthcare providers, but medical geneticists and genetic counselors remain some of its most outspoken supporters. Given these professional values, and the influence these clinicians have had on the personalized medicine movement, it is not surprising that the vision for personalized medicine tends to emphasize patient autonomy. As we saw earlier, the vision for independent patient action, a key element of personalized medicine, emphasizes that patients should be able to access their *omics*-based laboratory results through online patient portals and take action to improve their health. This is, in some ways, the ultimate expression of patient autonomy.

It may seem odd, then, that there is one particular application of this principle that is controversial within the personalized medicine movement. Specifically, a recommendation document published in 2013 by the American College of Medical Genetics and Genomics (ACMG) set off an intense debate over the importance of respecting patient preferences not to receive important incidental genomic results (Green et al. 2013). In this document, the authors argued that laboratories performing clinical sequencing to answer a specific clinical question should analyze the remaining genomic data to look for incidental (subsequently renamed secondary) findings. This recommendation focused on a specified panel of genes – the so-called

“minimal list” – that the authors felt could reveal important medical information for patients. A search for incidental findings in these genes, the authors argued, should be carried out by laboratories regardless of the medical indication that prompted the testing, and regardless of the preferences of the patient. While they allowed that patients could still choose whether to undergo testing, they denied that patients should have a choice about whether to receive findings included on the “minimal list.”

Their justification for this recommendation is complex, and the brief recommendation document did not provide space to develop it completely. But it is clear that they considered at least two justifications for this policy recommendation. First, they observed that it can be challenging to elicit patient preferences about the large number of genetic results that can potentially be generated using these technologies (Green et al. 2013, 567). Second, they argued that when an incidental finding has a high prevalence and an effective intervention is available, both laboratories and healthcare providers would have a “fiduciary duty to prevent harm” (Green et al. 2013, 568). They felt that this beneficence-based duty “supersedes concerns about autonomy” (Green et al. 2013, 568). In a clarification published shortly after the original recommendations were published, the ACMG reiterated this focus on the benefit that patients could receive from such results. “The rationale for our recommendations,” they argued, “was that not reporting a laboratory test result that conveys a near certainty of an adverse yet potentially preventable medical outcome would be unethical” (American College of Medical Genetics and Genomics 2013). They observed that even though patient preferences would not be elicited, patient autonomy could still be respected because patients who did not wish to receive incidental findings could simply choose not to undergo clinical sequencing.

The first justification for this recommendation – that eliciting and applying patient preferences is impractical – was striking, given that several of the authors were at the time actively involved in research focused on developing the types of techniques that would be needed to elicit patient preferences and incorporate them into laboratory and clinical care processes. However, it is the second justification that is most interesting given our earlier discussion of the influence of the professional values of genetic counselors and medical geneticists. In the professional tradition of genetic counseling, it is considered extremely important to provide patients with both “pre-test” counseling and “post-test” counseling. Pre-test counseling is focused on providing patients with the information they need to decide whether they want to undergo testing. This counseling focuses on helping patients understand possible results, and think through the responses they might take to these results. In other words, pre-test counseling is designed to support patients’ autonomy in deciding which information they want to pursue through testing (Rhodes 1998).

This interpretation of autonomy links the right to decline testing that might generate beneficial information with the right to decline beneficial treatment. Just as patients have a right not to consent to beneficial, even life-saving, interventions, they also have a “right not to know” (Wolf, Annas, and Elias 2013). This interpretation of autonomy supports the right of patients to control which medical procedures, including laboratory tests, are performed. Any analysis performed on sequencing data that is not approved by the patient, therefore, inappropriately overrides patient autonomy (Ross, Rothstein, and Clayton 2013).

The ACMG recommendations, on the other hand, argued that the potential for certain genomic results to benefit patients “supersedes concerns about autonomy” (Green et al. 2013, 568). It is telling, however, that the authors did not concede at this point that their

recommendations conflicted with patient autonomy. They argued instead that the potential benefit of genomic incidental findings supersedes *concerns* about autonomy. They seem to be splitting the same hair elsewhere in the recommendations document when they state, “We recognize that this may be seen to violate existing ethical norms regarding the patients’ autonomy and ‘right not to know’ genetic risk information” (Green et al. 2013, 568). In both cases, they seem to imply that they anticipated critics would object to this recommendation by evoking autonomy, but that they had an implicit reason to believe that their recommendation did not conflict with autonomy.

One possible reason for this assessment is implied later in the paragraph when they observe that, “Patients have the right to decline clinical sequencing if they judge the risks of possible discovery of incidental findings to outweigh the benefits of testing” (Green et al. 2013, 568). In other words, they view the opportunity to decline testing altogether to be an acceptable process for ensuring autonomy. But this raises another question: Why would it be acceptable to decline clinical sequencing, but not acceptable to decline incidental findings from that testing?

To find the source of this apparent inconsistency, we need only to take a closer look at the “right not to know.” For this conventional account of autonomy, including the one advocated by genetic counselors, the “right not to know” is simply another instance of a competent patient’s right to decline healthcare that is potentially beneficial. There is no inherent difference between the benefit provided by health information and the benefit provided by a medical intervention. Patient autonomy implies the right to decline both. However, the authors of the ACMG recommendations do not endorse this conception of a “right not to know.”

In the next section, I will argue that this implicit rejection of a right not to know reflects another set of non-scientific values that have shaped the personalized medicine movement. I will

argue that the roots of this cultural trend can be found in the values that have grown in importance during the so-called “digital age.”

The Hacker Ethic

In order to discover the roots of personalized medicine’s tendency to endorse autonomy while rejecting the right not to know, we need to turn, of all places, to a community of hackers at the Massachusetts Institute of Technology in the 1960’s and 1970’s. Although other groups of hackers had developed by this time, it was this community that journalist Steven Levy examined in his classic book, *Hackers: Heroes of the Computer Revolution*. As the title implies, Levy saw this group as champions for a distinctive set of values. Later labeled the “hacker ethic,” these values centered on a belief that individuals should have free access to information through computer networks. With free access to information, these hackers believed, individuals would realize opportunities to improve themselves and the world around them.

In the hacker ethic, free access to information is closely related to the “hands-on imperative.” According to Levy, hackers “believe that essential lessons can be learned about the systems –about the world – from taking things apart, seeing how they work, and using this knowledge to create new and interesting things” (Levy 2001, 24). The hands-on imperative provided part of the motivation for the practices for which hackers are popularly known, including circumventing the security measures of government and corporate networks. By digitally “breaking in” to such networks, hackers were able to learn about the security measures these institutions employed. They could then use this knowledge to develop new, more effective measures.

The hands-on imperative also had a more positive dimension. Because of this value, hacker culture encouraged individuals to solve their own problems instead of turning to

specialists. For example, a hacker whose car had stopped working might not seek the help of a mechanic. Instead, he would be more likely to take advantage of freely available information to learn how to fix his automobile himself. An important implication of the hacker ethic is a belief that “if you can’t fix it, you don’t own it” (2010).

Another important dimension of the hacker ethic is a mistrust of authority. This mistrust was rooted in the belief that government and corporate authorities maintain power over individuals by controlling information (Levy 2001). Individuals can empower themselves, therefore, by gaining access to the information controlled by these institutions. This belief also contributed to the hacker practice of gaining unauthorized access to computer networks. For hackers, the release of “secret” information is a form of civil disobedience that removes power from institutions and places it in the hands of individuals.

My thesis in this section is that the account of patient autonomy, and thus of practical reasoning, that has developed in the personalized medicine movement has its roots as much in the hacker ethic as it does in the professional values of genetic counselors and medical geneticists. Given that this connection is far from obvious, however, I will need to demonstrate this link in at least two ways. First, I will explore how the values of a group of hackers in the 1960’s and 1970’s could have found their way into a scientific and entrepreneurial movement within medicine in the 21st century. Second, I will demonstrate that elements of the hacker ethic are reflected in the values of the contemporary personalized medicine movement.

From Hacker Community to Personalized Medicine Movement

Although it may not be immediately intuitive that hacker culture has influenced the personalized medicine movement, there are a number of connections between personalized medicine and information science. We already saw in Chapter 3 that the systems biology

paradigm reflects the application of big data principles to *omics*-based laboratory technologies. The techniques utilized by this paradigm are highly technical and have developed through significant contributions from experts in information sciences.

Even beyond big data analytics, the management of *omics*-derived laboratory data implies a need for information technologies. The raw data from a human genome is equivalent to 200,000 pages of A's, T's, C's, and G's. It would take 200 Manhattan phone books to store the data in just one human genome (Jha 2010). This data also must be analyzed, but not even the most renowned experts in clinical genomics are capable of manually generating clinically useful findings from raw genome sequences. Such analyses require advanced tools that “read” the genome in terms of coding and non-coding regions, introns and exons, etc. As a result of these factors, information technologies are important to personalized medicine. These technologies make it possible for next-generation sequencing technologies to be used in clinical care by supporting the storage and interpretation of genomic data.

