Rethinking Ethics Assessment in Health Technology Assessment: A Nonlinear Approach

Aimee Zellers

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RETHINKING ETHICS ASSESSMENT IN HEALTH TECHNOLOGY

ASSESSMENT: A NONLINEAR APPROACH

A Dissertation
Submitted to the McAnulty College and Graduate School of Liberal Arts

Duquesne University

In partial fulfillment of the requirements for

the degree of Doctor of Philosophy

By

Aimee D. Zellers

May 2015
RETHINKING ETHICS ASSESSMENT IN HEALTH TECHNOLOGY

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Approved April 30, 2015
ABSTRACT

RETHINKING ETHICS ASSESSMENT IN HEALTH TECHNOLOGY ASSESSMENT: A NONLINEAR APPROACH

By
Aimee D. Zellers

May 2015

Dissertation supervised by Henk ten Have, PhD, MD

The primary question this dissertation aims to answer is how ethics can be meaningfully integrated into health technology assessment (HTA). The contribution of this dissertation is two-fold. The first is to provide an honest and critical evaluation of current HTA practices, including those that involve ethics assessments and those that do not. This evaluation will identify gaps and deficiencies in current HTA practices. The second contribution of this dissertation is to propose an approach for meaningful ethics assessment. The nonlinear approach contains five methodologically sound phases aimed to support both ethics assessment and scientific progress. The approach will be applied to emerging genetic health technologies, with a specific hypothetical application to expanded genomes.
These contributions will be systematically addressed in the following chapters. The first chapter will provide a general introduction to the connection and relationship between technology and values. It will examine value statements and normative statements that are made about technology, including whether technology is value-neutral, value-free, or value-laden. This chapter will ultimately argue that technology is value-laden, and the relationship between society and technology is but two sides of the same coin. Chapter two will address current HTA practices in both the USA and Europe. A distinction between technology assessment (TA) and HTA will be reviewed, as well as a number of basic procedural aspects in HTA. Chapter three will critically assess the current methods of ethics assessment in HTA, including the role ethics plays, identify their shortcomings, and provide a justification for rethinking ethics in HTA. In chapter four, the foundations, methodology, benefits and limitations of the nonlinear approach are delineated. The nonlinear approach consists of five phases with methodologies grounded in multiple disciplines. A detailed description of the function and projected benefits of the nonlinear approach will be given in Chapter five. Chapter five will apply the nonlinear approach to an emerging genetic health technology. Chapter six will consist of a brief summary of the arguments, address the strengths, weakness and feasibility of nonlinear approach, as well as concluding remarks regarding the future genetic health technologies and the role of ethics assessment.
DEDICATION

To my mother, Denise Zellers, and father, Kent Zellers, for their unconditional love and unwavering support.

To my husband Todd, and our dogs Madison and Ace, for their understanding, encouragement, and love.

To my family, immediate and extended, whose support will always be remembered and cherished.
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Chapter 1: Society, Technology, and Values

1.1 Introduction

Over the past five decades, advances in technology yielded a plethora of significant and innovative devices and interventions in healthcare. Breakthroughs in biotechnology, antivirals, surgical interventions, organ and tissue transplantation and generation, and diagnostics improved not only patient care but also efficiency, and effectively advanced healthcare delivery. The term health technology applies not only to those devices and innovation used in the clinical setting, but also to a much wider range of fields including health promotion, preventative health, and rehabilitation, as well as all drugs, devices, substances and processes that may affect one’s health. Assessing each new intervention, device, or process is an important and, at times, challenging task. However, it is not always guaranteed to happen. Health technology assessment (HTA) generally uses an interdisciplinary process that includes researchers, investigators, stakeholders, and other relevant parties to assess the medical, social, economic, and ethical issues in new health technologies in an effort to guide policy development. There is no standard approach; the scope and role of HTA is still hotly debated. Most HTA approaches focus on two aspects, safety and economic issues, and often limit the assessment of ethical and social issues or ignore them altogether.

There is consensus that systematic HTA is important; and there is a growing acknowledgement that ethics should play a larger role in assessment. The question is how this can be effectively accomplished. Many articles provide ideas on how to integrate ethics into existing HTA practices, as well as develop entirely new approaches.
While many of these suggestions and frameworks are useful, they are often incomplete or deficient in some way. It is imperative to address emerging technologies now, rather than later when the rapidly changing pace of technology may obscure important ethical considerations. Ethics should be an integral part of HTA. Many concerns that arise under the categories of benefit, risk and cost effectiveness are inextricably linked to moral concerns. Nearly everyone values health and considers it a societal good. Emerging health technologies directly impact health; thus, a variety of perspectives must be taken into account in technology assessment because it is relevant to everyone. Technological advancements in healthcare influence much more than the medical field alone. In many instances other aspects of society are affected as well, specifically our legal codes, economy, and societal norms.

Part of this inextricable tie between HTA and ethics is the very nature of technology itself. Technology is value-laden. If technology truly revolves around purposeful human action then it is never value-neutral. Many agree that the integration of ethics into HTA is both necessary and beneficial; the question is how to go about developing an effective ethics assessment process. This process is needed now more than ever given the exponential growth of technologies applicable to human health. A sound HTA model is necessary to address emerging technologies.

The next major technological watershed is the creation of a protocell or an artificial cell. Protocell research is still in its infancy. Craig Venter made a breakthrough with the creation of the synthetic cell in 2010. However, a true bottom-up protocell—one created from spontaneous assembly in inorganic matter—has yet to be created. The application of a protocell, more so than its development, presents the greatest risk the
environment, human health, and society. Therefore, to responsibly and comprehensively consider risks, the potential applications of protocell research must be assessed. The reason protocell creation is the next major watershed is because it will give researchers the capacity to synthesize life in a laboratory. Also, the creation of protocells is the first step towards the next major development in intelligent machines. Some scholars predict that protocells will help bridge the gap between the living and nonliving, the animate and inanimate. This would allow scientists to dramatically increase the capacities of both living and inanimate systems. If these technologies can be harnessed, there are an abundance of practical applications including, environmental, pharmacological, and medical diagnostic functions. One specific benefit will likely be the advancement of human health. Better-quality or personalized drugs and vaccines and their delivery methods could be adapted to pharmacogenomics and improve through the use of protocells. Protocells could be used as vehicles for drugs tailored to an individual’s genetic code to combat a specific disease or disorders such as immunodeficiency virus and cystic fibrosis. This type of scientific breakthrough would greatly assist research efforts in gene therapy and other emerging genetic health technologies. If HTA does not adequately take ethics into account for existing technologies, then it is not likely that current HTA approaches will be able to adequately address emerging technologies. Emerging technologies that are likely to be applied to human health devices and interventions need to be assessed much earlier in the design and development process.

This dissertation has two primary aims: first, to understand the nature of the relationship between emerging genetic technologies—specifically those technologies that impact protocells and gene therapy—and society, and second, to propose a reasonable
way to conduct ethics assessment in the research and development phases of these technologies. In order to accomplish this one must first define “society” and “technology.” Both terms are value-laden; and understanding these values enables one to make judgments about each.

Chapter One lays the foundations for the thesis. In order to accomplish this, there are several central concepts one must explore, including the complex relationship between technology and society. When two concepts appear to have a natural association we tend to think of them as related. However determining the nature of that relationship can be very challenging. Society relies heavily upon technological advancements, most of which it values intrinsically without openly addressing the ethical considerations associated with adopting the advancements to everyday life. Consciously addressing the relationship between society and technology exposes the ethical considerations, and forces society to acknowledge the impacts.

1.2 Technology

This section examines the nature of technological development in relation to norms and values. In everyday language, it is common to speak as if technology is good or bad. Individuals use normative terms to describe and assess it. Norms are those social behaviors that individuals in a given society are expected to follow. Values, while very similar to norms, are comprised of those value judgments individuals make surrounding personal preferences and beliefs about what is good or bad, right or wrong. The important question is whether technology is value-free, value-neutral,\(^1\) or value-laden.\(^2\) As William Petty wrote in *Political Arithmetic* that “Ships, and Guns do not fight
themselves, but Men who act and manage them do."\textsuperscript{3} This perspective suggests that humans use technology for good and bad purposes, and perhaps ships and guns are not endowed with any particular values until they are put to use. This represents the value-neutral concept.\textsuperscript{4} Value-free refers to the idea that social, ethical, political and legal values have no influence on science. Scientists should not pay attention to these additional considerations; rather, they should focus solely on progress and the advancement of scientific knowledge.\textsuperscript{5} Value-laden refers to the notion that technology is inextricably tied to society’s values and norms; the latter are inherent within the technology.\textsuperscript{6}

Technological developments are a hallmark of the twenty-first century. Significant debate ensues among scholars in the philosophy of science and technology as to whether technology is value-free, value-neutral, or value-laden. Two other important debates also directly impact value considerations. The first is the relationship between means and ends as it pertains to technology. The second is the relationship between technology and society. The following section provides a conceptual clarification of technology, as well as the arguments surrounding norms, values and technology.

1.2.1 Description of technology

Technology is a broad concept that describes the knowledge of tools or equipment and how their use affects “the ability to control and adapt to the social and political environment.”\textsuperscript{7} Technology is generally applied for a specific purpose. It is often characterized as the application of science to practical needs. In the nineteenth century, individual physicians and scientists most often produced medical innovations. This
paradigm has now expanded in the past generation to include physicians, engineers, industry leaders, national governments, and private entrepreneurs in the development of technology for medical advancements. Currently, the application of technology to medicine goes far beyond diagnostics. Technology has the ability to “process information and present it in comprehensible forms; to treat disorders effectively when diagnosed; to monitor treatment and evaluate its efficacy; and to prevent disease.”

Michael Anbar, in *Penetrating the Black Box: physical principles behind health care technology*, notes that health care technology evolves in two primary ways. First, it evolves in response to a particular medical problem: technology is developed or improved to resolve the specific medical problem. Second, a developed or existing technology can be applied to a specific medical problem for which its use was not originally intended, and thus provide new or better results. The adaptation of existing technology, as well as the development of new devices and techniques, assists medical practitioners in achieving two primary goals: gaining an accurate assessment of the state of the patient; and, in turn, alleviating the patient of their physical or mental infirmity. There are many benefits of technology in its medical applications. Anbar offers three examples that clearly demonstrate this including the refinement of prosthetics, surgery, and chemotherapy. Technology benefits the patient by providing services and therapies, and the ability to improve and refine both. Anbar contends that if technology is going to be used appropriately, three criteria must be met: there must be an understanding of the physical aspects of the technology—that is, whether the technology works. Second, the efficiency and usefulness of the technology must be assessed against alternatives. Finally, the risks, including side-effects and financial costs, must also be
evaluated against alternatives. Technological advancements in health care are not strictly limited to influencing the medical field. In many instances, other aspects of society are affected as well, particularly legal codes, economy and societal norms.

1.2.2 Norms and technology

In the past, technology was thought to be a means to an end. Some scholars argue that technology is now an end to itself. As a result, technological advancements become so significant that individuals comprising entire societies adapt their lives to it without a second thought.

Martin Heidegger, an influential twentieth century German philosopher, impacted many different areas of philosophy including phenomenology, political theory, existentialism, and postmodernism. He also produced one of the most pivotal works in the philosophy of technology. His essay, entitled *The Question Concerning Technology*, was not only foundational, but also highly controversial. In this essay, he addressed three important aspects of technology: the activity of technology; the ends of technology; and identifying the means used to achieve technological ends. In asking these questions, Heidegger did not attempt to demonize technology in any way. Yet, he did caution that technology could present a danger of sorts. However, he did not simply refer to the harms and benefits of specific technologies; rather, he referred to the danger technology posed to the understanding of individuals, their sense of being, and their understanding of their existence in the world—in a word, their ontology. This technological lens through which one views the world dramatically impacts one’s perception and understanding of ontology, and tightly ties one to the constraints of efficiency. The recognition of this way
of thinking leads one to understand how very much technology shades one’s understanding of existence and worldviews. Heidegger called this “revealing;” technology was a way of revealing. He argued that one begins to see their world, other humans, and nature simply as other resources. This led Heidegger to conclude that technology is not neutral; rather it is a way that one understands themselves in the world. When individuals recognize this framework for what it is, the process of thinking outside of the framework can begin. At this point, values existing outside of the technological framework—other than efficiency—can have meaning in the world and individual lives.\textsuperscript{14}

1.2.2.1 Technology as value-free or value-neutral

The primary distinction between value-free and value-neutral is that the former rejects any association of values with science and technology. The value-neutral position, while there are varying degrees, generally asserts that technology has no inherent value but might be utilized by humans for good or nefarious purposes. The value-free position is most often applied to science exclusively, as it is often difficult to maintain that the use of technology has no moral or ethical bearing.\textsuperscript{15} This section will focus on the value-neutral arguments, as they are the stronger than value-free ones.