Because of this dependence on information technologies, informaticists have played a pivotal role in both the entrepreneurial and scientific efforts to translate personalized medicine science into real-world applications. A few examples will suffice to demonstrate this trend. The Clinical Sequencing Exploratory Research (CSER) Consortium and Electronic Medical Records and Genomics (eMERGE) Network are two NIH-funded research collaborations focused on applying genomic data to clinical practice. In both of these networks, bioinformaticists play a key role. In fact, the request for applications for both networks emphasized the importance of collaborators from informatics (2014b, 2012).

In the entrepreneurial realm, many of the most prominent companies contributing to the development of personalized medicine-based products and services are, first and foremost,

information technology companies. 23andMe, one of the most prominent players in the direct-to-consumer genetic testing industry, was founded by Anne Wojcicki, the former spouse of Google founder Sergei Brin. Google was an investor in this company, contributing \$3.9 million to its start-up funds (2007).

We have already seen another mark that Google has made on this movement, although I did not highlight this connection at the time. Leroy Hood, the systems biology advocate who proposed the P4 medicine account of the vision for personalized medicine, originally proposed only three P-words to define this movement (Hood et al. 2004). It was another Google founder – Larry Page – who proposed to Hood that “participatory” should also be included (Carlson 2010).⁵

Despite the direct links between personalized medicine and information science, however, I suspect that major cultural shifts brought about by computer technologies are the primary mechanisms by which the hacker ethic has been incorporated into the personalized medicine movement. When Levy first published *Hacker: Heroes of the Computer Revolution*, he could not have known that the revolution he predicted would have such far-reaching implications. The subculture of hackers he observed in the 1960's and 1970's has since become a worldwide community. This more distributed hacker community largely retains its emphasis on the ethic that Levy described. The “hands-on imperative,” for example, persists in a worldwide community of programmers who cooperate on free or open source software (F/OSS) projects (Coleman and Golub 2008, Leach, Nafus, and Krieger 2009).

The most striking implication of the hacker ethic, however, has been its remarkable influence on mainstream society. Just as network technologies have become a part of everyday

⁵ In the final portion of this chapter we will return to the concept of “participatory” medicine to demonstrate how it reflects the influence of the hacker ethic on the personalized medicine movement.

life for billions around the world, so too have values inspired by the hacker ethic grown in importance. That this trend has been influential in medicine is apparent from its effect on other movements that fall well outside the tradition of personalized medicine. One such effort is the scholarly and professional community referred to as *healthcare 2.0* that was mentioned in an earlier chapter. This vision draws its name from “Web 2.0,” which describes internet technologies, like social networks, that allow users to generate their own content and interact with others. Advocates for healthcare 2.0 propose to bring this concept of interactive web tools into the healthcare industry (Randeree 2009). Although a number of technologies and approaches have been proposed by healthcare 2.0 advocates, personally controlled health records (PCHRs) are an especially important technology in this vision for healthcare, since they offer the opportunity for patients to contribute content to the health record (Hoffman and Podgurski 2009, Ball, Smith, and Bakalar 2007). Some advocates for healthcare 2.0 have even proposed that patients could use PCHRs in concert with social networks to share parts of their health record with other patients (Van De Belt et al. 2010) or with researchers (Hood and Friend 2011). This proposal, among other elements of the healthcare 2.0 movement, demonstrate an apparent endorsement of the value of freedom of information.

It is certainly plausible that the healthcare 2.0 vision has been a direct inspiration for the personalized medicine movement. It is also possible that the overlap in these visions came about through an independent interest in the values and technologies of the digital age. Regardless of the mechanism, however, it is clear that the values of the digital age are reflected in the vision for personalized medicine. In the next section, we will examine this influence of the hacker ethic in the personalized medicine movement. Through this examination, we will come to see how the

independent patient action model reflects on the role of provider practical reasoning in the vision for personalized medicine.

From Hacker Ethic to Vision for Personalized Medicine

According to Levy, the hacker ethic centers on a commitment to making information freely available. This emphasis on freedom of information has already been an implicit element in many of our observations about the personalized medicine movement. One context where we have seen this influence is in the systems biology paradigm. Because big data approaches require large amounts of data, they typically depend on technologies and policies that make information freely available. This dependence is reflected in the recent claim by Google founder Larry Page that he could save 100,000 lives each year if patients consented to making their EHR data freely available for research. The model Page had in mind was not strictly systems biology, but it did reflect the dependence of big data analytics on freedom of information (Hern 2014). Those working in the field of systems biology also frequently point to freedom of information as an important element of this approach. Leroy Hood has argued, for example, that:

The issues of data ownership (by scientists and by institutions) and a reluctance to believe in open source and open data policies will have to be overcome if we are to mine the incredible potential of the exploding opportunities of patient data accumulation (Hood and Friend 2011).

The commitment to free access to information is also reflected in the clinical vision for personalized medicine. In this context, however, the interpretation of access emphasizes individual control over one's own information. The individual patient information stored by healthcare institutions is understood to be owned by the patient, not the institution. If the patient wishes to view their medical record or transfer it to another platform, their right to do so is supported on the basis that it "belongs" to them.

The obligation to make individual clinical information publicly available is not emphasized in this context, however. In hacker communities, the mistrust of authority focuses primarily on the way governments and corporations restrict access to information. Free access to information is a means to limiting the power these entities maintain by controlling access to information. In the context of clinical informatics, this aim is fulfilled by tools that give individual patients access to their own information. The discourses on healthcare 2.0 and personalized medicine frequently highlight patient portals as a tool for supporting patient rights; they are seen as helping to “level the playing field” in terms of the power dynamic among patients, providers, and healthcare institutions (Gerber and Eiser 2001, Spevick 2002, Van De Belt et al. 2010). In both the hacker ethic and the personalized medicine movement, information is power.

And it is the issue of power that brings us to our primary motivation for exploring the hacker ethic and its influence on the personalized medicine movement. Recall that we pursued this line of enquiry with the goal of understanding how the personalized medicine movement could endorse patient autonomy with such enthusiasm, while at the same time questioning the legitimacy of patient claims to a “right not to know.” It is to this end, then, that we now turn to the hands-on imperative.

The Hands-On Imperative and Patient Empowerment in Personalized Medicine

The hands-on imperative derives from the hacker ethic conception of information as linked with power. This link has at least two dimensions. First, information is a prerequisite for self-determination. Not having access to information restricts power, and gaining access to information removes that barrier.

The second dimension is even more important, however. On this account, having information changes one's sense of control. When an individual accesses information about how to fix problems herself, she realizes that she has control over her path. In the language of health psychology, she gains a sense of "self-efficacy." And this explains why, in the hacker ethic, a hands-on approach is an imperative and not just an opportunity. Free access to information provides individuals with the two resources they need to fix their own problems: the opportunity to gain know-how, and the motivation to take hands-on action.

In this way, the hacker axiom "if you can't fix it, you don't own it" has two implications. Taking the example of a digital device, this axiom is a condemnation of manufacturer practices that intentionally restrict phone purchasers from repairing their devices. Another implication, however, is that once manufacturers remove these barriers, phone owners have an "imperative" to fix the device themselves. Those who fail to take advantage of available resources to learn how to make repairs and then take action to do the repairs are condemned for not "owning" their device at all. The same applies to "owners" of a human body: now that the digital age has removed barriers to "repairing" one's own body, it is everyone's responsibility to "fix" his or her own health.

This hands-on imperative is alive and well within the personalized medicine movement, where it is usually framed under the rubric of "empowerment." A wide array of stakeholders in the personalized medicine movement cite patient empowerment as a key benefit of patient access to genomic results through online patient portals.(Juengst, Flatt, and Settersten 2012) Academic institutions with programs in personalized medicine frequently identify patient empowerment as an important aim of their programs (Juengst, Flatt, and Settersten 2012). NIH director Francis Collins, one of the key leaders of the Human Genome Project, is a particularly strong advocate

for this idea. As we saw earlier, in his book *The Language of Life: DNA and the Revolution in Personalized Medicine* he implores readers, “If you are interested in living life to the fullest, it is time to harness your double helix for health and learn what this paradigm shift is all about” (Collins 2010).

Here, empowerment stands in for all three elements of the hands-on imperative: (1) that access to information removes barrier to individual power, (2) that accessing information improves patients’ sense of self-efficacy, and (3) that the first two elements create obligations for patients who are offered access to information. One of these is the obligation to take “hands-on action” by using the information that has been made available to improve one’s own health. This implies a separate obligation to accept the offer to access information. As philosopher and personalized medicine contributor Rosamond Rhodes explains, “the reason for providing information in the typical medical context is that the patient is presumed to be an autonomous agent. Without the relevant information, the patient cannot make autonomous choices” (Rhodes 1998, 18). As a result of this framing, intentional ignorance is an infraction of the hands-on imperative. When a patient decides not to accept information that is offered, she implicitly decides to leave what happens with respect to health up to chance. “If autonomy is ground for my right to determine my own course, it cannot also be the ground for not determining my own course” (Rhodes 1998, 18).

This explains why, in the ACMG recommendations and other debates in the personalized medicine movement, the “right not to know” is often rejected as inconsistent with patient autonomy. If patients do not receive potentially useful *omics*-based predictions, they cannot undertake health-preserving action. This is unacceptable, since in this vision patients are obligated to take an active rather than passive role in self-direction; this is *participatory*

medicine. The “right not to know” is, ultimately, rejected by personalized medicine because it is antithetical to the hands-on imperative.

CHAPTER 5

ON SQUARE PEGS AND ROUND HOLES

Personalized Medicine's Distinctive Account of Practical Reasoning

When I introduced the idea of practical reasoning in chapter 2, I observed that the two traditions currently dominant in clinical practice share three important characteristics: (1) They are methodical. That is, they prescribe a specific structure for deliberating on individual circumstances. (2) They are teleological. They frame practical reasoning as an effort to determine the how best to attain certain goals, which is usually the health and well-being of a patient. (3) They utilize rational frameworks that are explicitly scientific. Reasoning about how to attain the desired outcomes is based on an account of causality or probability suggested by a set of related scientific paradigms.

I also observed that the vision for personalized medicine does, to some extent, accommodate these two traditions of practical reasoning. Personalized medicine as a whole is not fundamentally opposed to either evidence-based medicine or experimental medicine. My concern about integrating personalized medicine into contemporary medical practice, however, arises from the observation that this vision also includes a nascent account of practical reasoning that is distinct from these two models. For the sake of simplicity, I have been calling this the “personalized medicine account of practical reasoning.” We are finally ready to synthesize our observations of this account into a complete picture.

It is clear that the personalized medicine account of practical reasoning, like the accounts of evidence-based medicine and experimental medicine, is explicitly scientific. Scientific paradigms like the GWAS and systems biology paradigms are used to generate predictions. The

rational framework that guides practical reasoning is based on using these predictions to take specific actions intended to mitigate that risk.

Although the personalized medicine account of practical reasoning is similar to evidence-based medicine and experimental medicine in this way, it differs with respect to the other two features shared by the two existing traditions. First, it does not provide a methodical approach to practical reasoning. A methodical approach is one that prescribes specific methods for applying general and specific knowledge to the task of deciding on a course of action. The personalized medicine account of practical reasoning does call on patients and/or providers to decide on a course of action, but this process is not methodical because there is no proposed method for utilizing predictive results to decide on a specific course of action. We saw that GWAS-based predictions serve only as red flags, indicating that action might be needed. They provide no information relevant to deciding on a specific course of action. Systems biology-based predictions can provide predictions about how a patient may respond to different interventions, but because the big data approach used to develop them is opaque to providers, they cannot be interpreted and applied methodically. In the end, providers simply have to decide whether to trust the predictions.

In the personalized medicine model of practical reasoning, it is more important that providers and patients take action than it is to select the course of action that will lead to the best outcome. In other words, the personalized medicine model of practical reasoning is not exclusively teleological. Action is considered to have inherent value even if it is unknown how efficacious the action will be. And information, in turn, is of inherent value because it creates the opportunity to take action. The hands-on imperative is thus treated as an adequate justification both for receiving predictive results and for taking action in response to these results. This

rational framework does not require a justification for action that depends on demonstrable utility for improving patient outcomes.

The net effect of this non-methodical, non-teleological account of practical reasoning has been an overall devaluing of the role of healthcare providers. In the evidence-based medicine and experimental medicine traditions, providers are important because all interventions are treated as justified only if they lead to improved patient outcomes. And the method for determining what outcomes are likely to result from the available interventions is careful deliberation by a provider with expertise in either empirical clinical research or mechanistic causality in the human body.

When both the methodical and teleological elements of practical reasoning are discarded, however, the role of an expert is no longer justified. If action is of inherent value, patients can fulfill this imperative on their own. It is quite consistent, then, that the personalized medicine movement involves a strong emphasis on independent patient action. This is clearly derived from larger cultural trends, but is especially at home in the vision for personalized medicine because of the implications of its scientific paradigms.

Given this analysis, and given my own background as a healthcare provider, it may seem that I consider the devaluing of healthcare providers to be an inherently problematic implication of the personalized medicine movement. I admit that I find this conclusion troubling, but at the same time I hope not to beg the question in this analysis. In the remainder of this chapter, I hope to demonstrate that the personalized medicine model of practical reasoning, and in particular its account of independent patient action, are problematic not because they render providers obsolete, but because the vision for personalized medicine, if it is to be attained, requires more practical reasoning from providers, not less.

The Cartesian Anxiety and the Rhetoric of Disruption

In Chapter 2 when I introduced Thomas Kuhn's idea of scientific paradigms and Alasdair MacIntyre's idea of traditions of moral thought, I pointed out that each these was developed as a solution to an historical problem that arose in the wake of the Enlightenment. After the Enlightenment, scientists and moral thinkers alike had come to expect that the rational framework they used in their work should be objective. That is, when they gave an account of their actions they should be confident that the rational justifications they referenced would be convincing to others. In other words, such judgments should not be subjective, based only on the opinions of individuals.

In this Enlightenment vision, however, it was assumed that such a rational framework would need to be universal in order to be objective. After all, how could one be sure that everyone would agree with a justification unless "everyone" included all people in all places and times? In order for a scientific explanation for a phenomenon to be considered objective, it would need to be convincing to all scientists, both today and in the future. The same should go for moral actions, as well.

Kuhn and MacIntyre were both responding, then, to the realization that no universal rational framework has been discovered, either in science or in moral philosophy.⁶ One response to this problem was the so-called "post-modern" response: there is no objectivity, only subjectivity. Given what was at stake in scientific enquiry and moral thought, however, Kuhn and MacIntyre were aligned in their refusal to accept utter subjectivity. Instead, they proposed very similar accounts of objectivities that, while not universal, could be accepted by individual communities as adequate to their needs. Such objectivities would involve rational frameworks

⁶ In fact, they were both rather suspicious that no such framework could ever exist. The very account of objectivity they advanced, however, prevented them from making this claim too strongly.

developed and refined within a community, with enough consensus around key issues to allow participants to provide justifications that would be accepted by others. And in fact, both found extensive evidence that this is exactly how communities have operated since before the Enlightenment.

The solutions proposed by Kuhn and MacIntyre have proven extraordinarily successful, and since their introduction in the mid-twentieth century they have proven fruitful in dealing with what Richard Bernstein calls the “Cartesian anxiety” – the feeling that we should have an objective ground to stand on, but that no such ground exists. An obvious problem for non-universal objectivity, however, is that when the accounts of rationality accepted within two different communities or contexts do not agree, there is no “objective” way to settle the disagreement. MacIntyre recognized this challenge and labeled it *incommensurability*. There is no measure external to conflicting accounts of rationality, he argued, that is capable of comparing them and identifying the “better” of the two. Any reason for prioritizing one tradition over the other can only seem to be a “good reason” from the perspective of a particular tradition.

MacIntyre also observed that even a more modest approach of transferring one element of a tradition into another is destined to fail. The concepts and commitments that comprise traditions gain their meaning and significance only within the larger context of the tradition and its rational framework. When such an idea is interpreted in a new tradition, it will necessarily be understood within that tradition’s framework. It is unavoidable, then, that any concept or commitment interpreted outside the context of its tradition will be misunderstood from the perspective of other traditions.

This is precisely the reason that I do not find the implications of the personalized medicine account of practical reasoning to be inherently problematic. While the devaluing of

provider practical reasoning seems dangerous from the perspective of evidence-based medicine and experimental medicine, this perspective inevitably misinterprets the personalized medicine perspective. Such an evaluation applies the perspective of evidence-based medicine or experimental medicine to this issue, and thus removes it from the context of personalized medicine within which it makes sense.

A more generous interpretation of personalized medicine's account of practical reasoning would simply identify it as problematic because it contrasts with two traditions that are already dominant within medical practice. Although there is nothing inherently wrong with this account, it fits poorly into the models of science-based practical reasoning currently used in clinical practice.

In some ways, the personalized medicine movement acknowledges some inconsistency with current clinical practice. It is actually quite common for advocates of this tradition to identify the laboratory and informatics technologies on which it is based as "disruptive." While this term is often meant to indicate that these technologies and practices will be disruptive to current business structures (Becla et al. 2011, Carlson 2009, Glabman 2009, Parkinson and Ziegler 2009, Schulman, Vidal, and Ackerly 2009), it is also clear that the vision for personalized medicine is understood as disruptive to existing clinical practice (Downing 2009, Parkinson and Ziegler 2009, Schulman, Vidal, and Ackerly 2009, Tonellato et al. 2011).

The rhetoric of disruption, however, reveals what is perhaps the most troubling implication of incommensurability among the three science-based traditions of practical reasoning. As we have seen, one of the primary ways the vision for personalized medicine proposes to disrupt current medical practice is by engaging patients in accessing their own

medical record information and taking independent action. As we have seen, this form of disruption is thoroughly supported by the personalized medicine account of practical reasoning.