There are a number of arguments supporting the value-neutral position, which has resulted in its growing acceptance among scientists. First, a decision is made. The individual chooses whether to develop or utilize technology. Second, existing technologies can be adapted for new uses for different purposes. Again, one makes that choice. Third, and most controversial, is the argument that technology is based on
science; and science is value-neutral. Thus technology is inherently value-neutral. To the second point, there are times in which one does not have a choice regarding the use of a particular technology. For example, if an individual is dying, and a specific medical device is required to save the individual, then there is no choice whether to use the technology, or perhaps on a very limited range of options. To the third point, if science is considered value-neutral, that fact that technology has its basis in science does not necessarily make technology value-neutral. To the contrary, what makes technology value-laden is its function. To ignore the function of technology is to ignore its inherent characteristics.

When humans use and develop technologies, whether aware of it or not, they are making choices about values. For example, when scientists developed dialysis machines, the resultant implication of being able to sustain life, despite kidney failure, is adjudged good or beneficial. Likewise, the development of weapons of mass destruction implies that on some level it is beneficial to kill groups of people or subdue them with the threat. Depending upon one’s perspective, such goals are deemed worthwhile or valuable. Disregarding or completely ignoring the intersection of values and technology can lead to the development of unchecked values. There is a very real danger in assuming technology exists in value-free or value-neutral space. The following section will reject the arguments supporting technology is value-free or value-neutral and will offer instead that technology is inherently value-laden.

1.2.2.2 Technology as value-laden
Current technologies are developed and produced with a particular function in mind. Bjørn Hofmann, a prominent Norwegian bioethicist, gives the example of bacterial weapons and respirators to demonstrate this point in the article When means become ends: technology producing values. The purpose for creating bacterial weapons is to harm other human beings. The purpose for creating a respirator is to sustain artificial respiration. Not only do these two technologies have specific intended functions, but they also promote specific values. In the case of bacterial weapons, Hofmann concludes that it is good to hurt people by making them sick or causing death. In the case of respirators, it is good to provide artificial respiration for those in need of it. There are obvious health benefits surrounding the use of respirators. These technologies invoke specific ethical questions about their use. When considering broader technologies, those with multiple and varying applications and capacities, such as genetics and emerging genetic health technologies, Hofmann notes that there are more general questions regarding good and bad, or appropriate and inappropriate, as opposed to those particular questions raised by technologies with a specific function. For example, genetics can be very beneficial to advancements in human health. However, it can also be used for controversial or, at worst, nefarious purposes. For example, diagnostic ultrasounds can be used for screening fetus to determine any malady with the intent to abort a less-than-healthy fetus. One must ask whether genomic screening, diagnosis, and in the near future modification or engineering, is good or bad, and ethically acceptable or impermissible.

Values and norms are important to recognize and evaluate because they reflect current social context. Considering ethics at the macro level can illuminate ingrained,
Understanding underlying values and norms raises questions surrounding the term ‘normative’ and what precisely it means. Jonathan Dancy, a British philosopher, proposes an adequate characterization of ‘normative’ that will be used throughout this dissertation. According to Dancy, what is normative has to do with the different facts about the world and how those facts impact actions, desires, and beliefs. A normative fact or statement is what he terms a “second order fact.” This means that facts about the world or facts about a particular technology have relevance to human action, belief, or wants. Dancy is not trying to establish a paradigm distinction between what is normative and what is purely non-normative. Rather, he is trying to accurately capture facts that are commonly understood and have practical implications. They necessarily have to include the facts pertaining to what particular individuals believe, want, and do. Desires and beliefs form a very important part of behavioral motives. Individuals often speak of technological artifacts as having normative features. One might hear a college undergraduate commenting “this is a good smartphone” or “this is a bad tablet.” Whether it is a good smartphone cannot be analyzed as well as the statement that “it has certain features,” and these features make it the case that the person, or any person, has a reason to use it. The latter is a fact-value characterization. The connection of action with desire is an important philosophical tradition dating back to David Hume, as Maarten Franssen, notes. Desires can be evaluated morally but are indifferent to rational reasoning and grounds.
Logically, the fact-value and is-ought distinctions are very similar; some might even say essentially the same. However, Sven Ove Hansson, professor of philosophy and chair of the Department of Philosophy and History of Technology at the Royal Institute of Technology in Stockholm, Sweden, notes that normative concepts and value concepts are not the same. He provides a very interesting example: if someone says they believe one should do x, and then follow it up by recommending that they do not do x, then one would conclude that they are behaving erratically or at least inconsistently. Yet, one might say that doing certain acts would be good; however, they might not recommend doing those certain acts. There are many reasons why this could be the case, Hansson suggests actions that are of a supererogatory nature fall into this categorization, and one would not conclude that this person is acting inconsistently. The connection is that, logically, it is not sound to conclude that something ought to be a certain way because it is a certain way or exists in a certain way. Likewise, it is not sound to conclude that something has a defined value based on its facts.

Hansson makes another critical observation. He suggests that presuming an artifact is good is not always easily reconcilable with the notion that technology should be treated as value-neutral. He notes that the way one thinks and speaks about technology—in the patterns of thought that are clearly encoded in our linguistic practices—are more positive towards technology than negative. This implies that categorizing technology as value-neutral is not an accurate categorization. Rather, it is an inconsistency, or tension, between the characterization of technology as neutral and the way in which humans talk, think, and apply values to technological artifacts. Hansson concludes that language is more easily compatible with a positive view of technology
than with a value-neutral view of technology. Furthermore, he goes on to argue that using technology as an extension of human capacities and capabilities is itself a positive value. It is not considered, at least in Western society, as being value neutral. To accurately describe the way one thinks and talks about technology is not the same as to say “technology is neutral but it can be used for good or bad purposes;” rather, Hansson writes it would be more accurately categorized by saying “most technology is good but there is also bad technology and good technology can be used for bad purposes.”

1.2.2.3 Analysis

Adopting a specific view of the nature of technology will directly impact any perspective on the relationship between technology and society. The goal of this endeavor is not to generate a list of characteristics that categorize some technologies as “bad” and others as “good.” Rather, the aim is to make an observation applicable to all technology. The valuation of technology as a whole differs from the valuation of specific technical artifacts. Technology raises questions of values that are general and not artifact-specific. However, certain technologies raise value questions, which are specific to that technology and cannot be separated from it. Hofmann makes the argument quite simple—these ethical issues are related to the function of the technology. “Every technology has a function, and every function is related to a purpose and value.” The arguments surrounding the purposeful function of technology, linguistic patterns, and the valuation of technology make a stronger case that technology is value-laden than do the arguments against this position. The value-laden nature of technology, specifically health technology, will be further explored in chapter 3.
1.3 The relationship between technology and society

As a result of this analysis it is clear that in order to address the question of technology in medicine in any meaningful way one must first examine the relationship between technology and society. Five dominant perspectives on this relationship exist, including: technological determinism, social construction of technology (SCOT), actor-network theory, systems theory, and structuration theory. The aim of this section is not to solve the puzzle of the relationship between technology and society; rather, it is to arrive at some well-founded observations and generalizations that can provide the basis for understanding the value nature of technology and its relation to society. Provided and assessed below are high-level, broad overviews of these five theories. Having an understanding and holding an position on this issue will shed light on the role of ethics in HTA, and how to better engage or conduct ethics assessment in HTA, if at all.

1.3.1 Technological Determinism

Technological determinism encompasses particular ideas about technology, determinism, and their combination. Technology, as described in the previous section, consists of any tools, equipment, or artifacts, as well as the requisite knowledge to utilize these. Determinism is a reductionist philosophy. As such, it stands contrary to other doctrines such as free will and social constructivism. Taken together, the term “technological determinism” is the idea that technology directly alters, shapes, and reshapes human behavior. This impacts actions, thought patterns, values, and codes of
conduct, as well as society as a whole. Under this principle, technology is the only, or at the very least the primary, driver of human behavior and society.\textsuperscript{30}

There are several different accounts and varying degrees of technological determinism that take on different meaning in different contexts. Two dominant versions include those introduced by Jürgen Habermas and Van Inwagen. The most common explanation of technological determinism attempts to explain technology’s influence on history and modern society. Jürgen Habermas, in \textit{Toward a Rational Society}, suggests that technological advancement occurs without the requisite human reflection and recognition of the impact on political and ethical structures and discourse. As Heidegger noted, efficiency seems to take hold on the technical deterministic worldview. Without being aware of this or understanding the implications, it may very well be argued that society is driven by technology, to no rational or coherent ends, only efficiency.\textsuperscript{31} When efficiency becomes the primary value one loses all sight of ends. Habermas explains that society can utilize ethical considerations in the development of technical artifacts and thereby willfully control the norms associated with technological development. Those individuals who develop new technologies, or adapt existing ones, have aims and specific judgments about both private and public goods.\textsuperscript{32} Furthermore, Habermas argues that the characterization of technology as autonomous is not correct due to several observable factors, one of the most influential being public investments. He gives the example of the United States investing heavily in military defense and space programs.\textsuperscript{33} Habermas concludes that neither technological development nor society can exclude the other. However, he describes technology as a “project of the human species as a whole.”\textsuperscript{34} Thus, technology takes on a non-social aspect. For Habermas, it is not that there is too
much technology or too much dependence upon it; rather, it is the way humanity utilizes technology in society. He concludes that technology is neutral; it is simply a means for completing human tasks.\textsuperscript{35}

Another interpretation of technological determinism comes from philosopher Peter Van Inwagen. In \textit{An Essay on Free Will}, he argues that “given the past, and the laws of nature, there is only one possible future.”\textsuperscript{36} Bruce Bimber \textit{Karl Marx and the Three Faces of Technological Determinism}, and G. A. Cohen in \textit{Karl Marx’s theory of history; a defense} provide a useful discussion on Van Inwagen. They suggest that technology itself has a causal influence on social practices. Taking the past as well as the laws of nature into account, they contend that there is only one possible future course for society and social change.\textsuperscript{37} Hence, technology determines societal development. As with many theories, there are varying degrees and extremes in these interpretations. Some claim the absolute primacy of technology and its sole control over society. Other scholars suggest that there are multiple drivers of society, yet technology is by far the dominant driver.

\subsection*{1.3.2 Social Construction of Technology (SCOT)}

Social construction of technology is an approach that emerged in the 1980s. Social construction theories maintain that “the truth of scientific facts and the working of technical artifacts are studied as accomplishments—as being constructed rather than as intrinsic properties of those facts and machines.”\textsuperscript{38} There are two prongs to the social construction of the technology. First, it studies technical change in society. Second, it analyzes the relationship between the development of technology and society. There are
mild and radical versions of social construction of technology. Mild ones emphasize the inclusion of social contexts when assessing technology. Radical versions claim that technology is entirely socially-constructed. This means that technology development and all meaning and use prescribed to it, derives from the existing social structure and related processes.  

Wiebe Bijker, Professor of Technology and Society at Maastricht University, argues that any techno-sociological framework ought to fulfill five requirements. First, it must provide an account for technological change. Second, it should explain constancy and lack of change throughout history. Third, it must also evaluate failure and success with symmetrical modes. Fourth, the actor’s approaches and constrains must be considered. Finally, the framework must shun distinctions based on a priori assumptions. Bijker’s social constructivist framework is primarily a descriptive model that includes steps to analyze and understand society, technology, and their relation to each other. In this schema, the initial focus is on an artifact. An artifact is essentially an invention or technology. It has an ever-changing character. The artifact takes on a different meaning depending upon the perception of the relevant social group. Each group changes the meaning of the artifact, thereby demonstrating a new set of problems and solutions that may or may not be addressed.

Social groups are very relevant for gaining a full grasp of the development of technology. The first step in Bijker’s model is to identify the relevant social groups through the “snowball” and “follow the actor” rules. The logic is that social groups are relevant for actors and thus relevant for analysis. The second step is to discern and describe the meaning of the artifact for all identified social groups. Bijker suggests that
an effective method for this would be to focus on the problems and solutions that the relevant social groups identify.\textsuperscript{43} The third step is to use the descriptions for a “sociological deconstruction” of the artifact. From this deconstruction the interpretative flexibility can be analyzed. Identifying and understanding interpretative flexibility of an artifact guides the way to accurate social analysis of technology.\textsuperscript{44} This is truly the first stage that goes beyond identification and toward analysis. After an artifact is deconstructed into different artifacts, their further development must be determined. For example, one artifact as it is perceived by the relevant social groups may become dominant while others fade. The key to understanding interpretative flexibility is to grasp that relevant social groups do not just perceive different aspects of the same artifact; rather, the meaning the group gives to the artifact is actually what constitutes the artifact. Therefore, Bijker notes that there are as many distinct artifacts as relevant social groups. An artifact does not exist unless it is given meaning by a social group.\textsuperscript{45}

This concept has its philosophical underpinnings in the principle of symmetry. One of the problems with traditional sociological approaches is the asymmetry of the analysis.\textsuperscript{46} Sociologists should use the same conceptual framework to evaluate truth and falsity of claims and beliefs, and in this case to evaluate the successful and failed artifacts. This is a similar notion to the historical adage that the victors of war write the history, not the losers. In this context, sociologists should avoid accepting a claim because it is the presently accepted belief. False beliefs, and in this case unsuccessful inventions and technology, can be immensely useful to study. They can provide a new perspective with regard to social implications as they can demonstrate social dynamics
that were previously overlooked. The concept of interpretative flexibility produces this radical social constructivist approach to the sociology of technology.

The final step is then to establish the social construction of the artifact. This is accomplished by evaluating the closure process. This process ends interpretative flexibility due to the successful stabilization process in the relevant social groups. The concept of closure is closely connected to interpretative flexibility and is best reflected through inter-group analysis of artifact development. As mentioned above, the concept of interpretative flexibility is best evaluated in light of the meaning and problems relevant social groups attribute to an artifact. Closure in technology begins to occur when a relevant social group perceives a problem with the artifact as being solved. This process involves stabilizing the artifact. To close a technologic controversy or problem is to solve the technical problem and glitches perceived by a relevant social group, thus inducing a stable set-up.

Bijker introduces a wide interpretation of the “technological frame.” This is important because the concept must include non-engineers and non-scientists. It also must have a wide breadth in order to recognize different problems and available solutions. Bijker claims that a technological frame is “a combination of current theories, tacit knowledge, engineering practice such as design methods and criteria, specialized testing procedures, goals, and also handling and using practice.” This concept describes the interaction between all the relevant actors. The technological frame is not simply the individuals involved or system as a whole; rather, it is the interaction between the actors, not the actors themselves. Technological development is a two-sided coin: one side is social impact and the other is social shaping. Bijker uses the concept of technological
frame to demonstrate this. The technological frame of a social group is shaped by an artifact’s development and stabilization within that social group. This demonstrates social impact. On the other hand, technological frames also influence and, to differing degrees, determine the design process within a specific group. This demonstrates social shaping. This holistic approach forms the concept of the technological frame.\footnote{53}

The sociological study of technology is not simply a combination of different social and technical aspects shoved together, nor is it simply applying an existing social model to technology. What Bijker has laid out is a mechanism for analysis that engages a “sociotechnical ensemble.”\footnote{54} He argues that this approach allows one to find the socially-constructed character of an artifact while simultaneously being able to determine what constitutes a stable set-up. Bijker concludes, “society is not determined by technology, nor is technology determined by society. Both emerge as two sides of the sociotechnical coin, during the construction processes of artifacts, facts and relevant social groups.”\footnote{55}

\subsection*{1.3.3 Actor Network Theory}

Actor network theory contends that all relevant entities and values linked to an invention or technology at its final stages of development have, in fact, been there from the start. From the very inception of an invention the technical, scientific, social, economic, and political considerations and characteristics are indivisibly integrated in a single unit or network. All actors are not sporadically introduced but, rather, present from the start; they are “interwoven in a seamless web.”\footnote{56} Michel Callon, Professor of Sociology at the École des mines de Paris, argues that some engineers can actually act as
sociologists during the process of innovation and invention. An actor network is not reducible to a single individual, entity or network. It encompasses many heterogeneous components including individuals, organizations, and animate and inanimate objects, all connected for a particular reason at a specific time. In short, “an actor network is simultaneously an actor whose activity is networking heterogeneous elements and a network that is able to redefine and transform what it is made of.”

He explains this through the example of the introduction of the electric car (VEL) in France in the early 1970s. The project engineers designed the car with the characteristics of the vehicle they desired, as well as with the characteristics of the social context in which the car would exist. Thus scientific, technical, economic, and social considerations were present from the start. The actor networks give rise to the simultaneous evaluation of society and technology together. This concept can also be used to explain the phases of invention and institutionalization.

The thrust of Callon’s theory is the “actor network.” An actor network is not a reducible single individual, entity, or network. It encompasses many heterogeneous components including individuals, organizations, and animate and inanimate objects all connected for a particular reason at a specific time. Callon explains “an actor network is simultaneously an actor whose activity is networking heterogeneous elements and a network that is able to redefine and transform what it is made of.” This is beyond the current scope of sociological tools. He utilized the actor network through the lens of the engineer-sociologist, which is the capacity of engineers to act as sociologists. Callon argues that one must abandon traditional sociological paradigms and tools. The actor networks give rise to the simultaneous evaluation of society and technology together.
This concept can be used to explain the phases of invention and institutionalization. The actor network is essentially taking Hughes’ technological systems approach one step further. It avoids certain methodology problems like distinguishing the system from the environment and recognizing patterns.\textsuperscript{60}

To organize these heterogeneous associations in actor networks, Callon identifies two necessary elements: simplicity and juxtaposition. Theoretically speaking, reality can be infinite; however when one addresses a specific case at a specific time, those actors have a limited number of possible associations. These associations will have a finite number of discernible characteristics. This element allows for a finite number of associates to be identified and evaluated. The simplifications are only useful in an actor network if they are juxtaposed. Juxtaposition, the second necessary element, places all the relevant entities in relation to one another thereby defining the conditions of operation of the actor network. Moreover, this juxtaposition of associations supports “coherence, consistency, and structure of relationships that exists between the components that comprise it.”\textsuperscript{61} If a network did not exist, each component would individually fail. Callon’s actor network gives rise to the evaluation of society and technology simultaneously; society and technology impact and shape each other.

Those opposing this approach maintain that during the process of innovation there are areas and processes that are uniquely technical and scientific which are distinct from other activities and stages that are economically- or commercially-minded. Others argue that these heterogeneous components are interwoven by the end of the technological development, but are introduced and integrated throughout the development process.\textsuperscript{62}
1.3.4 Systems Theory

Systems theory posits that technological systems both shape society and are socially constructed. Technological systems include artifacts, organizations, inventors, engineers, scientists, managers, economists, scientific processes, research programs, and other relevant groups. Technological systems solve problems using everything at their disposal. Many problems arise in artifacts; and the technological system must have the ability to reorder the physical world as a way to benefit those in the technological system.

The development, expansion, and evolution of technological systems can be identified through a pattern involving several phases. The pattern is flexible; and the different elements do not have to necessarily fall in a specific order. Evolving technological systems go through the stages of invention, development, innovation, transfer, and growth, competition, and consolidation. As systems stabilize they gain style and momentum.\(^{63}\)

Systems can be described as social, biological, technological, or material patterns; and these all operate for one common aim or purpose. Systems theory developed primarily out of the discipline of biology, which harkens back to understanding the natural world primarily as ecosystems. Most philosophers who study systems theory describe systems as very abstract. These systems are independent and lack substance. They do not really exist in time and space as most understand it. The aim of these philosophers and sociologists is twofold. First they must describe the world in which they live and how it consists of different systems. Second, they must view the interplay of elements in a holistic way so that they can truly understand their functions.\(^{64}\)
System theory has evolved and been adapted to other disciplines in the course of the last century. Herbert Spencer and Joseph Needham were pioneers in systems theory, as they developed and articulated key aspects of the theory. Herbert Spencer, in 1862, was one of the first to articulate the idea of increasing complexity among systems. Following Spencer, Joseph Needham provided tremendous insights in fundamental aspects of the theory, specifically in the area of integrated levels. Combined, their work resulted in the articulation of nine characteristics of integrated levels. These characteristics primarily described the organization and interaction of various levels. Needham’s ideas surrounding integrated levels laid the groundwork for the current discourse surrounding adaptations of systems theory. Systems theory has been adopted in the fields of comparative psychology, biology, biochemistry, and others. Subsequently, different articulations of system theory have developed, including but not limited to General Systems Theory (GTS), the Systems Approach, cybernetics, and operational analysis.

The influence of systems theory can be tracked in other disciplines such as management science, mathematics, political science, psychology, sociology, and library and information science. However, such development is not without criticism. One of the most damaging criticisms, by Robert Lilienfeld, is that systems theory is far too idealistic and that it, at times, escapes reality.

1.3.5 Structuration Theory

Structuration theory is similar to, but distinct from, systems theory. The study of structuration in social systems consists of examining the modes in which systems
“grounding in the knowledgeable activities of situation actors who draw upon rules and resources in the diversity of action contexts are produced and reproduced in interaction.” Structuration is, in essence, the arranging and structuring of social relationship through time and space, taking into account the dual nature of structure. The duality of structure refers to the notion that agents and structure are not two separate or independent aspects of phenomena; rather, they are integrated components of a recursive organization process. As a result, this provides a unique perspective on human behavior. Rather than human nature being constrained by vast societal structures, structuration theory acknowledges and embraces these relational aspects of society.

Many structuration theories posit that human behavior is a result of the individual’s socialization within a structure. Anthony Giddens, a sociologist who focused his research on structuration theory, argues that structuration theory is a means by which one can understand social actions and behaviors. This is accomplished by resolving competing views of “structure-agency” and “macro-micro” perspectives. In this process, the interface between the actor and the structure is analyzed. The crux of the argument lies in that actor theories and system theories cannot alone explain these behaviors; rather, they must be examined simultaneously. This could be conceived of as an integration of key elements from actor network theory and systems theory. One of the interesting ramifications is that social rules and structures do not exist outside of human action because they are socially-constructed. Giddens proposed a framework consisting of three kinds of structures in social systems. The first structure is signification, where meaning is derived from practice and language. The second structure is legitimation, where meaning is derived from normative perspectives, which are embedded and
expressed as social and cultural norms. Domination is the third structural element, whereby meaning is assessed by examining power structures and relations, specifically surrounding the control and allocation of resources.\textsuperscript{75}

Since the articulation of his theory in 1984, Giddens has faced harsh critiques, specifically from Jon Clark et al in the book \textit{Anthony Giddens: Consensus and Controversy}.\textsuperscript{76} Despite criticism of this theory, other scholars have adapted Giddens’ work to examine the relationship between society and technology including publications from G. DeSanctis and M. S. Poole as well as Wanda Orlnkowski. Specifically, DeSanctis and Poole have articulated an “adaptive structuration theory”.\textsuperscript{77} Orlinkowski also adapted this theory when she provided a very nuanced critique of Giddens’ duality of structure as applied to technology. She argued, “The duality of technology identifies prior views of technology as either objective force or as socially constructed product—as a false dichotomy.”\textsuperscript{78} Much of her work surrounds issues at the corporate level. However it is arguably applicable to wider ranges of technology and the structures in which technology exists. In addition, as a result of her work, this theory can be adapted to account for issues that arise surrounding gender and technology.\textsuperscript{79} Michael Workman, Richard Ford and William Allen, professors at the Florida Institute of Technology, also utilized key elements of structuration theory in their adaptation, primarily agent theory aspects. They adapted the revised theory and applied it to examine the socio-biological structuration in security software. Specifically, they examined how humans behave in relation to information exchanged and communication.\textsuperscript{80}

In sum, structuration theory is a social constructivist theory aimed at understanding human behavior within social structures while recognizing the impact of
external forces. It differs from other social constructivist theories in the way that it interprets duality. It is a flexible framework, which resulted in multiple adaptations.

1.3.6 Collective analysis of the relationship between society and technology

All of these theories or perspectives have a common goal to provide a paradigm by which a realistic and accurate study of the relationship between society and technology can take place. Traditional approaches to technological determinism leave much to be desired, as they are typically linear and treat technology as a value-neutral “black box,” of sorts. If the development of technical artifacts can be more clearly understood, it would enhance comprehension of the social-technical relationship. Then the assessment of new technologies might be possible as a fundamental understanding of this relationship. Strong versions of technological determinism—those that eliminate the role of social influence—are very difficult to maintain. Equally difficult to sustain are strong versions of social constructivism which maintain that technology has limited or no causal impact on society.  

The social construction theories, including SCOT and structuration, provide some explanation for the development of technology. However, if one takes a very strong constructivist position, it is extremely difficult to show that technological trajectories are solely influence by a myriad of social structures and forces. In recent decades, research has enhanced the understanding of the nuances of technological change and the interrelatedness of science, technology, and society. One of the most important concepts is the notion of technological trajectories, or how technology develops on a certain path. Clearly, the development, adaptation, and effects of a given technology depend to some
extent on social context. For example, social context will determine whether or not a particular technology is adopted or whether it is repurposed for some other worthwhile use, thereby impacting the technologies impact on society. This is consistent with Bijker’s work on the technical and social development of the bicycle.  

The ultimate question is whether society is shaping technology or vice versa? Most of the scholars would agree, to some degree, that it is a two-sided coin; society is shaped by technology, and society impacts the design and evolution of technology. Each author takes a unique approach to developing a new paradigm. Hughes has the most limited approach, as he appeals to the use of flexible patterns. Whereas Bijker, while employing steps, identifies them all occurring very rapidly on the end of the analysis. There is not a step-by-step process for the development of technology; rather, the steps are for the analyst. He does not describe patterns, but rather general observations regarding the development of each technology he examines in his dissertation: bicycles, Bakelite, and florescent lighting. In the example of the bicycle there was neither a single social group with an accompanying technological frame that was dominant, nor a clearly dominant technological frame guiding interactions. In the second configuration, demonstrated in the Bakelite example, one technological frame was dominant and characterized by one social group. In the third configuration, demonstrated in the florescent lighting example, two or more social groups with developed technological frames were vying for dominance; and several technological frames were simultaneously important for understanding interactions related to the artifact. The difference between the first and third example have the largest disparity. The first example did not, initially, have a dominant social group or technical framework, while the third example had
multiple developed social groups and technical frameworks. Bijker has a very robust approach; this is in part because he is able to support his theory with detailed evidence. While the evidence is a small sample, there are still insights he offers which are very beneficial to the sociology of the technology.