The problem with this particular disruption, however, is that it eliminates the opportunity for methodical, teleological practical reasoning proposed by the other two traditions. In other words, even if there was a universal rationality that would allow these three traditions to be integrated, the disruption created by the independent patient action model would preclude this integration from occurring. On pragmatic grounds, the direct patient action model is incompatible with practical reasoning in both the evidence-based medicine and experimental medicine traditions.

We have identified, then, at least two major challenges that seem to preclude the integration of personalized medicine with existing medical practice. The first is conceptual, and is based on the apparent incommensurability among the evidence-based medicine, experimental medicine, and personalized medicine traditions of practical reasoning. The second is practical, and arises from the personalized medicine vision to bypass provider practical reasoning in certain cases.

Fortunately, these challenges do not seem intractable. After all, despite the apparent incommensurability between evidence-based medicine and experimental medicine, these two traditions have successfully co-existed, albeit with occasional conflict, for almost two hundred years. In the next section, we will examine this uneasy peace, as well as some helpful insights from moral philosophy, with the goal of developing an account of clinical practice that will help address these challenges.

Speaking Two Languages and Speaking in Fragments

Despite MacIntyre's observations about incommensurability, he did not rule out entirely the possibility that one could understand two traditions with an "insider" perspective. He observed this remarkable ability, in fact, in St. Thomas Aquinas. According to MacIntyre, Aquinas was able to create a new tradition of moral thought precisely because he was a "native speaker" in both the Aristotelian and Augustinian traditions (MacIntyre 1988, Chapter 10, 1990, Chapter 5).

It is tempting to conclude that most contemporary physicians have replicated this feat by becoming "native speakers" in both the evidence-based medicine and experimental medicine traditions. However, this framing does not get us very far. MacIntyre did not attribute to Aquinas the ability to simultaneously utilize two traditions. Instead, MacIntyre sees Aquinas as remarkable because he was able to generate a new tradition that synthesizes the ideas of two existing traditions. In the case of medicine, the equivalent would be to create a single rational model that incorporates evidence-based medicine and experimental medicine into a single framework. Given that no synthetic framework exists, even among those physicians who are facile with both evidence-based medicine and experimental medicine, it is doubtful that this is the approach that has allowed physicians to use both traditions so effectively. Similarly, this approach does not seem promising in terms of providing a way to integrate personalized medicine with the existing traditions of medicine.

The pragmatist approach of Jeffrey Stout can get us somewhat closer. Unlike MacIntyre, Stout does not assume that individuals must always utilize a single rational framework when they settle on a course of action. As a pragmatist, he argues that something like practical reasoning is important not only for determining how to act in particular situations, but also for determining

which frameworks to use in making such decisions. For Stout, individuals are capable of moving among different rational frameworks in order to find the approach that is best suited to help them attain their goals.

How do they do this? To explain this, Stout borrows the image of a tinkerer from Claude Lévi-Strauss, who used the French term *bricolage* (Stout 2001, 211). According to Lévi-Strauss, a *bricoleur* is a person “who works with his hands and uses devious means” (Lévi-Strauss 1966). Unlike an engineer who depends on formal, planned procedures, a *bricoleur* depends on creativity and ingenuity.

For Stout, we are all *bricoleurs*. Through our human capacity to solve problems creatively, we demonstrate the resourcefulness of a tinkerer. And we utilize this skill when we attempt to solve moral problems. Stout says that a *bricoleur*:

start[s] off by taking stock of problems that need solving and available conceptual resources for solving them. Then [he proceeds] by taking apart, putting together, reordering, weighing, weeding out, and filling in (Stout 2001, 75).

This description does evoke some of the fluidity that MacIntyre attributes to individual traditions, but for Stout individuals can draw on pieces of multiple traditions to find an approach that works. In this account there is still a concern that an individual will misunderstand traditions that are unfamiliar. But rather than accepting that this risk renders different traditions incommensurable, Stout argues that we can develop adequate understanding over time (Stout 2001, 66).

As a result of *bricolage*, Stout observes, we tend to draw from a variety of different frameworks when we use moral language. But whereas MacIntyre would dismiss this phenomenon as fragmented and incoherent, Stout sees it as rich and dynamic. Taken together,

these fragments comprise a moral language in their own right, and one that is eminently useful for our purposes (Stout 2001, 69).

Stout's account resonates with "on the ground" medical practice. Providers typically experience themselves as utilizing a range of approaches to solve clinical challenges. It is common, for example, for physicians discussing a course of action to move freely among justifications rooted in evidence-based medicine and justifications based on biological mechanisms. They also tend to freely incorporate pragmatic concerns like the resources available in particular care units and the preferences of patients and their families.

Stout's account seems limited by the Cartesian anxiety, however. If providers can draw freely from a variety of rational frameworks, what is to keep this selection from introducing subjectivity into these types of decisions? In fact, this is the very problem that MacIntyre set out to solve. He argued that in our post-modern world moral claims seem only to reflect our arbitrary preferences and interests. This is not because our claims fail to reference a rational framework, since we usually do have some standard of rationality in mind when we make a moral claim. The problem is simply that we do not agree on the standard we should use, and thus any claim to one of the competing standards of rationality seems arbitrary.

Stout's response to this problem emerges from his pragmatist approach. When he speaks of moving among moral languages, he evokes the language of practical philosophy. That is to say, the task of selecting from among the available rational frameworks and moral languages is itself a kind of practical reasoning. And the effort we put into moving among different frameworks and combining their insights into a final decision is a kind of practice.

Unfortunately, Stout does not develop this idea further. His pragmatist account can be summarized simply as "do what works." This is, to be sure, an excellent starting point. In fact, it

is probably adequate for good clinical practice in the vast majority of cases. But our aim in this chapter is to provide a robust account of a way personalized medicine can fit into contemporary medical practice. In order to attain that aim, we will need to develop Stout's account somewhat further. To that end we will next turn to the practical philosophy of Hans-Georg Gadamer.

Knowing One's Way Around

In some respects, Gadamer's thought is a natural fit for addressing MacIntyre's problem of incommensurability. Like MacIntyre, Gadamer's thought is rooted in the ethics of Aristotle. This account of ethics focuses on the everyday comportment of persons engaged in practices of all types. So although MacIntyre focused primarily on ethics in the modern sense, we found that it is rather natural to apply MacIntyre's work to the practice of medicine.

Gadamer's work focuses on yet another application of Aristotle's thought: hermeneutics. Hermeneutics is the field explicitly focused on the approaches interpreters take in order to gain understanding with respect to a subject matter. This field of enquiry originated with biblical exegesis, the field of study focused on attaining understanding with respect to biblical scriptures. Although Gadamer was incidentally interested in this and other practices that focus on attaining understanding, the main thrust of his work on hermeneutics had to do with understanding in general. He wanted to describe how humans go about attaining understanding whenever they encounter something outside themselves. This framing is extraordinarily helpful for our purposes. This is because Gadamer proposes that we understand other people in much the same way that we understand texts, paintings, and perhaps even scientific research results. Gadamer's framework for hermeneutics can therefore give us a flexible model for talking about the interpretations and choices that go into deciding on a clinical course of action.

For Gadamer, the process through which we gain understanding of the world around us is a type of “knowing how” (Gadamer 1996, 4-5), or what Gadamer called *Sichverstehen* – “knowing one’s way around” (Gadamer 2004, xvii). Gadamer’s framing in this case explains, in some respects, why medicine is also referred to as an “art.” For Gadamer, methodical practices like the practical reasoning called for in the evidence-based medicine and experimental medicine traditions depend on “knowledgeable mastery of operational procedures” (Gadamer 1990, 92). *Knowing one’s way around*, in contrast, is a less structured type of skill that we develop through practice. When it comes to understanding, it refers to a way of engaging one’s self with a resource – a text, a work of art, a scientific result – in order to discover the meaning that it holds.

Gadamer proposes that the application of a legal statute provides a useful example of the the practical value of *knowing how* (Gadamer 2004, 309). As a legal scholar, one could develop propositional knowledge about a statute. In such work, one might ask questions such as “Why would a legislature pass such a law at this point in history?” or alternatively “Why does this type of law take different forms in different jurisdictions?” Such a study would reveal propositional knowledge about how legal statutes come to be in particular contexts, but it would leave untouched the issue of a particular statute’s *meaning*. The meaning of a statute lies in its power as a type of authority that makes a claim upon those living in a jurisdiction. This meaning can only be understood as it develops through application in particular cases. Those who discover and create the *meaning* of a statute are those judges and lawyers who use their know-how related to legal practice to negotiate in particular cases how that statute should be interpreted and applied. The know-how of lawyers and judges is not a procedure that prescribes and restricts movement, but rather a type of freedom that “implies the general possibility of interpreting, of seeing connections, of drawing conclusions” (Gadamer 2004, 260).