Callon’s version of the actor network theory is very appealing because of its initial simplicity. The actor network contends that all relevant entities that are linked to an invention or technology at its final stages of development have in fact been there from the start. This is a very difficult thesis to manage. The course and trajectory of the technology or invention is unknowable in its entirety at its inception. Therefore, when Callon claims that they are all present in the earliest stages, it does not appear that they exist in any real fashion. This is, they may exist inherently or in some underlying fashion; but they are unknowable in the early stages. If they are unknowable, then they cannot be made use of in the early stages. Therefore, while it might be convincing that the network is integrated from the very beginning, it is of little consequence because it is only something that is beneficial in retrospect and reflection. Some factors are simply unknowable at the onset.

Systems theory and structuration theory are both on the same end of the spectrum leaning toward social constructivism. While systems theory was useful in providing a paradigm parallel to the actor network theory, it remains incomplete due to one-sidedness in its analysis of social structures. Structuration provides a slightly more balanced approach by adopting the strengths of both actor network series and systems theory. However, as John Clark and others point out, there are massive challenges to overcome.
The connection of these theories to ethics assessment in HTA is fairly straightforward. The work completed thus far in Chapter One, provides the philosophical underpinning and theoretical understanding for the integration of ethics in HTA. The argument will be more fully developed at the end of the following section.

1.4 Technology as value laden and its relationship to society

The final two sections of this chapter will introduce the concepts above in relation to health technologies. The nature of values in health technologies, specifically emerging health technologies, will be discussed as well as the relationship between emerging genetic health technologies and society.85 When applied to technologies in health care one will see how the relevant social groups interact with the various technological frames in modern techno-medicine. In evaluating the theories, two currents are immensely important for this dissertation. First, acknowledging that what drives technological innovation is not society or technology alone, it is both together. These authors have persuasively made their point. Technological development is not a determined, linear process. The second important aspect to consider is that these studies are, academically speaking, relatively new concepts. They must be further developed and refined; and then it will be possible to effectively introduce them into bioethics discourse to gain a greater understanding of the physician-patient-medical technology relationship.

This dissertation will not adopt a specific perspective. It is enough to observe that technology alone does not shape society and that society alone does not shape technology; rather, the relationship is symbiotic—society is shaped by technology; and society impacts the design and evolution of technology. The first portion of this chapter
introduced emerging genetic health technologies, HTA, and primary goal of this
dissertation. Taking into consideration the position specified above, it is concluded that
emerging genetic health technologies will influence society, and society will influence
the nature and development of emerging genetic technologies.

Technology is value-laden which means that it inherently carries normative value.
Society, made up of diverse human beings, is pluralistic, carrying with it a plethora of
perspectives, opinions, values, and norms. Technology shapes society and society shapes
technology. Both of these are laden with values. Hence, ethics is useful and necessary to
make meaningful progress in understanding and unpacking this relationship, as well as
examining and impacting technological and social development. However, this particular
dissertation will not be taking on the former of these projects as it is outside the scope.
Rather, this dissertation will examine and argue that ethics can contribute to
technological development, specifically in the area of emerging genetic health
technologies. These arguments will be fully developed in Chapter 3.

1.5 Conclusion

This chapter has explained how the connection between values and technology is
important; if there is a connection, a stronger case can be made for the role of the
ethicists, philosophers, social scientist, and other disciplinary experts. Moreover, when
the complex nature of the relationship between technology and society is discussed, a
very strong case will be made for the inclusion of ethics in Chapter 3. This was
accomplished by reviewing some of the dominant theories surrounding the relationship
between society and technology, including technological determinism, social construction
of technology, actor network theories, systems theory, and structuration theory. Both ends of the spectrum were addressed, ranging from technological determinism to pure social construction. The argument presented and basic assumption made in this dissertation, is that technology and society influence and shape one another, it is not a one-sided relationship.

When emerging health technologies are examined, the argument for ethics assessment will be strong. Health in itself is considered a “societal good” not just in the sense of a commodity, but also in a very positive or normative sense of the term. Health is desirable. So when talking about emerging health technologies, HTA is incredibly important because these technologies will be applied directly to humans and human health, which in itself is considered good.

It is not difficult to argue for the inclusion of ethics in HTA, however; in fact, many scholars agree that ethics should play a role. This will be explored fully in Chapter Three. Yet, very few explicitly state the reasons. Moreover, there is no consensus on how this is best accomplished within existing HTA processes. Through the articulation of these philosophical and socio-biological foundations, a substantive starting point is provided. From this juncture, Chapter Two will assess the current status of HTA practices at the local, national, and global levels. This includes examining the organizations responsible for carrying out HTA, as well as the methods they use. Chapter Three will provide an in-depth analysis of ethics methodologies currently paired with or integrated in HTA. Chapter Four will present the nonlinear approach. The dissertation will close by applying the nonlinear approach to emerging genetic health technologies.
ENDNOTES


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5 Douglas, Rejecting the Ideal of Value-Free Science, 120-142.


11 Anbar, Penetrating the Black Box: Physical Principles behind Health Care Technology, 23.

12 Anbar, Penetrating the Black Box: Physical Principles behind Health Care Technology, 34.


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16 Hofmann, When Means Become Ends: Technology Producing Values, 6.


23 J. Dancy, "Should We Pass the Buck?" in *Philosophy, the Good, the True, and the Beautiful*, ed. A. O'Hear (Cambridge: Cambridge University Press, 2000), 159-174.


26 Hansson, *Valuation of Artefacts and the Normativity of Technology*, 112.

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32 Habermas, *Toward a Rational Society*, 81-90.

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77 DeSanctis and Poole, Capturing the Complexity in Advanced Technology Use: Adaptive Structuration Theory, 121-147.


81 Bijker, Three Faces of Technological Determinism, 82.

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83 Hughes, The Evolution of Large Technological Systems, 80. 1987


Chapter 2: Health Technology Assessment (HTA)

2.1 Introduction

Chapter Two builds on the philosophical and sociological foundation delineated in Chapter One, and specifically addresses health technology assessment (HTA). The aim of this chapter is to explain the nature and origins of HTA and a number of current approaches and methods in HTA. This will be accomplished by examining the current agencies and organizations responsible for HTA, as well as analyzing orientations, frameworks, established pillars, and basic practices.

2.1.1 Connecting value and assessment

Chapter One presented several positions explaining the relationship of technology and society. The position adopted in this dissertation is that society and technology impact each other; and furthermore that technology is value-laden.

The Food and Drug Administration (FDA) provides a list of reasons why the U.S. government engages in HTA: to promote advances in science; support intellectual property rights and patent protection; support aging populations; address the increased prevalence of chronic disease; address emerging pathogens and other health threats; insurance; incentives from technology and pharmaceutical companies; issues surrounding direct-to consumer advertising; off-label use of pharmaceuticals and devices; and increased costs of unnecessary tests, unexpected results, among others.¹

The items delineated by the FDA reflect the value placed upon them by the nation and the larger global community. Even more so than emerging technologies, the
technologies created to improve human health hold a special place of importance. Health is considered a human and societal “good.” One of the primary goals of medicine is to improve and maintain health. Health technologies are meant specifically to help people. This presents several interesting philosophical debates on one’s moral obligation to pursue technological development, which will be fully explored in Chapter Three.

2.2 Health Technology Assessment (HTA)

This section will set the stage for the rest of the dissertation. First, HTA will be described, and its origins outlined. This will be further clarified by a discussion surrounding the scope for HTA, as well as some foundational topics including risk, uncertainty and the acceptability of risk. The current status of HTA will also be addressed in subsequent sections.

2.2.1 Defining and explaining HTA

Health systems across the globe have developed at different rates with varying degrees of complexity. Development often reflects the diverse cultural, political, and social structures and conditions in each country. One of the very few generalizations that can be made about these diverse systems is that they are created in an effort to improve health. Defining and describing HTA and its role can be a challenge since there are multiple perspectives and methods. The Institute of Medicine, based out of Washington, D.C., defines HTA “to denote any process of examining and reporting properties of a medical technology used in health care, such as safety, efficacy, feasibility, and indications for use, cost, and cost-effectiveness, as well as social, economic, and ethical
consequences, whether intended or unintended.” Health Technology Assessment International (HTAI) expands the definition further, identifying HTA as “a field of scientific research to inform policy and clinical decision-making around the introduction and diffusion of health technologies [in a] multidisciplinary field that addresses the health impacts of technology, considering its specific healthcare context as well as available alternatives.” HTAI further identifies several contextual factors in the definition of HTA, including “economic, organizational, social, and ethical impacts.” Of equally important interest is the HTAI position that such assessment can be adapted due to the policy considerations of a particular health care system. Finally, the European Network for Health Technology Assessment defines HTA as “a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner.” The goals of HTA, the network claims are to “inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value.” Above all, the network concludes, HTA must maintain a foundation in rigorous research and the fundamental principles of the scientific method, more so than adapt to any particular policy considerations.

From these various definitions, one can conclude that HTA is a process to gather and disseminate information about new health technology to politicians, scientists, researchers, and the wider public in an effort to provide the necessary information so they can make informed policy decisions. Concrete problems can arise from new technical developments; and HTA attempts to provide relevant information that can be used in addressing these challenges. In many cases, the problems are not with the technologies
themselves, but rather in the greater context of real-life applications. As a result, engaging multiple disciplines is necessary, which forces HTA to be an inter/trans/multi-disciplinary process. HTA must be, at the very least, multidisciplinary because it is impossible for a single discipline to have the capacity to adequately deal with the scientific, technical, economical, ecological, legal, ethical, political, and societal issues that must be taken into account when developing health care policies.

Health technologies can be assessed at different times in development and trial phases; these are called stages of diffusion and maturity. HTA can be initiated by policy-makers, health professionals, health administrators, third-party payers, patient advocate organizations, or HTA institutions. The reasons for assessments are many, including, but not limited to, new technologies, adjustments in old technologies, adaptations of old technologies, organizational changes that affect technology, safety issues, social and ethical concerns, economic concerns, or the emergence of the new problem that requires action. The variation in orientations, frameworks, and practical functions in HTA will be addressed throughout this chapter.

2.2.2 Origins of TA and HTA

To provide a historical perspective, this section will address technology assessment juxtaposed with health technology assessment. Technology assessment (TA) emerged in the 1960s as scholars and society as a whole began to critically reflect on developments in science and technology, and their relationship to policy-making. In short, TA is a concerted effort to supply politicians, scientists, researchers, and the wider public with information regarding the social aspects of technology. There are concrete
problems that arise from new technical developments; and TA attempts to provide advice on addressing these challenges. A consensus emerged that the negative effects of scientific and technological developments ought to be curtailed as much as possible. TA developed out of this discourse as a policy research tool aimed at identifying and anticipating problems as well as solving them. The aim was to control the unintended consequences of emerging technologies. It would be accurate to consider TA as a type of early warning system.8

The United States Congress formed the Office of Technology Assessment (OTA) in 1972; and it operated until 1995.9 Technology assessment is a form of policy research. It attempts to address for short-term impacts and long-term effects. While the primary concerns center on safety, efficacy and cost-effectiveness, there was some consideration given to ethical, legal and social issues. These additional considerations were deemed necessary in order to provide policy makers with the most accurate and helpful information.10 Technology assessment can be undertaken on any variety of technologies, ranging from health technologies to motor vehicles, and so on. The focus of this dissertation is health technology assessment, which pertains to those technologies applied in a health care setting or more broadly to human health in general.11

David Banta et al, in Toward Rational Technology in Medicine, note that there is confusion about technology and its relationship to society stemming from past “unbridled optimism” and a “new wave of negativism.”12 Arguably, over time, the function of technology has changed very little, yet its scale and power have dramatically increased. This has altered the function of technology insofar as it has increased the role it plays in daily life as well as in the biomedical field.13 Banta et al suggest that there is an
identifiable process of technological change. It begins with general analysis and theoretical research, advancing to basic empirical research, which provides knowledge to properly assess where technological advancements can be made in a given system. To demonstrate feasibility, applied research is carried out along with the development of implementation strategies, testing manufactured goods, marketing, and diffusion of the technology.\textsuperscript{14} This is a fairly limited, one-dimensional perspective. Models such as these should be expanded to include social contexts and a broader understanding of the impact society and technology have on each other. There is some recognition that assessment is needed. By the early 1990’s, some scholars suggested that the rule should be “no evaluation—no technology.”\textsuperscript{15} The fundamental claim is that the inappropriate use of technology has led to inflating the price of health care and dehumanizing the practice of medicine. Thus, it is important not only to assess the efficiency and cost of a particular technology but the social and ethical dimensions as well.\textsuperscript{16} The assessment of a specific technical intervention is not the only activity of the OTA. There are also abstract considerations, such as examining the role of technology and society and understanding the rapid acceptance of new technology.

Banta et al identify four primary concerns that arise as a result of advancements in medical technology including benefits, risks, financial costs, and social impact. These in turn have a direct correlation to ethics, the economy, legal, and political systems.\textsuperscript{17} Many systems develop as a result of existing technology; medicine has not, according to Banta et al. The medical infrastructure was not designed to provide cost-effective technology to patients; rather, technology entered an existing system and as a result evolved almost haphazardly with no rational plan for development or implementation.\textsuperscript{18}
In 1976, the OTA provided a list of questions for consideration when introducing a new technology. By the 1980’s there were only two agencies in the United States charged with examining the social implications of technology; the Office of Technology Assessment and the National Center for Health Care Technology. Past HTAs have focused on individual interventions such as diagnostic and therapeutic technologies and to a lesser degree organizational systems. Typically evaluation is done of the singular intervention rather than the integral program in which it is embedded.

Robert Reuzel, a scholar at Nijmegen University Medical Centre, Department of Medical Technology Assessment, provides several reasons why HTA was, and in some cases continues to be, restricted in focus to emphasize on cost-effectiveness and efficacy. The first reason can be derived from history. One of the primary reasons technology assessment started in health care was to determine whether certain expenditures could be justified by benefits. Second, assessment requires input from highly specialized researchers and others who work in the development of health care technologies, which typically does not include ethicists and sociologists. Finally, the political context of health care technologies must be considered. Generally it is believed that determinations of cost and effect are scientific considerations and hence provide strong basis for decision-making. Social and ethical considerations are considered debatable; and thus provide a weaker basis. The effectiveness, safety, and market approval are often equated with acceptability of a technology. HTA as it currently stands can take one of two paths. First, it can be a tool for estimating cost and effectiveness. Second, it can be “recast as a formative evaluation framed in a constructivist scientific paradigm.” Reuzel argues that HTA should aim at directing and managing health technology at the
political level. This means that assessment must be grounded in a decision-making framework; otherwise it is not likely to affect decision-making at all. Assessment research should result in the ability to provide the necessary information to manage technology in society. Surveys of recent HTAs show that there are two primary approaches. The first emphasizes effectiveness, safety, and economic considerations of the new technology. The second perspective is much broader, taking into consideration not only the items listed above but also social and ethical consequences.

2.2.2.1 Difference in scope

There is a difference in scope between TA and HTA. There are three central considerations in TA: (1) how to identify a problem (2) when should TA step in, and (3) what TA method should be employed. The second consideration when TA should step in is an interesting one because it is very dependent up on the first step. So how does one determine when a problem is relevant for political leaders, policy makers, researchers, and the general public? There is no clear-cut or easy answer. Whenever advice is solicited and there is evidence of desire for advice, then it is clear when to take up TA. Yet an organization that conducts TA or HTA can prioritize assessment needs as they see fit. There is no structure for prioritization of TA and HTA needs. There is another reason why this particular consideration is important—TA institutions have limited resources (time, staff, and money). Multiple problems that require solutions could arise simultaneously, which would necessitate the need for prioritization (most likely based on urgency) of projects.
Comprehensive approaches to TA were originally intended; however, those practicing TA realized that partial approaches could serve as appropriate alternatives, and in fact might be preferable in situations where limited time and funds were available. Thus, rather than having a full, robust holistic approach to TA, many only addressed specific concerns and issues. While this is not ideal, when faced with time and fiscal restraints, the calls for both timely and affordable TA and HTA became consistent.

The following sections will address risk, specifically issues surrounding uncertainty and the acceptability of risk. These are critical concepts because of the very nature of the health technology. It is a human and social good; health technology is produced to make a positive impact on the lives of individuals and entire populations. As such, a robust understanding of risk is crucial if one is to fulfill any moral obligations ingrained in HTA processes (these will be addressed in Chapter Three).

2.2.2.2 Understanding risk

Risk and uncertainty must be addressed in any discussion about emerging health technologies. The mere fact that they are “emerging” complicates the situation because this increases the potential for risk of harm due to uncertainty. Therefore, a brief explanation of risk and uncertainty is necessary in order to fully understand the task of HTA when it comes to evaluating the emerging genetic technologies which will be addressed in Chapter Five. An understanding of risk is important for the broader concept of HTA because safety, especially from uncertain or unknown risks, is one of the primary evaluative aspects in HTA. This section will address how risk can be viewed and evaluated.
A risk is a chance or probability of a bad or negative outcome. One is concerned with negative outcomes that manifest as harm to an individual or multiple persons. Risk analysis has several sub-disciplines including probabilistic risk analysis, health risk analysis, ecological risk assessment, risk-benefit analysis, risk perception, and risk communication. To begin, one should have a clear and distinct understanding of the terms. Most people have general notions of how to characterize risk and harm; however, there are ambiguities. When considering harm, it may be tempting to equate it to physical injury. However, this leaves out other dimensions of harm. Other types of harm include but are not limited to physiological, social, and economic harm. So a more appropriate characterization of harm might be Joel Feinberg’s, an American political philosopher, definition which states: “someone is harmed when his or her interests have been thwarted, defeated, invaded or set back.” Identifying harm as any setback to the interests of an individual is attractive because it accounts for a multiplicity of harms, not just physical harm. Many scholars begin the discussion of risk-benefit analysis without identifying what constitutes a risk. For the purposes of this essay, risk is characterized as the probability and magnitude or severity of a potential, future, and undesired harm. The nature of risk is two-fold; it describes the probability or chance of the harm happening, yet also accounts for the severity of the potential harm. Thus, there are two levels of uncertainty: first it is uncertain that the harm will occur—that is why the probability is estimated; and second, it is uncertain because the severity of the harm could vary per participant since no two participants are identical. This means that the estimated probability of a risk will occur, as well as the severity or magnitude of the risk based on the average participant, is determined by the inclusion/exclusion criteria of the study.
Unfortunately, risk and harm are sometime conflated to share an identical meaning. This is a mistake that should be avoided. Risk is not harm; they are related but not identical or equivalent. This is a convincing argument based on the distinctions outlined above, namely that risk and harm are not parallel constructions. Stephen Perry, a scholar in the field of jurisprudence and political theory from the University of Pennsylvania, makes a different type of argument when asserting that risk is not harm. When an individual has been subjected to a risk because of the actions of another, this exposure is not in itself a harm. However, the U.S. legal code does not embody this sentiment. For example, in tort law an individual can be awarded damages by simply being exposed to a particular risk. Perry notes that there has been an increase in the number of medical malpractice cases in which legal liability has been declared based on the exposure of a patient to risk. For example, a case might unfold like this: the defendant is found to be negligent; and the plaintiff, as a result, of this negligence suffered exposure to risk which is then interpreted as “harm in the form of a lost or reduced chance of avoiding an adverse physical outcome.” Perry argues that this is a mistake in logic; risk cannot, logically, be conflated with harm and result in compensation. The basis for Perry’s assessment and argument—that risk is not harm—is derived from the well-known “multiple reference classes” problem.

2.2.2.3 Understanding uncertainty

Uncertainty, or a lack of information, is a characteristic of most decisions. Uncertainty exists when probabilities are either completely unknown, or are known only with insufficient precision. Therefore, decision-making under uncertainty consists of
making decisions with no or insufficient information about risks and harm. Most of the decisions made in human life are made under uncertainty. Few circumstances exist in which the probabilities of possible outcomes are completely known; and many of these situations include closed contexts such as flipping a coin or rolling dice. This section examines how humans with limited capabilities and knowledge cope with uncertainty in risk.37

In HTA, all data represents certain thresholds and endpoints from which patients and populations are sampled. While uncertainty is intentionally minimized there is always the possibility for errors in data collection, the measurement and benchmarking mechanisms, and the interpretation of data. Later in this chapter a number of the methodologies and frameworks will be addressed. Most of these rely on conceptual models; standardized best practices available at this point. Some methods are assessed as better than others; but there are currently no concrete standards. This very fact calls into question levels of uncertainty in HTA reports themselves. For example, it is not unheard of to have two countries produce contradictory reports on the same device or pharmaceutical.38 Despite uncertainty, recommendations and decisions must still be made.

2.2.2.4 The acceptability of risk

Attempting to determine the acceptability of risk necessarily includes some form of moral reasoning, whether explicit or implicit. When determining what is good or bad, beneficial or negative, the decision involves value-judgments that invoke ethical considerations. This brief section will expose a very important connection between the
use of value-judgments and risk and uncertainty. The connection involves ethics and other social considerations. This connection strengthens the argument for an enhanced HTA approach with a substantial ethics component.\textsuperscript{39}

Why is philosophy, specifically ethics, needed in risk analysis? Many approaches to risk assessment and evaluation are based on quantitative methodology, which in many cases focuses on utility maximization.\textsuperscript{40} Risk is measured based on the probability and severity of the outcome. Probabilistic risk analysis is very useful; however it does not provide the decision maker with all the necessary contextual information to make an informed decision. Risks are not created from nothingness; they are contextual. Risks are either taken, run, or imposed. Taking or imposing risks entails issues such as agency and relationships.\textsuperscript{41} These are very difficult to incorporate into an evaluation that looks at probability and severity of risk. Therefore, to have any meaningful computation it should be determined who is doing what action and their reasons for doing it. Hansson notes that, morally, it makes a substantial difference if one puts their life on the line and assumes that risk versus risking someone else’s life to further their own ends.\textsuperscript{42} Another moral aspect to consider is whether taking a risk is done so willingly or freely without coercion, manipulation, or exploitation. Clearly, there are moral ramifications if one is not acting of their own free-will. It is evident that while traditional risk calculations of a purely quantitative nature are necessary and provide a useful starting point, quantitative risk analysis must be accompanied with ethical considerations pertaining to risk.\textsuperscript{43}

Hansson argues that current moral theories are not equipped to deal with risk and uncertainty. If one approaches risk from a utilitarian perspective, it suggests that pure interpersonal rectification of risks and benefits is acceptable. Therefore, a risk for one
person could always be dominated or outweighed by a greater benefit for someone else.\textsuperscript{44} If one examines risk from a deontological framework the converse problem exists. It would be difficult for the deontologist to justify any action that would intentionally put another at risk. Hansson notes that there appears to be a \textit{prima facie} right at work: “everyone has a \textit{prima facie} moral right not to be exposed to risk of negative impact to her health or her property, through the actions of others.”\textsuperscript{45} It is useful to view exposure to risk not as any type of moral maxim but rather as a \textit{prima facie} rule or principle because a \textit{prima facie} rule can be overridden. It is self-evident that one should not intentionally be exposed to negative risks. However, risk is involved in everyday life and social interaction. One cannot live without subjecting others and themselves to risk. For example, simply by driving a car to and from work one puts not only other drivers at risk but oneself as well. Hansson explains that there is a way to maintain the \textit{prima facie} rule despite unavoidable risks. There must be an agreed upon normative account for overriding this rule and making some risk impositions acceptable. Hansson suggests this can be done through an “appeal to reciprocal exchanges of risks and benefits.”\textsuperscript{46} Every individual takes risks in order to gain some benefit. For example, one risks driving to the grocery store—and all the potential risks that arise while driving a car and interacting with other humans—in order to benefit from buying food to sustain their family’s nutrition. Therefore, it is reasonable for them to extend this practice to others. As a result, everyone engages in mutual exchanges of risks and benefits. Put another way, since other people are permitted to drive cars and expose others to certain car-related risks, then they are also allowed to drive their car and expose them to those similar risks. This reciprocal exchange of risk and benefits clearly benefits all of society.\textsuperscript{47}
In subsequent sections, it will become evident how the understanding of risk and uncertainty impact HTA. Also, in Chapter Three, it will be argued that ethics provides useful methods for determining socially acceptable thresholds and endpoints of risks.

A recent article has taken up the issue of ethical acceptability of risk. Patenaude et al, in the article titled *Framework for the Analysis of Nanotechnologies’ Impacts and Ethical Acceptability: Basis of an Interdisciplinary Approach to Assessing Novel Technologies*, argue that the acceptability of risk is an issue for ethics, and provide evidence that market interests and state regulations do not provide an ethical justification for certain technologies. Furthermore, the authors present a framework for the analysis of both impact and acceptability of emerging technologies. In this particular article the authors are most specifically concerned nanotechnology. Given the recent crisis and public rejection surrounding genetically manipulated organisms (GMOs), the authors suggest that researchers in nanotechnology stand to learn of few lessons.

The authors address two important distinctions in risk assessment, they are the physical risk that is any aspect of the emerging technology that may be harmful to humans or the environment, and the other is comprised of the value judgments surrounding emerging technologies. The authors argue that the very nature of risk assessment is value-laden. This is because the risk assessment must not only weigh and balance the physical consequences of technology, but also must answer issues surrounding the weighing of social benefits versus regulation.