Gadamer argues that interpretation, understanding, and application are indivisible elements of the same process. When we think of ourselves as being positioned in a particular historical context, we begin to see that directing ourselves toward a statute (or a patient, or a scientific finding, or a predictive genomic result) is always to interpret that object from within that context and to apply it to the demands of that context. That is to say, lawyers are always reading statutes and cases in terms of the expectations that emerge from their context. Likewise, healthcare providers are always reading scientific research findings and specific patients' cases in terms of the expectations that arise for them in their particular context. Gadamer calls these expectations *prejudices*, and further clarifies that these prejudices take the form of questions. The knowledge providers are capable of discovering from research findings or from patients' stories are not unlimited, but instead are limited by the questions they come to pose within their context. But framing the issue in this way obscures a more important implication of questions: it is only because providers are able to pose questions that they are able to discover any meaning in research findings or patient stories in the first place (Gadamer 2004, 362f, 1990, 106).

Gadamer's insight that we "read" the world in terms of questions has at least two powerful implications. First, insofar as we approach a text or another person through questions, we are capable of discovering answers we do not expect. Our expectations are not the types of prejudices that only allow us to see what we want to see. Rather, they open up the possibility that what we expected is not the case, that we could be wrong. Second, when we ask questions that matter to us, it becomes possible that we will find answers that will be compelling to us in our context. In this way it becomes possible that statutes or research findings may provide us with convincing reasons for following the law or changing our practice; Gadamer says we discover their "truth" (Gadamer 2004, 297).

Gadamer describes this process of question and answer through the metaphor of a circle (Gadamer 2004, 293). Gadamer's hermeneutic circle is similar in some respects to Stout's interpretation of *bricolage*: both suggest a creative, intuitive process focused on completing a task using the resources at hand. In Gadamer's account, however, the process of "tinkering" is described in more detail. Specifically, this process is described as a circle because it involves iterative movement between interpretation and application. In the context of clinical decision-making, the hermeneutic circle involves movement between (1) "reading" scientific knowledge in light of patients' stories and (2) "reading" patients' stories in light of scientific knowledge.

In practice, a provider starts the hermeneutic circle by obtaining knowledge about her patient through the clinical encounter. She "reads" (interprets, understands, and applies) the patient's words and actions from her perspective as a healthcare provider situated in a particular clinical setting and within the larger context of biomedicine. But she also reads the patient from her perspective as a human engaged in a type of relationship that, like all relationships, involves interpreting, understanding, and applying the intentions and expectations of other persons. In other words, the knowledge obtained through the clinical encounter includes the structured knowledge recorded in a "history and physical," but it also involves the phenomenological knowledge that comes through confrontation with another person.

The next step involves a "turn" from the patient's story to the science-based frameworks for interpreting the patient's situation. Insofar as she is utilizing evidence-based medicine, she will take a methodical approach to "reading" scientific reports, systematic reviews, and meta-analyses, including by analyzing this literature for its validity and importance. But already in this procedural process she will begin to narrow her search for relevant reports by applying her patient's story to her "reading" of the medical literature. She will also utilize criteria for validity

and importance in ways that are most relevant in the context of her patient. The task of evidence-based analysis becomes anchored in the compelling questions that arise for her in thinking about the concrete situation of her patient; her patient becomes the guiding question. It is because she can approach the evidence in this way that she attains the freedom that “implies the general possibility of interpreting, of seeing connections, of drawing conclusions” (Gadamer 2004, 260).

And although the procedure looks quite different when she turns to experimental medicine or personalized medicine frameworks, this effort similarly involves discovering or developing the meaning of scientific knowledge, laboratory results, and predictive analyses in light of this particular patient’s story. Insofar as the results generated through various scientific paradigms provide general scientific knowledge, they are merely general; they are propositions detached from a context. But when they are treated as an authority that could cause the provider to change her practice in a particular circumstance, they communicate meaning that must be discovered and developed in specific cases.

As the provider begins to identify meaning by moving among the available scientific frameworks, she will then complete the circle by turning her hermeneutic questioning once again toward the patient. Now she will ask, “Given the meaning I discovered in scientific articles, laboratory results, and predictive analyses, how does my reading of this patient’s story change?” She may even find that there were relevant questions she had not previously asked. She will begin to notice ways research paradigms cause her to discover new elements in her patient’s story. Critically, though, she will also begin to notice ways her patient’s story carries meaning that has no analogue in research findings. And all of this effort will be guided by her ultimate aim: to help her patients realize health and well-being.

Knowing One's Way Around: The Case of Dennis

Gadamer's model is useful for our purposes because it explains in detail how providers are able to incorporate otherwise incompatible rational frameworks into a single clinical decision. Breaking down practical reasoning in this way, however, may create the impression that this is necessarily an involved process. While clinicians certainly encounter difficult clinical decisions that require exhaustive deliberation, this is not typical. In most cases, providers are able to work through the hermeneutic circle rapidly, taking advantage of the fact that they "know their way around" the relevant issues.

The vignette about Dennis from Chapter 1 helps demonstrate that working through the hermeneutic circle can be both rapid and indispensable. In this vignette, the hermeneutic circle began when Dr. Thompsen first met Dennis during his preventive care visit. Although this visit was not informed by a specific medical complaint, Dr. Thompsen certainly used her expectations about common medical problems among middle-aged men – her "prejudices" – to inform the types of questions she asked and the elements of the physical exam that she performed. At this stage, then, she was engaged in a hermeneutic process to understand Dennis, including which medical problems he was at risk for developing, which preventive measures might provide benefit to him, and which social or psychological barriers might pose barriers. This involved a "turn" from an interpretation of Dennis' story in light of her knowledge about men's health to an interpretation of the risks and potential benefits of whole sequencing in light of her developing knowledge about Dennis and his health needs. At this stage, Dr. Thompsen might have used one or more traditions of science-based practical reasoning to consider the risks and benefits to Dennis. She might, for example, have considered research findings from clinical trials examining outcomes for middle-aged men who had undergone whole genome sequencing. This might not

have required Dr. Thompsen to search for and read new studies; if she had read relevant research articles in the past, she might have been able to utilize the information she retained from them without undertaking a new literature search. She might also have used her understanding of genetics as a cause for illness to evaluate whether whole genome sequencing was likely to provide useful information for Dennis.

After this step, Dr. Thompsen made another “turn” in which she reconsidered Dennis’ story in light of her deliberation about the applicability of whole genome sequencing. Was there more information she needed to obtain from Dennis before deciding whether whole genome sequencing would be useful? Were there barriers or other considerations that might prevent Dennis from deriving benefit from this test? Through this process of practical reasoning she decided to recommend whole genome sequencing. The hermeneutic circle then took on a different form, involving the back-and-forth of a discussion between patient and provider about the risks and potential benefits of obtaining this test.

Once the laboratory results were reported to Dr. Thompsen, this hermeneutic circle continued to turn. Although she might have known a great deal about the available treatments for patients diagnosed with hemochromatosis, she might not have known whether the finding of homozygosity for a mutation in the HFE gene was significant in Dennis’ case. She would have turned to the available medical literature guided by the unique question that Dennis’ situation, in all of its complexity and particularly, posed for her search for knowledge. She would consider articles reflecting the evidence-based medicine tradition (Whitlock et al. 2006), those reflecting the experimental medicine tradition (Muckenthaler 2014), and those reflecting the personalized medicine tradition (Fullerton et al. 2012). She would interpret all of these in light of Dennis’ result and his clinical situation. Once she had increased her knowledge about this gene, she

would then turn to applying it to Dennis' situation. Had she already missed subtle signs of iron overload in Dennis? Are there efforts that she should undertake now to clarify whether hemochromatosis would be likely to cause problems? Based on available evidence and her mechanistic understanding of the disease, what interventions would be likely to provide more benefit than harm?

When I originally presented this vignette in Chapter 1, I did not draw attention to the process of deliberation that Dr. Thompsen put into deciding whether to recommend whole genome sequencing and how to respond to Dennis' HFE genotype. In some ways, this is the way we usually tell clinical stories. Even though most of us are aware that healthcare providers help make decisions of this sort, we tend not to delve into the details of this process. In some ways, Stout's account is the typical one: Providers do what works. They tinker.

Gadamer's account of the hermeneutic circle does not reject the image of tinkering. What it helps us understand is that tinkering is a remarkably complex process that, in the hands of an experienced clinician, can appear rather straightforward. The "turning" of the hermeneutic circle can incorporate a remarkable number of factors, but can take place remarkably quickly. So quickly, in fact, that many providers would struggle to describe what they do when they engage in practical reasoning. They simply "know their way around" the task. Philosopher Michael Polanyi, who influenced both Kuhn and MacIntyre, emphasized that human skill is a type of knowledge that is often "tacit." As he observed, "we can know more than we can tell" (Polanyi 1966).

The hermeneutic circle reflects Gadamer's attempt to make the process of understanding explicit. He believes that this model is normative; it reflects what we always do when we seek understanding about that which is "other." For the personalized medicine movement, it

highlights that practical reasoning should not be disregarded simply because its tacit nature causes it to appear straightforward. It is a crucial element in the effort to ensure that healthcare is helpful rather than harmful, and that it accounts for all of the knowledge – both tacit and explicit – that is relevant to this effort. In the next chapter, I will propose a number of ways this insight could be reflected in the vision for personalized medicine.