This article primarily focuses on nanotechnology however some of the basic arguments are the same as those used for the justification of ethics’ role in HTA. The authors, a group of interdisciplinary researchers, suggest a model that complements
existing risk assessments in nanotechnology. This seems to parallel the work that is being done in many other emerging technology venues, such as synthetic biology and emerging genetic health technologies. Again, the aim is not to disrupt the process or move ethics to a special place outside of the process but rather to provide meaningful integration for a comprehensive impact on the acceptability analyses pertaining to risk.\textsuperscript{50}

2.2.3 A brief history of HTA

The origins of HTA are fairly well delineated, as it is a recently developed practice. The concept of technology assessment emerged in the 1960s as a recognition of the impact technology had on society as well as the unintended (or intended) and potentially harmful consequences. This occurred simultaneously with the recognition that some technologies raise important ethical and social concerns. The Office of Technology Assessment (OTA) was formed by the United States Congress and operated from 1972-1995. Technology assessment is a form of policy research. Long-term and short-term consequences of the application of a given technology are assessed at the societal, economic, ethical, and legal levels. The purpose is to provide policy makers with accurate information so they can develop new policies or alternatives to existing policies. In the US, issues such as the implications of supersonic transport, environment pollution and the ethics of genetic screening were a few of the first issues addressed by OTA.\textsuperscript{51} Technology assessment can be undertaken on a wide variety of technologies. The focus here is health technology assessment, which applies to those technologies applied in a health care setting. The primary considerations in this field revolve around efficacy, safety and cost-effectiveness.\textsuperscript{52}
2.2.4 Agencies responsible for HTA

There are a variety of agencies and organizations that undertake HTA to varying degrees. These agencies and organizations include regulatory agencies, government and private sector companies, government policy research agencies, managed care organizations, health professions organizations, standards-setting organizations, hospitals and health systems, group purchasing organizations, patient and consumer organizations, private sector assessment or policy research organizations, academic health centers, biomedical research agencies, health product companies, venture capital groups, and other investors. Furthermore, these agencies often approach the process different depending upon the perspective. There are four general perspectives on HTA including societal, hospital or health system, company, and consumer or user perspective. These will be addressed in the discussion of basic procedural aspects, in the subsequent sections. To begin, the survey of HTA organizations and agencies specific countries and regions will be addressed as they carry the bulk of the workload in conducting HTA.

2.2.4.1 USA and Canada

There have been wide range of HTA efforts in the US. Many federal HTA efforts have failed. B. Luce and R. S. Cohen argue that there are four politically-charged reasons for this. First, scientists and investors perceived HTA as a threat to new medical technologies. Second, some thought that HTA threatened the medical autonomy of organized medicine and practitioners. Third, HTA was perceived by patient advocacy groups as a threat because it could restrict access to new innovations. Fourth, with regard
to health care and economics, HTA was perceived by some as a mechanism to potentially ration care and contain costs. Due to these perceived threats, HTA met substantial political opposition in the US. When OTA was disbanded in 1995, it received an annual budget of $21.9 million and employed 143 personnel. OTA came under fire in the 1980s in a publication by Donald Lambro, a reporter in the 1980s and now chief political correspondent for The Washington Times, that regarded OTA as excessive and worthless because, he claimed, that the work it did overlapped and duplicated the work done by other government agencies. Despite these perceived threats and political opposition, many still recognized the necessity of HTA and the importance of the inclusion of ethics in the assessment.

Since the 1960s many federal HTA initiatives have failed. Currently, the US federal government plays a large role in HTA as a regulator. Congress passed The Food, Drug, and Cosmetic Act in 1938; and as a result created the Food and Drug Administration (FDA). One of the primary roles this agency fills is to determine whether new pharmaceutical products are safe and meet industry standards before they are made available to the public. In 1976, this role was expanded to include the assessment of medical devices. However, the FDA only tests the safety of the proposed device or pharmaceutical. Ethical and social considerations are not primary concerns if they are even addressed at all.

In 2005, the Veterans Health Administration (VHA) established the Technology Assessment Advisory Group (TAAG). The purpose of this group is to provide evidence-based policy recommendation to VHA leaders and policy makers. TAAG is comprised of interdisciplinary experts primarily in the fields of clinical, research, and health
systems. They select and prioritize topics for evaluation and have the power to call ad
hoc panels of experts and physicians to disseminate information. Several other centers
and committees exist in a similar fashion—that is, under the direct control of a larger
agency. In the past decade several other terms have been introduced that are related to
HTA including “evidence-based medicine” (EBM) and “comparative effectiveness
research” (CER). They are all related terms, but not completely identical. One way of
conceptualizing this is that EBM and CER answer “does it work?” while HTA answers
“is it worth it?” This distinction is important because some assessments focus only on
evidence-based medicine and practices as opposed to comprehensive HTA. Evidence-
based practice in medicine has been characterized as “the conscientious, explicit and
judicious use of current best evidence in making decisions about the care of individual
patients.” The origins of evidence-based practice of medicine focus primarily on the
patient at the health care delivered application level. However evidence-based decisions
quickly expanded. For example, making decisions for populations or the community
should also be based on evidence; thus public health initiatives and interventions as well
as health policy should be based on solid evidence.

One successful HTA-related initiative in the US was the establishment of the
Agency for Health Care Policy and Research (AHCPR) in 1989. The Center for Medical
Effectiveness Research was located within this agency, which was responsible for
improving the effectiveness and appropriateness of medical practice “by developing and
disseminating scientific information regarding the effects of presently used healthcare
services and procedures on patients’ survival, health status, functional capacity, and
quality of life.” This agency subsequently transformed into the Agency for Healthcare
Research and Quality (AHRQ). The primary aim is now to improve the health care system in the US by increasing safety and quality in health care. The AHRQ tries to achieve this by increasing patient safety through reducing risk from health care interventions and services by conducting evidence-based research. The AHRQ also tries to find ways to increase access to necessary services and contain costs. The AHRQ makes their research available to the public in hopes that patients and providers will use the evidence-based information to make informed decisions.64

It is unclear how AHRQ addresses HTA. The majority of the information they publish deals directly with patient safety, quality of care, and evidence based practice. As recently as 2012, there were five assessment initiatives underway including one that focuses on creating a framework for “best evidence” approaches in systematic reviews. There is no mention of ethics.65 This leads to the obvious question—how are they doing comprehensive HTA? Their methods are clear; and it appears that each topic has its own working group. Furthermore, the topics selected are such that they do not always address a specific intervention or technology but rather a broad category such as cancer and blood disorders or musculoskeletal disorders.66 What can be gleaned from this lack of information is that ethics and HTA are not fully integrated; and there are no standards or specific guidelines for HTA.

In the US, many federal HTA efforts have failed as well. Some argue that this was due to politically charged accusations. OTA was disbanded in 1995.67 Some strides at the national level have been made including initiatives by the VHA established the TAAG in 2005, as well as the creation of AHCPR in 1989.68 In the US, the FDA is one of the largest HTA regulators; however, they do not engage in a formal HTA process.
Their mission requires them to systematically assess all new pharmaceuticals as well as health devices for safety and efficacy. Other aspects such as cost-effectiveness and ethical or social considerations are outside of their assessment scope. Although the agency’s charge was created under the Food, Drug, and Cosmetic Act in 1938, it was not until 1962, when federal criteria was established for evaluating the effectiveness of new drugs, that manufactures actually had to demonstrate both the safety and effectiveness of the drug.

In Canada, HTA started in the late 1980s. The Conseil d’évaluation des technologies de la santé (CETS) was founded in 1988, and was later renamed the Agence d’évaluation des technologies et des modes d’intervention en santé in 2000. This organization operated primarily out of Quebec, and was ordered to focus their evaluation efforts on safety and efficiency of health technologies. Canada formed a national agency, Canadian Coordinating Office for Health Technology Assessment (CCOHTA), in 1989. National guidelines for economic evaluation of HTA were put in place by 1994. In 2006, CCOHTA was restructured and renamed the Canadian Agency for Drugs and Technologies in Health (CADTH).

CADTH has been utilizing innovative methodologies to address HTA. There has been an increased demand worldwide for faster and high quality HTA in order to make informed and urgent decisions. CADTH developed and implemented a rapid review approach, which aims at providing an accurate and expedited mechanism to synthesize evidence. Rapid response reports are written specifically for Canadian health policy-makers and decisions-makers. As of 2014, CADTH has produced over 2,000 rapid reports.
Canada is not the only country utilizing rapid review processes; they are being used in various ways around the world. However, there is no consensus surrounding a specific methodology or process for rapid reviews. In fact, little is actually understood about the approach to evidence synthesis, specifically, what are the trade-offs when reducing the amount of time for a report.74

2.2.4.2 Europe

HTA methods vary considerably throughout Europe.75 HTA in Europe dates back to the 1970s as interest grew in examining the economic impact of emerging health technologies.76 It was not until the 1980s that countries started to engage in organized evaluations. Most of these early efforts were at the local or regional level in France and Spain.77 In 1987, Sweden was the first European country to establish a national organization for HTA.78 In the following years, HTA practices started to become institutionalized by many countries. At present, nearly all countries in the European Union engage in HTA whether it is through a private foundation or institute, an HTA program at a university, or through a government agency or organization.79

This section will address the UK specifically, Central and Eastern European countries collectively, the European Union, as well as multinational and transnational HTA agencies and organizations.

The UK began addressing health technology issues in the 1980s. The first national action was in 1988, when the House of Lords released a report that set the priorities for medical research.80 The following year the Committee on Science and Technology was formed. Throughout the 1990s, HTA efforts became more intentional
and more successful with the formation of the formal HTA program. The National Institute for Health and Care Excellence (NICE) was created in 1999, and has grown substantially. For example, the annual budget of the HTA program increased from £12 million in 2005 to £70 million in 2012, and the projected budget for 2015 is £88 million.\textsuperscript{81}

Currently, the NICE, like the FDA, must contend with the unwieldy task of licensing new pharmaceuticals and medical devices as well as performing holistic HTA. NICE is an independent institute charged with providing guidance on health technologies and clinical practice to the National Health Service (NHS). In order to address the wide variety of pharmaceuticals, interventions, and medical devices, NICE has organized itself into four committees. Each committee addresses one of the following responsibilities: technology appraisals, medical technologies, diagnostics, and public health.\textsuperscript{82} NICE attempts to have consistency across the four different committees; however, this is still a work in progress, as there appear to be significant differences in some of the methodologies according to W. Green and J. Hutton, of the University of York.\textsuperscript{83} Given NICE’s exclusive focus on the UK, international collaboration with other organizations and agencies has been rare.\textsuperscript{84} Also, the agency does not fund research programs outside of the UK.

A recent article by A. Gulásci et al, a scholar from the Institute of Experimental Medicine, Hungarian Academy of Sciences, Hungary, conducted a survey of HTA in Central and Eastern European countries (CEE). The study focused on Poland, the Czech Republic, Hungary, Romania and Bulgaria. The vast majority of HTA developments have happened in the last decade. In 2005, Poland established the Agency for Polish
Health Technology Assessments (AHTAPol), and corresponding guidelines in 2007.\textsuperscript{85} Hungary established the office of health technology assessments in 2004. Between the years 2004 and 2013 the Hungarian agency conducted an estimated 1,247 evaluations.\textsuperscript{86} In both Romania and Bulgaria, HTA mechanisms and programs have just recently been established. Romania, in consultation with the NICE, began integrating HTA into government functions in 2011, with the primary reason to use it as a cost-containment mechanism.\textsuperscript{87} In Bulgaria, the National Pricing and Reimbursement Council (NPRC) was charged with HTA responsibilities in 2013. However, as of late 2014, they have not published HTA guidelines. Their primary activities appear to focus around price setting and safety of pharmaceuticals.\textsuperscript{88} The Czech Republic does not have an independent or national HTA organization or agency. They do have an institute responsible for pricing and reimbursement of pharmaceuticals and other health devices. This indicates that some HTA practices might be occurring; however, they are not formally recognized as such.\textsuperscript{89}

Although HTA practices are occurring in all five of these countries, the emphasis, comprehensiveness, and competence vary widely. Clearly, all the HTA activities primarily revolve around financial concerns; and nearly all these countries are conducting HTA on those technologies that will either be licensed or reimbursed by the government. There is still a lot to be accomplished when it comes to the institutionalization, standardization, adoption, and execution of guidelines and professionalization of HTA in CEE.\textsuperscript{90}

There have been multiple reviews of European HTA institutions and practices, each with a slightly different focus. As a result of these comprehensive reviews, it is difficult to get a true vision of HTA in Europe. This is because of the number of
institutions performing HTA and the aim of their HTA practices. For example, some HTA institutions are aimed at focusing on the cost effectiveness of technology and the investment aspects as opposed to patient safety or other organizational impacts.

There are multiple organizations that attempt to coordinate efforts between countries in Europe and the rest of the world. These international efforts began in 1985 with the formation of the International Society for Technology Assessment in Health Care (ISTAHC). ISTAHC has since transitioned into Health Technology Assessment International (HTAi). In 1997, the report for the EUR-ASSESS project was published. This document provided the foundation for the initial steps towards standards and methods, specifically for priority setting, and HTA.

Currently, there are many international networks, agencies, and institutes that emphasize global collaboration, including the European Network for Health Technology Assessment (EUnetHTA), which is funded by the European Union; the International Network of Agencies for Health Technology Assessment (INAHTA); and Health Technology Assessment International (HTAi). Utilizing international organizations and collaborative partnerships provides several important opportunities. It allows for the creation of new knowledge and information on global health priorities. It also provides the opportunity to maximize the full potential of the new HTA tools. Through collaboration, evidence-based research can more easily translated into practice. Even as evidence is shared globally, it still allows for localized decision-making.

From this account of some of the HTA agencies and organizations in Europe, it becomes clear that the levels of intent, organization, and function vastly differ among countries. The aim of many of these international organizations is to provide the
assistance to countries that have no HTA functions or primitive HTA bodies and processes, as well as to support those countries that have more advanced HTA mechanisms and organizations.

2.2.4.3 The global HTA community

This section will briefly address HTA outside of Europe and North America, which have some of the most developed HTA organizations and processes. This includes Latin America and Africa. In Latin America, HTA is significantly less developed. A study conducted in 1998, by the Pan American Health Organization (PAHO), concluded that HTA was underdeveloped in Latin America for two primary reasons. First, governments and other decision-makers did not understand the importance of HTA and healthcare systems. Second, there was a general lack of specialized staff and experts. Since 1998, HTA has made some progress in Latin America. Red ESTA, created in 2010, is an international organization commissioned as part of PAHO to address HTA. There were thirteen initial members including Argentina, Bolivia, Brazil, Canada, Chile, Costa Rica, Cuba, Ecuador, Mexico, Paraguay, Peru, and Uruguay. That total has now risen to twenty-two. Although some level of HTA may now be occurring in Latin America, Carolina Martin et al make a very important observation, in the article Ethical Health Technology Assessment in Latin America: Lessons from Canada and Argentina, regarding the quality of the practice. They argue that technical reports typically lack any form of direction or recommendation to policymakers and decision-makers about whether to include a specific technology in a given health care system.
The story of HTA in sub-Saharan Africa resembles that of Latin America. However, there are additional challenges especially in resource-poor countries. Arguably these resource-poor areas face more critical circumstances requiring even more accurate HTA. With limited information, including availability of evidence-based choices, the threat of the inappropriate adoption or use of health technologies substantially increases. Sub-Saharan Africa also poses a unique question because the countries do not have the infrastructure or the educational resources to engage in traditional HTA. The questions remain as to how appropriate HTA methods and tools will develop in resource-poor regions. A recent analysis suggests that given all the HTA protocols, tools, and methodologies, there are six that are appropriate for the sub-Saharan Africa continent. These include the KNOW ESSENTIALS tool, Mini-HTA, Multi-Criteria Decision Analysis, and the WHO CHOICE method. Rather than focusing on building infrastructure, the current approach promotes the development of user-friendly, fiscally conservative, and timely HTA tools. However, trade-offs due to the adoption of such approaches include a lack of depth, robustness, and holistic nature of the assessment.

2.3 Methods in HTA

This section will address current approaches to HTA. There are several orientations to address the issues that new and existing health technologies pose. These dominant orientations—technology oriented, problem oriented, and project oriented—are recognized primarily in those countries and organizations that have fairly advanced HTA practices. Within each of these orientations, there are typically three pillars that comprise HTA assessments: comparative effectiveness, economic evaluation, and organizational
impact. The HTA methodologies utilized to assess these pillars or categories vary widely within counties and throughout the world; however, commonalities exist. Given the vast array of methodologies available, only a few examples will be provided; and exhaustive assessments will not be provided here. The last portion of this section will review three dominant frameworks approaches, the pillars of HTA, and how HTA is conducted, specifically with emerging innovations.

2.3.1 Dominant frameworks/approaches

There are three general or basic approaches to HTA: a technology-oriented approach, a problem-oriented approach, and a project-oriented approach.

2.3.1.1 Technology-oriented

A technology-oriented approach is typically descriptive in nature and attempts to outline the characteristics and potential impacts of a given technology. For example, a government agency like the FDA will want to determine the various impacts of adopting and utilizing electronic health record systems. They want to determine the clinical, economic, social, and ethical impact of the technology.98

2.3.1.2 Problem-oriented

A problem-oriented approach is comparative in nature. It focuses on identifying a problem and finding adequate solutions or management strategies. Problem-oriented strategies attempt to find solutions for anything ranging from specific maladies to the use of alternative or emerging technologies in the treatment of patients. For example, if
health professionals wanted to develop guidelines that involved the genetic sequencing of
the patient's genome in order to identify hereditary and genetic abnormalities related to
cancer, such as the BRCA 1/BRCA 2 mutations, they might call for an HTA to inform
this process.  

2.3.1.3 Project-oriented

Project-oriented approaches, also referenced as program-oriented approaches at
times, evaluate the use of technology, process, or program in a specific institution or
designated project area. For example, an HTA could be employed when a hospital
system or even a specific hospital is attempting to determine whether to purchase a piece
of new equipment or technology. There are a number of key considerations including the
facilities needed to operate the new equipment, or system readiness if it is a new piece of
technology, personnel to operate it, financial resources, intended benefit; and etc.  

2.3.1.4 Analysis

These broad approaches—technology-oriented, problem-oriented and project-
oriented—may overlap and are not exclusive. Yet, each may be an appropriate choice
depending upon the case. All approaches draw on a similar body of knowledge,
scientific evidence, and contextual aspects. A technology-oriented approach would be
immensely useful in determining how the new technology might be used and whether it is
the most appropriate fit given the contextual circumstances (needs, personnel, finances,
etc.). Problem-oriented approaches are more comparative in nature because the primary
objective is to solve an identified problem. Thus, comparisons in efficacy, efficiency,
safety among possible technical solutions would be most appropriate. Project-oriented approaches encompass aspects of both technology-oriented and problem-oriented approaches with one additional explicit layer—special attention to specific local contexts. Data analysis of local needs is required to determine which solution is appropriate for the hospital and hospital system. HTA approaches are often a blend of these orientations.\textsuperscript{102}

Some scholars call for a more structured orientation, and prioritize some orientations over others. Decker and Fleischer, two prominent TA scholars, argue that problem-oriented approaches should only be used from the very outset of an HTA project.\textsuperscript{103} Other scholars advocate for entirely different orientations of HTA frameworks. For example, a decision-oriented framework, advocated for by Ritrovato\textit{ et al}, in the article \textit{Decision-Oriented Health Technology Assessment: One Step Forward in Supporting the Decision-Making Process in Hospitals}, is built on integration of multiple frameworks and very specific HTA methodologies. This will be explored in subsequent sections.\textsuperscript{104}

2.3.2 Pillars of HTA

Within each of these orientations, there are three pillars of HTA assessment: comparative effectiveness, economic evaluation, and organizational impact of medical devices. These pillars are essentially the three categories that must be addressed in order to have a holistic HTA. Each of these will be described in detail in the sections below. This dissertation focuses on the specific methodologies of ethics assessment which, in the following descriptions and categorizations, fall in the organizational structure category. This will be explored in Chapter Three. Therefore, only identification and high-level
overviews will be provided of any methodologies that might be using comparative analysis and economic evaluations.

2.3.2.1 Comparative effectiveness

There is a demand for evidence which demonstrates the effectiveness of the pharmaceutical or medical device in order to gain market access. Most national licensing committees or reimbursement programs require this. Comparative effectiveness addresses how the new technology compares to other similar technologies already in existence, as well as new technologies. Comparative effectiveness aims to answer the questions surrounding whether the technology works, how well it works in relation to other options, and whether it can work in specific contexts. Some technologies function properly only under greatly controlled conditions. This assessment must consider how the technology will be deployed in reality, which requires understanding how the technology will be used and how it will function on a routine basis, not necessarily in ideal conditions. The technical aspects, including but not limited to reliability, user-friendliness, required maintenance, overall design, composition and tolerances are taken into account. Safety is a primary component of this assessment. It is typically assessed in relation to the acceptable level of risk posed by the implementation and use of the new technology. For example, this HTA pillar may consider the probable outcome for a patient with health issue x, when operated by a health professional with training level z, in a given setting.

One must draw a clear distinction between efficacy and effectiveness. Efficacy answers the question of whether the technology can work. Effectiveness answers the
question of whether it actually does work in a particular context. These are important
distinctions when it comes to understanding HTA’s impact on patient outcomes. The aim
is always to maintain or improve patient outcomes.\textsuperscript{107}

In the last decade, this is taken on a far more prominent role in HTA for a number
of reasons. Around the globe there has been increasing evidence of inappropriate and
ineffective health technologies, such as over- or under-use. In some cases, such as
surgical procedures, there are at times insufficient rigor or lack of evidence because these
technologies are often not subject to oversight. National licensing organizations, such as
the FDA, do not require full HTA. As a result, they are only given the evidence required.
This is often insufficient evidence upon which policymakers or health system decision-
makers can base their decisions because efficacy is often prized over effectiveness.

The NIH articulates seven attributes of quality comparative effectiveness research
which promotes direct comparisons of alternative interventions as opposed to
comparisons with placebos or indirect comparisons. Comparative effectiveness research
should apply to all types of health technologies. Effectiveness should be measured
among populations and realistic healthcare contexts. Healthcare outcomes should be the
central focus. Multiple research methods data sources and analytical tools should be
utilized; and they should be applied and integrative or complementary way. The ability
to differentiate between patient types and populations should exist. This research should
take into account the emphasis on priority research, priority diseases, and priority
populations.\textsuperscript{108}

\textbf{2.3.2.2 Economic evaluation/cost-effectiveness
Economic evaluation addresses the cost-effectiveness of the new technology. Health care cost and expenditures have rapidly increased since the 1960s. This is largely attributed to the introduction and unfettered diffusion of health technology. US health care is generally thought of as technology driven. That, taken together with the general sentiment that physicians should do all that is medically possible for patients (the technological imperative), adds to the pressure to adopt new and expensive technologies.109

Economic evaluation is conducted at the micro-level and, when appropriate, at macro-levels as well. At the micro-level, the assessment primarily revolves around cost (e.g. price, maintenance charges, utilities, expected revenues, upkeep and payment plans).110 The financial impact of the new technology is often compared to and balanced against current costs and expenditures and patient outcomes. There are a number of different types of economic analyses including cost minimization analysis, cost effectiveness analysis, cost utility analysis, cost benefit analysis, and budget impact analysis. Cost minimization analysis attempts to find the lowest costing product assuming the outcomes are equivalent. Cost effectiveness analysis attempts to compare money with quantitative outcomes such as reduced mortality or morbidity. Cost utility analysis compares monetary costs with outcomes defined by quality-adjusted life-years (QALY). Cost benefit analysis compares the monetary cost with the benefits; however, the difference from cost effectiveness analysis is that both the costs and benefits are quantified in the same units, typically monetary units. Budget impact analysis attempts to determine how the newly adopted technology will impact a given budget.111 These are just a few types of economic analysis that can occur in HTA. These evaluations can
occur in conjunction, or overlap, with other processes. Each organization adopts what is most practical for their purposes. In addition, within each of these frameworks are additional tools and methodologies that vary from organization to organization.

In some cases, it is beneficial to conduct an assessment of the technology’s macro-level impact. This is especially relevant for agencies addressing HTA to inform national reimbursements, rates, and policies. This can be as broad as the impact on a nation’s GDP, impact on national health costs, international relations and trade, and resources allocation in a given nation or throughout the world.\textsuperscript{112} Global markets are becoming increasingly attuned to the inner workings and potential financial benefits of healthcare, ranging from pharmaceuticals to biotechnology advances, health insurance, etc. Recently, there have even been articles and reports published on the bioeconomy, which indicates that there are very specific market interests and patterns emerging in these areas that are driving research and production.\textsuperscript{113} The bioeconomy is a relatively new concept dating back to the mid-1990’s, and has emerged as a topic of significant interest in 2005. The Organization for Economic Co-operation and Development (OECD) spurred this discourse.\textsuperscript{114} The OECD characterizes bioeconomy as “a world where biotechnology contributes to a significant share of economic output.” The three primary elements of bioeconomy, according to the OECD, include “the use of advanced knowledge of genes and complex cell processes to develop new processes and products, the use of renewable biomass and efficient bioprocesses to support sustainable production, and the integration of biotechnology knowledge and applications across sectors.”\textsuperscript{115}
The bioeconomy may become disruptive to existing business models. This is because there is the possibility that the new technologies may not come to fruition. There are a number of reasons for this, including overcoming economic challenges (e.g. the demand for capital upfront for development) and the additional challenge of overcoming social hurdles (e.g. public acceptance). Exaggeration and overpromising is often a problem among researchers driven by the need to secure funding for their projects. They must convince investors that their approach and research is a good investment. This dramatically impacts how local, national, and multinational corporations invest and conduct business. The emergence of the bioeconomy has demanded so much attention that, in 2012, it became a federal government priority in the US. That year, the U.S. Office of Science and Technology Policy released the *National Bioeconomy Blueprint*. This document details how certain agencies will take specific steps to “drive the bioeconomy” because this will allow “Americans to live longer and healthier lives, develop new sources of bioenergy, address key environmental challenges, transform manufacturing processes, and increase the productivity and scope of the agricultural sector while generating new industries and occupational opportunities.” Other macro-issues include regulation of technology, patent systems and intellectual property issues, and any policy changes at the state, national, or global level that impacts the development, integration and diffusion of technology.