CHAPTER 6

A MODIFIED VISION FOR PERSONALIZED MEDICINE

Given this account of clinical reasoning using the image of the hermeneutic circle, the unique features of personalized medicine no longer seem to pose a problem for its integration into clinical care. We can see now that it is the hermeneutic know-how of clinicians that will create an opportunity for principles of personalized medicine to be incorporated into clinical decisions alongside evidence-based medicine, experimental medicine, and a whole host of non-scientific concerns. As shown in Figure 2, the provider would enter a hermeneutic process to “ask questions” of the evidence-based medicine, experimental medicine, and personalized medicine traditions. Within each tradition, she would utilize the body of scientific knowledge and rational framework appropriate to each tradition. She would then use a more general type of practical reasoning to understand how to integrate the insights she gains from each tradition, and use those insights to “ask questions” of the patient’s story.

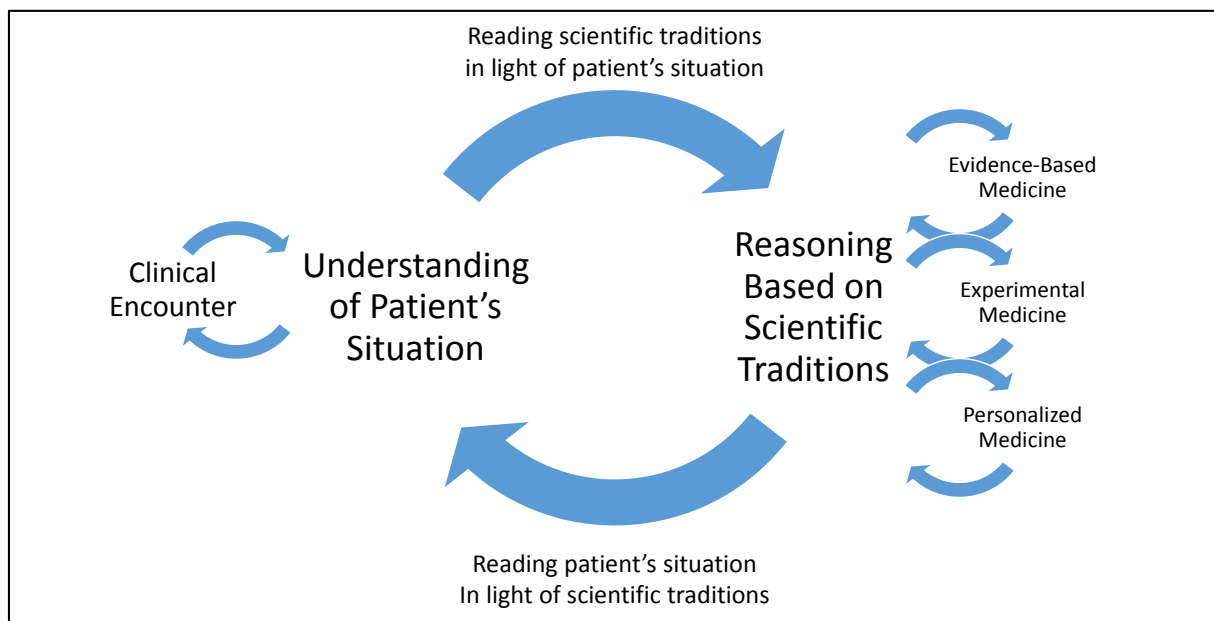


Figure 2: Schematic of the hermeneutic circle in clinical practical reasoning.

Unfortunately, this solution seems to solve one problem by sharpening another. In order to solve the problem of integrating three science-based accounts of medicine into clinical decisions, I have argued that a synthesis needs to occur through provider practical reasoning. The independent patient action model, however, precludes an opportunity for the provider to engage in practical reasoning. This conflict seems to create a difficult choice: either provide results through a provider who can help synthesize the available science, or return results directly to the patient with an automated, but incomplete, analysis.

There are at least two potential solutions to this problem. First, it is possible that a computer algorithm could synthesize the insights provided by the three science-based traditions of practical reasoning. This solution is suggested by the overall emphasis in the personalized medicine movement on technological solutions. Second, it is possible that individual patients could perform the practical reasoning needed to apply laboratory results to their health conditions. This proposed solution seems to fit well with the hands-on imperative, which emphasizes the opportunity for non-experts to learn how to handle problems on their own. In the two sections that follow, we will examine each of these proposed solutions in turn.

Practical Reasoning *in Silico*

In some ways, the idea that a computer could simulate the practical reasoning of an experienced healthcare provider is a topic that belongs to science fiction. The 1990's television show *Star Trek: Voyager* featured a holographic doctor whose clinical reasoning was driven by a starship's powerful computer, and the *Star Wars* series of movies featured a number of scenes in which medical care was rendered by "droids." We do not need to travel to "a galaxy far, far away," however, to find compelling ideas about the potential for computers to simulate the practical reasoning of healthcare providers.

As we have already seen, the systems biology paradigm is based on a conception of the body that construes biological mechanisms as nodes in a biological computer. Inspired by the thought of Alan Turing and Alonzo Church, this framework suggests that a silicon-based computer could simulate the physiological function of the body's organic computer. Given that extensive work is currently underway to understand how the neurological "wiring" of the human brain is assembled (2015a), it is likely that interest in simulating the computational function of the human brain, including the brain of healthcare providers, will continue to grow.

It is apparent, however, that a meaningful simulation of the human brain is a long way from becoming a reality. The writers of *Star Trek: Voyager* may well have been prescient when they predicted that such a technology would only become available in the 24th century. More importantly, though, even if a successful simulation could be created, and even if it were capable of simulating the extraordinarily complex processes that comprise the hermeneutic circle, we would still be faced with a number of problems. How could we know that such a simulation is dependable? What standard could we use for evaluating its performance?

The most important problem with simulating the brain of a healthcare provider, however, is the problem of choice. Practical reasoning involves choosing what is best in a particular circumstance. As we have seen, this involves making a number of smaller choices about which pieces of scientific knowledge are relevant to the circumstance of an individual and how they should be applied to a patient's situation. Choices of this type depend on a robust understanding of the individual patient and his or her situation. Practical reasoning also involves making choices about which rational frameworks to use, how to weigh them, and what to do with conflicting conclusions. In short, entrusting medical decisions to a computer simulation would

involve trusting such a simulation to choose wisely. Surely this is a convincing reason to involve a human in the process rather than a computer.

Even if a computerized simulation of practical reasoning is not in the offing, it may be possible to utilize a less sophisticated algorithm to generate a recommendation without attempting to simulate the hermeneutic circle of the healthcare provider. There are a number of technical approaches that could be taken to generate this type of recommendation, and many of these are based on predictive analytics. Consider, for example, that Amazon has used predictive analytics to create a successful “recommendation engine.” This algorithm utilizes the purchasing patterns of millions of Amazon users to predict what an individual user, with his previous shopping patterns, might want to purchase. The Amazon website then presents these recommendations to the user. This tool makes no attempt to formally simulate the decision-making process of shoppers, but rather attempts to predict (and ultimately influence) what the outcome of that process might be.

Adapting this type of approach to medical decision-making would be problematic for at least two reasons. First, this type of big data approach can be useful for supplementing or easing a decision-making process, but it cannot replace it. Amazon shoppers need to have the final say in deciding which items they actually buy, just as patients and providers ultimately need to decide which course of action to take. In other words, choice poses a challenge for this approach, as well. While electronic decision-support tools based on predictive analytics may one day prove quite useful for medical decision-making, they cannot replace this all-important final step.

Second, any single model designed to replace the hermeneutic process of clinical decision-making would be subject to the limitations of incommensurability. Consider, for example, the implications of using a big data-based algorithm to simulate a deliberative process

that integrates insights from the traditions of personalized medicine, evidence-based medicine, and experimental medicine. Such an approach amounts to interpreting the rational frameworks of the evidence-based medicine and experimental medicine traditions through the lens of the personalized medicine tradition. As we saw earlier, such an approach cannot truly incorporate the considerations of the other traditions, but is instead destined to misconstrue them.

Understanding in Relationship

If the independent patient action model requires a human rather than a computer algorithm to engage in practical reasoning, then perhaps patients themselves can provide the needed deliberation. After all, if providers are able to apply various types of knowledge to the medical condition of individual patients, then patients are also capable of doing this. This point is well-taken. Gadamer's account of hermeneutics emphasizes that while experts often utilize specialized techniques to understand the objects they are studying, his description of the hermeneutic circle is normative. It describes how humans, expert or not, always engage with "the other." In fact, he is very critical of the claim that expert methods are capable of attaining an understanding that more clearly approximates the "true" meaning of an object. On this account, we should reject the idea that the methodical hermeneutics of experts like physicians are fundamentally different from the "amateur" hermeneutics of patients.

At the same time, however, Gadamer's account acknowledges that our perspectives are always limited. He suggests that our ability to find meaning in that which is other is somewhat like our ability to see out to the horizon. It is because of our prejudice – our point-of-view – that we are able to see the world around us at all. But we are not able to see "everything;" there is always a horizon which marks the limit of our perspective. Still, there are ways that our encounters with new experiences allow us to change, and in some ways expand, that view.

This is not meant to imply that healthcare providers have a wider horizon – that their point-of-view gives them a more complete picture of the world. It simply implies that providers and patients “stand” in different places. Providers have a view of the world that encompasses a great deal of specialized knowledge, and this view is augmented by the fact that they “know their way around” specialized approaches to selecting diagnostic and therapeutic courses of action. Patients, on the other hand, bring their own perspectives to bear on questions of health. They know a great deal about the world they live in, and what they seek to achieve. Even more importantly, however, they “know their way around” their own lifestyles, what they are capable of doing to improve their health and how their body tends to respond to new situations.

For Gadamer, when two horizons encounter one another, the goal is not to choose who has the best or more comprehensive perspective but to work together to gain understanding. Gadamer emphasizes the potential for humans to expand their understanding through relationships. When two people work together, one “thinks along with the other from the perspective of a specific bond of belonging” (Gadamer 2004, 323). Medical care, then, involves a patient and a provider joining together in a process of deliberation with respect to a concern that becomes shared.

And by joining together to understand, a patient and a provider each learns something about how the other sees the world. Gadamer calls this a “fusion of horizons.” This image is apt, because it implies bilateral or symmetric movement. Patient and provider each learn about health by seeing something of how the other sees it. And because all understanding is self-understanding, this means that each comes to understand more about him or herself.⁷

⁷ MacIntyre comes to a very similar conclusion about the importance of feedback to our self-understanding. For an analysis of this insight in the setting of clinical practice, please see my article entitled “Dependent Rational Providers” in the *Journal of Medicine and Philosophy* (Brothers 2011).

In actuality, however, this clarification of the hermeneutic account of clinical practice does little to resolve the challenge of independent patient action. This reciprocal interpretation helps remove the provider from the center of our account of medical care, but replaces it with the provider-patient relationship. This account, too, views the provider as indispensable.

If we have learned anything in this exploration of personalized medicine, it is that the application of scientific paradigms to the concrete situations of patients is an extraordinarily complex task. In light of this complexity, perhaps it is absurd to expect that independent patient action could replace meaningful collaboration between a patient and provider in the vast majority of clinical situations. But it might also be premature to dismiss the possibility that both direct patient access to healthcare records and an increased sense of power on the part of patients could provide novel opportunities to improve health, even if only in specific circumstances. I will close, then, by proposing two revisions to the vision for personalized medicine that may still allow elements of the independent patient action model to contribute to improving health outcomes for patients.

Cooperative Empowerment

I have argued that the independent patient action model fails because important healthcare decisions need to account for multiple domains of scientific knowledge and practical reasoning. Returning predictive results directly to patients precludes the contribution of the provider point-of-view, which is an important element of synthesizing these concerns. There are at least two circumstances, however, when joint practical reasoning with a healthcare provider could become unnecessary.

First, there may be ways for patients to develop the practical reasoning skills they need to respond to certain laboratory results. Consider, for example, that patients with Type 1 diabetes

typically use portable glucometers to adjust their doses of insulin throughout the day. This management approach is usually informed by a protocol provided by a physician. However, patients with Type 1 diabetes also learn to make adjustments on the fly and respond to unexpected circumstances. These self-management skills depend on patients developing the ability to reason practically without the involvement of a provider.

Obviously, patients do not possess these skills just because they have Type 1 diabetes. And they do not learn these skills through brief didactic education. Rather, they develop them over time through interaction with a set of healthcare providers including endocrinologists, nurse practitioners, and diabetes educators. They also develop tacit knowledge about the way their body tends to react to insulin, carbohydrates in food, and other factors.

We can think of this phenomenon as the outcome of an ongoing process of fusing horizons. Through a process of learning and skill-building, the patient comes to extend her perspective to include domains of practical reasoning not “visible” to typical patients. Through this process she “learns her way around” her diabetes care, including learning how to independently manage most routine elements of this chronic medical problem.

This example of self-management in Type 1 diabetes can provide us with a number of insights relevant to personalized medicine. First, this example suggests that the personalized medicine vision of “patient empowerment” is too reductive. As we have seen, this account attributes central importance to access to information. Once barriers to access are removed, patients are assumed to have the resources they need to become empowered. However, earlier discourses on patient empowerment within the fields of diabetes education and health psychology have proposed more nuanced accounts of patient empowerment (Roberts 1999, Wallerstein 1992). Diabetes educators have proposed, for example, that patients become

empowered when “they have the knowledge, skills, attitudes, and self-awareness necessary to influence their own behavior and that of others” (Funnell et al. 1991). Based on this theory, health psychologists have generated considerable empirical evidence on successful techniques for helping patients become empowered. In one study, investigators provided participants with skill-building sessions aimed at supporting patients’ ability to ask questions during clinic visits (Roter 1977).

In more recent work, efforts in health coaching and chronic disease management have led to the development of dependable methods for empowering patients to improve their health. Health coaching programs allow patients to work with nurses or other specially-trained healthcare workers in order to build their skills and increase their motivation to manage their health (Huffman 2007). Chronic disease management programs use human resources, like health coaches, in concert with electronic tools to help patients manage their chronic diseases on a day-to-day basis (Ceriello et al.).

The vision for personalized medicine could benefit greatly by incorporating this more substantive account of patient empowerment. This account focuses on helping patients expand their horizon of understanding through approaches that emphasize “knowing one’s way around” the task of practical reasoning. In other words, an approach that emphasizes skill – “knowing how” – and not just information – “knowing that.” This is, broadly speaking, already the approach taken by healthcare providers who assist patients with type 1 diabetes, and could be adopted widely in an “era of personalized medicine.”

This account of patient empowerment would not necessarily restrict access to individual health information to those patients engaged in health coaching or a chronic disease management program. Some patients not involved in these programs may still find that access to their

laboratory results through online patient portals or PCHRs will be adequate to help them feel empowered to manage their health. But the vision for personalized medicine should not treat this as a “one-size-fits-all” solution. For many patients, patient empowerment will require a great deal more from healthcare providers and the healthcare system. For these patients, the personalized medicine movement should acknowledge that cooperative approaches to empowerment are likely to be far more effective (Brothers and Rothstein 2015). And, ultimately, it will take human attention to determine which empowerment efforts are best suited to each patient.

Reasoning vs. Routine

Even if the vision for personalized medicine comes to integrate a more robust understanding of patient empowerment, there still remains the question of when, according to the hermeneutic model of practical reasoning, predictive laboratory results could be returned without intervention or preparation from a healthcare provider. Although the hermeneutic model of practical reasoning provides an important rationale for limiting the use of such an approach, it does not preclude this altogether. Consider how practical reasoning proceeds in routine medical circumstances. As providers become skilled at moving within the hermeneutic circle – at moving between reading scientific understanding in light of patients’ stories and reading patients’ stories in light of scientific understanding – they notice that for specific circumstances they no longer need to engage in explicit deliberation. This is because they begin to develop expectations – prejudices – that allow them to easily identify the most promising treatment options for certain problems. This is because for certain medical conditions practical reasoning reveals virtually no elements of patients’ particularity that change the general treatment approach they recommend.

This tendency for certain elements of medical practice to become routine implies that other mechanisms can replace practical reasoning in these circumstances. Just because an intervention is routine, however, does not mean that practical reasoning is not needed. For example, providers may still be required to recognize routine circumstances when they arise, or more importantly to identify the subtle indications that an apparently routine situation is more complex than expected. In some ways, this vigilance for unexpectedly complex situations is one of the most difficult elements of primary care medicine.

Many routine practices in healthcare no longer involve the involvement of a physician, but still require oversight from another type of healthcare worker. These providers receive training on the skills and knowledge needed to determine when a “routine” intervention is appropriate, and to ensure that it is carried out properly. For example, the decision to perform a heel stick for newborn screening does not typically require an effort of practical reasoning from a physician provider. Still, the nurses and phlebotomists who perform this routine procedure need to utilize practical reasoning to determine when it is appropriate to perform this procedure and how to deal with non-routine situations.

The independent patient action model, however, typically depends on processes that are automated; there is no healthcare provider who makes an affirmative decision that returning a specific result to a specific patient is likely to lead to a positive outcome in this case. The protective role of the provider must be replaced by a set of policies. Which types of results should be automatically returned through online patient portals, and which should only be returned once a provider has reviewed them? What procedures should be used to allow providers to protect patients who are vulnerable to harm if otherwise routine results are returned automatically?

These questions highlight the challenge associated with personalized medicine's commitments related to access and action. The value this movement attributes to access to information is a powerful driver for utilizing new technologies to help patients become more involved in their healthcare. But it is simply not an adequate basis for the development of policies designed to improve health outcomes and protect patient safety.

Policies of this sort therefore need to be rooted in the evidence-based medicine and experimental medicine traditions. That is to say, local, regional, and national policy makers need to utilize a methodical, teleological approach to identifying results that are likely to benefit patients when they are returned automatically. To be clear, though, this does not just mean that we require evidence that such practices are safe. The teleological traditions in medicine focus on ensuring that practices adopted by providers and institutions are not only safe, but also improve health and wellness. Once clinical research becomes available on these issues, it should be used to drive policy decisions. Until then, psychological and physiological mechanisms should drive these deliberations.

In the domain of genomic results, such an effort is already being undertaken by ClinGen, an NIH-funded resource focused on identifying genetic variants relevant to human health. A workgroup assembled by ClinGen is working to identify standards for identifying genetic variants that could be returned directly to a patient through an online patient portal, and those that should only be returned after a provider has had an opportunity to communicate with the patient (2015b). Although national efforts of this sort will be helpful for addressing general concerns, but it will ultimately fall to local institutions to develop detailed policies on how results will be automatically returned to patients and how providers will be involved in this process.

The most effective methods for mitigating these concerns, however, are practices that integrate provider practical reasoning with online patient portals. Providers could, for example, be given the opportunity to flag results that are particularly sensitive, or patients who are particularly vulnerable. In these circumstances, the release of results through online patient portals could be delayed, giving the provider an opportunity to first return results using an approach she judges to be optimal. Another possibility are policies that allow providers to review results before they are returned. This practice would allow a provider to annotate results that are complex or misleading with contextualizing information that takes the individual patient's unique situation into account.

Another possibility, one that is already utilized in many healthcare systems, is to provide patients with a convenient way to communicate with their provider. When a patient receives a result whose implications are unclear, this type of tool allows her to communicate with her provider via e-mail or phone to receive the benefit of the provider's practical reasoning. The assumption that patients are able to identify circumstances when they require this assistance, however, needs to be verified under the framework of the evidence-based medicine tradition.

Finally, policies developed for online patient portals should account for diverse patient situations. Even patients who are empowered require additional resources in order to benefit from online patient portals. They need, for example, access to network-capable devices to view their results and the related recommendations. They must have adequate health literacy to understand this information and apply it to their situation. And perhaps most importantly, they must have the financial and social resources required to actually adopt the recommended course of action (Brothers and Rothstein 2015, Galbraith 2013). As long as the goal of medical practice is to help all patients improve their health and wellbeing, providers will continue to have a

responsibility to identify patients who are facing these barriers and provide assistance with addressing them. The transition to patient-centered health technologies will not absolve providers from their responsibilities; it will merely change how those responsibilities will need to be discharged.

From Vision to Standard of Care

Based on my account of the hermeneutic model of clinical decision-making, I have argued that healthcare providers play an indispensable role in most clinical situations, and that the importance of this role will increase as personalized medicine becomes more integrated into routine clinical care. This conclusion is based primarily on the observation that clinical decisions need to integrate multiple ways of approaching scientific knowledge. Practical reasoning performed by an experienced caregiver is the only dependable way to synthesize these different models into a single clinical decision.

Admittedly, my emphasis on the importance of healthcare providers seems to conflict with the emphasis in personalized medicine on patient participation. In the final analysis, though, it is not necessary for these priorities to be understood as conflicting. It is true that some elements of the vision for personalized medicine threaten to increase patient participation at the expense of careful application of insights from evidence-based medicine and experimental medicine. In this final chapter, however, I have proposed a number of innovative ways that patients can become more active in their healthcare while retaining the benefit provided by experienced providers.

While innovative, the general thrust of these ideas is to limit the “disruption” envisioned for personalized medicine. The emphasis on provider practical reasoning provides a powerful rationale for placing limits on free access to individual information. It also supports the retention,

in many circumstances, of direct collaboration between patients and providers. Medical practice in the “Era of Personalized Medicine” might not look so different from conventional medical practice. And in some respects this is probably a good thing. Given the improvement in health outcomes that existing medical practice is able to provide, it would be foolhardy to introduce disruption without careful and focused consideration of the consequences. What is required, I believe, is what Ken Goodman has called “progressive caution” (Goodman 1999, 221).

Personalized medicine should proceed with optimism, but also with prudence.

As we saw in Chapter 1, President Clinton predicted that it would be “the lives of our children” that would be most affected by genomic medicine. NHGRI director Eric Green echoed that message eleven years later by emphasizing that the benefits of personalized medicine would be realized primarily after the year 2020 (Green and Guyer 2011). The personalized medicine movement can bring those goals into reality by working now to increase the intentionality with which it draws on and works within the various traditions of medicine. In addition to innovative work in systems biology, scientists working on personalized medicine also need to build the evidence-base and mechanistic understanding that will one day guide medical practice. Clinicians and clinical researchers, for their part, will need to invest more time and effort into carefully considering how medical decisions are made, and how patient participation can be increased safely and productively. A remarkable future sits just over the horizon. By broadening our perspective, we may sooner bring it into view.

AFTERWORD

In January 2015, when my work on this dissertation project was nearing its completion, President Obama announced in the State of the Union address that he would pursue congressional funding for a research initiative focused on what he called *precision medicine*. This effort, according to the initial White House press release, would involve the creation of a large research collaborative focused on developing a repository of health records and genomic data from at least one million American patients (2015c). This biorepository would be designed to support research that would could lead to treatments “tailored to specific characteristics of individuals, such as a person’s genetic makeup” (2015c). *Personalized medicine*, it seems, had become *precision medicine*.

President Obama, however, did not introduce the term “precision medicine,” nor was he the first to apply it to the vision for medicine reflected in the name “personalized medicine.” This alternative term has been used, albeit with lower frequency, since the early days of the personalized medicine movement (Wasi 1997). In fact, many names have been proposed for this vision. In this dissertation, I have utilized the concepts captured by the name *P4 medicine* to demonstrate a number of features that comprise the vision for personalized medicine. Other proposed names have included genomic medicine, stratified medicine, and individualized medicine (Trusheim, Berndt, and Douglas 2007, Paul and Fangerau 2006).

It remains to be seen whether this proposed initiative, along with any new funding, will bring about a change in the preferred nomenclature for this vision. As I have argued in this dissertation, however, internal debates are of great interest because they reveal both areas important enough to debate, and areas where consensus is sufficient to allow meaningful disagreement. In this case, the proposal that this movement should adopt the name *precision*

medicine reveals at least one important trend that seems promising in light of the revisions to this vision I proposed in the final chapter of this dissertation.

Specifically, the name “precision medicine” eschews the rhetorical implication that interventions in this approach to medicine would be unique for each patient. In 2011, the National Research Council, a component of the National Academies of Science, released a report entitled “Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease” (2011b). The authors of this report observed that those who prefer precision medicine as a name for this approach often do so “because it is less likely to be misinterpreted as meaning that each patient will be treated differently from every other patient” (2011b, 12). In precision medicine, “the ultimate end point is the selection of a subset of patients, with a common biological basis of disease, who are most likely to benefit from a drug or other treatment, such as a particular surgical procedure” (2011b, 52).

In this way, the move toward the name *precision medicine* is promising not only because it communicates the scientific basis for this approach more accurately, but also because it emphasizes scientific paradigms accessible to provider practical reasoning. In the tradition of evidence-based medicine, practical reasoning involves the recognition that an individual patient might share important characteristics with patients studied in a clinical trial. The National Research Council’s interpretation of the term precision medicine implies that this approach would allow for groups of patients studied in trials of this sort to be divided into smaller subsets. Rather than an effort to eliminate clinical trials and practical reasoning based on them, this proposal could help refine this tradition.

In some ways, this model even emphasizes a possible link between evidence-based medicine and experimental medicine. According to the National Research Council’s definition of

precision medicine, subsets of patients might be generated based on “a common biological basis of disease.” In other words, biomarkers indicative of the specific biological mechanisms causing disease could be used in the stratification of patient populations studied in clinical trials. This conception of precision medicine might provide a fruitful way for linking the scientific paradigms that inform practical reasoning in the traditions of experimental medicine and evidence-based medicine.

In my preceding analysis of the personalized movement, I have been highly selective in identifying the elements of this movement that emphasize a novel interpretation of practical reasoning. I argued that the scientific paradigms reflected in genome-wide association studies and systems biology research support medical predictions that are not amenable to practical reasoning by healthcare providers. I further examined how this movement’s commitment to patient-centered health information technologies reflect its roots in the professional cultures of genetic counselors and medical genetics, as well as its broad influences in the digital age. My primary concern throughout has been that this emerging trend in the personalized medicine movement could contribute to the continued devaluing of provider practical reasoning, and ultimately could lead to practices and policies that produce more harm for patients than benefit.

This recent emphasis on the name *precision medicine*, however, provides some indication that this movement’s novel account of practical reasoning has not yet carried the day. Perhaps President Obama’s announcement is a first step toward a revised vision that embraces the critical role of provider practical reasoning. If this is the case, then this dissertation may prove a useful starting point for efforts parallel to the President’s Precision Medicine Initiative focused on developing a robust understanding of practical reasoning in the Age of Precision Medicine, and applying this understanding to the development of prudent policies and practices.

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