A recent international study conducted by Mathes *et al.*, analyzed the methods of economic evaluations utilized by 127 HTA organizations and agencies. The authors also requested information on methods used from these HTA agencies. This resulted in the identification of thirteen methodological aspects for economic evaluations, including:
analysis of methods of economic evaluation, purpose of evaluation, evaluated technologies, types of evaluation outcomes, choice of alternatives, time horizon, perspective, costs, measurement of resource costs, valuation of resource use, measurement or evaluation of outcomes, sources for outcomes, discounting, modeling, analysis of uncertainty or sensitivity, equity aspects, and presentation of results. Of the 127 agencies assessed, they found 63 relevant publications surrounding economic evaluations. Of those 63 documents, only 25 manuals fulfilled all inclusion criteria. A total of 14 HTA agencies representing 13 different countries were assessed.

The findings were rather stark, as the methods of economic evaluation varied greatly among the organizations. The primary difference focused around the evaluation of efficacy and effectiveness. The majority of HTA agencies carry out evaluations primarily to inform government-sponsored reimbursement decisions. Given the plurality of approaches, this requires duplicate work in each of the countries. The authors recommend generalizing the language to increase the transferability of studies. This will eliminate much of the duplicative work being done by individual countries and increase collaboration. Organizations such as EUnetHTA could play a prominent role in this. The other, more disturbing, observation made by the authors was that there were conflicting recommendations between organizations. Furthermore, the rationale supporting the recommendation was not always obvious. The authors could not find a way to explain these considerable differences among methodological recommendations.

2.3.2.3 Organizational impact
The organizational impact of new technologies looks specifically at how the new technology would fit into the existing health system. This is where considerations surrounding the ethical, legal, and social aspects of HTA arise. Sensitivities surrounding normative concepts, such as the sanctity of human life and basic human rights, should inform the choices made regarding how and when to adopt a specific technology. Also, the HTA processes themselves ought to be assessed for the highest levels of integrity.\textsuperscript{124} Social, ethical, economic, and legal consequences should be considered and balanced in the adoption and integration of technology. These considerations are taking on an important role in more recent national and multinational research. For example, in the Human Genome Project, five per cent of the budget—roughly eighteen million dollars annually—was devoted to the exploration of social and ethical considerations.\textsuperscript{125} As a result, the US National Institute of Health also established the Ethical, Legal and Social Implications (ELSI) Research Program.\textsuperscript{126} Recently, there have been discussions about broadening ELSI to HELPCESS (humanitarian, ethical, legal, public relationships, economics, safety/security and social implications); although it is yet unclear how these broadened considerations might be adopted into existing frameworks. The scope does appear to promote global health and brings personal dignity to the forefront of discussions.\textsuperscript{127}

There are many examples where technological innovation has challenged ethical, religious, or cultural norms. For example, as technology advanced and medical experts were more capable of determining the time of death, the result had significant implications for organ transplantation but also required one to consider what it truly means for someone to be dead. Hence, many ethical concerns around the practice of
organ donation through cardiac death arose. Whereas doctors in Western Europe and North America largely accept brain death criteria, other countries resist the notion and maintain that the individual, albeit brain-dead, is still alive. A non-health related example of technological impact was the influence of social media on the Arab Spring.

Currently, there are also concerns surrounding resource allocation of items that are scarce, yet lifesaving. Issues such as organ shortages and limited access to quality care prompt researchers, scientists, health professionals and everyday people to collaborate on innovative solutions to these problems. Examples more specific to the endeavor at hand revolve around genetic testing, genetic engineering, stem cell cultivation and use and pharmacogenomics. There are a host of political, economic, and ethical concerns surrounding the use, storage, and access to genetic information as well as the creation of genetically modified organisms. New technologies have the potential to negatively or positively impact patient autonomy as well as human integrity and dignity. Innovations pertaining to genetic health are no different. Stakeholder involvement and investments in decisions surrounding health technologies are critical.

The HTA processes in and of themselves should address the concerns between patients, practitioners, the general public, and technology.

2.3.2.4 Analysis of the pillars

Each of the three pillars brings important considerations to the forefront of HTA. It is immediately apparent why very accurate mechanisms for comparative effectiveness and economic evaluation are necessary. It would be foolish to integrate a new or existing technology without engaging in any process to anticipate and calculate the anticipated
effect or impact. It would also be unwise to adopt the technology without thoroughly investigating the cost. These two pillars are aspects of every HTA; there are well-founded methods by which one can accomplish a thorough investigation of each of these two pillars.

The third pillar, organizational impact, is generally perceived as being an integral piece of the assessment process. This is even a general consensus of its relevance and importance among the HTA community. However, the methods and processes by which ethics, legal, and social implications are assessed are woefully underdeveloped in comparison to the other two pillars. This assertion will be fully developed and articulated in Chapter Three. In the last decade, there has been a fair amount of discourse; and many publications have developed frameworks that analyze ethical and social implications of health technologies. However, these are not integrated into every HTA process.

While it may seem that comparative effectiveness and economic evaluation are independent or at the very least distinct pillars of analysis, it is important to recognize that they have become very closely linked. Y. Hoa and A. Thomas suggest, in a recent article on comparative effectiveness, that due to the ever-increasing healthcare expenditures and costs, there is increased pressure to include cost control as an aspect of comparative effectiveness. In the United States, there are two primary laws that push towards solid evidence-based practice of medicine as well as comparative analysis: the American Recovery and Reimbursement Act (ARRA) and the Patient Protection and Affordable Care Act (PPACA), passed in 2009 and 2010 respectively. The affordable care act also contained a provision that created the Patient-Centered Outcomes Research
Institute (PCORI). This institute is responsible for setting priorities in health research, funding studies, and, most relevant to this discussion, discerning methodological standards for comparative effectiveness research. The PCORI, in conjunction with the NIH, are wading through the multiple definitions of comparative effectiveness research and resulting plurality of technologies. There is a lot of tension, at least in the US, surrounding the role of economic evaluation within the context of comparative effectiveness. The fear lies in the potential for health care rationing and barriers to access due to cost considerations. This is also reflected in the current legislation, which prevents patient-centered outcomes research and comparative effectiveness findings from being used as “mandates for coverage appraisals, payment recommendations or even practice guidelines and federal health programs.”

It is evident from this overview of the pillars of HTA that their very conception or definition, scope, and related methodologies vary greatly among HTA agencies. Some aspects are even ignored altogether. The following section will address some very basic procedural aspects based on the aforementioned orientations and pillars.

2.3.3 Basic procedural aspects

The previous two sections have established the general approaches and key pillars in HTA. This section will explore a number of commonalities among procedural aspects. HTA is in no way a uniform practice or process; it varies from institution to institution and from country to country. Yet, there are common currents and steps that can be identified, most notably ten that are found in virtually all HTA methodologies: (1) identify technology for assessment, (2) identify and clarify the problem, (3) determine the
locus of assessment, (4) gather evidence, (5) retrieve new or additional data if necessary, (6) evaluate the evidence, (7) incorporate the evidence, (8) record findings and recommendations, (9) disseminate the findings and recommendations, and (10) monitor the impact.

While these commonalities exist, not all HTA processes and procedures include all ten; and likewise they are often not conducted in the exact order listed above. Many HTA programs utilize integrated methods that combine steps, which often allows for easier data collection and analysis. In some instance steps are even repeated multiple times until the data collection is considered comprehensive. Also, depending upon the role of the body conducting the HTA, steps nine and ten may or may not be in their scope. However, dissemination of findings and impact monitoring are very important steps in HTA.

There are also significant implications on the utilization and execution of HTA depending upon the scope of the inquiry and the agency carrying it out. For example, organizations that emphasize international collaboration will focus on overarching structures to guide all forms of HTA. Those institutions that are much smaller focus on solving very specific problems or asking very specific questions of particular technologies. Therefore, the focus is much more limited and questions of vision and overarching structure and collaboration are not on the table. In the following paragraphs, two examples will be given on the distinction between HTA conducted at international levels versus how it is conducted at local levels.

EUnetHTA has provided a robust international forum where discourse surrounding HTA's can be conducted. One specific model for conducting HTA,
developed by EUnetHTA, is called the “core model.” It was built to foster and enable international collaboration through results sharing. The core model consists of three distinct parts. The first element is ontology. This consists of a generic set of questions that help define the parameters and contents of an HTA. The second component consists of the sets of methodological guidelines. A set of questions is provided; and through answering these questions one begins to find the most appropriate methodology. The aim of this methodological framework is to encourage and facilitate the sharing of HTA information and joint projects. The final aspect is a common reporting structure. All reports and information have a standard reporting mechanism. Work is currently being done, through international collaboration, to enhance the usability of the core model.

At the national level, each country takes a slightly different approach to HTA. In the US medical devices, interventions, and pharmaceuticals must obtain FDA approval. However this approval is primarily based on safety, and no formal HTA processes are undertaken by the FDA. The AHRQ engages in technology assessments, many of which surround health technologies, but not all. Private insurers have also started to engage in each day practices for employer-sponsored by self-insured health benefits programs. However, little information is available regarding how HTA is conducted in the private sector and how each team reports impact decision-making. In sum, at the national level there are three general types of activities. First, is the licensing of specific medical devices, interventions, and pharmaceuticals. Second, are very specific in-depth systematic HTA processes (e.g. those undertaken by the AHRQ). Finally, HTA is occurring with regard to specific questions inquiries posed by national health systems.
HTA looks quite different at the local or hospital-based level.\textsuperscript{148} A recent survey conducted by N. Martelli \textit{et al} concluded that since 2008 the number of hospitals engaging HTA practices has increased.\textsuperscript{149} Yet, little is still known about the level of impact HTA reports and recommendations have at the local level.\textsuperscript{150} Marie-Pierre Gagnon \textit{et al} recently conducted a systematic review of how local hospitals utilize HTA. This builds on the work started by a subgroup in HTAi, which was primarily interested in understanding how hospitals around the world utilize HTA. The subgroup identified four primary approaches that individual hospitals use when conducting HTA: the ambassador model, mini-HTA, internal committee, and HTA unit.\textsuperscript{151} In the ambassador model, clinicians take on the role of the disseminating specific HTA information and champion the adaptation use of this information. Mini-HTA is a tool that provides support for decision-making. The tool consists of contextual questions primarily surrounding the patient, the organization (hospital and system), and fiscal considerations in the technology itself. A single person usually conducts this assessment. The internal committee is typically an ad hoc committee of relevant stakeholders at the organization; ideally the members should reflect the various perspectives and stakeholders. The committee is responsible for making recommendations. The HTA unit is a structured component of the hospital, with a structured organization and charge. Typically individuals who serve on this unit do so full-time and have specialized training.\textsuperscript{152}

Little is known about the impact of HTA on local decision-making cost effectiveness. This is primarily due to the lack of research and reports generated by those who are engaging local HTA practices. There is the added challenge that it often takes several years to realize the value accepting or rejecting an HTA recommendation.\textsuperscript{153} At
the local level, hospitals can commission HTA reports by private companies. Three popular companies in the USA include ECRI Institute, Hayes, Inc., and Blue Cross and Blue Shield Technology Evaluation Center.\textsuperscript{154} This is often a good option for hospitals that do not have the capacity to carry out their own HTA assessments. These companies provide context specific reports. However, the quality and comprehensiveness cannot be assessed here as access to these reports is limited.

The impact of HTA is challenging to describe. Multiple reports have been published attempting to discern the impact of HTA. These reports, many of which focus on NICE and other national HTA bodies, attempted to characterize the impact of HTA on health systems. By the late 2000s, approximately 17 of these studies had been conducted.\textsuperscript{155} Some of the reports concluded that health systems would act on the recommendations of the HTA reports, while other reports were not as conclusive. For example, one study concluded that health systems by and large reflected the recommendations of NICE appraisals; six appraisals were evaluated in the study.\textsuperscript{156} While other studies suggest that these reports had very little impact on health systems.\textsuperscript{157} Gerhardus et al suggest that while many recommendations are accepted at the policy making level, very few are actually implemented. It is only in those cases where there is significant risk or social issues that implementation of recommendations becomes evident.\textsuperscript{158}

It is clear from these descriptions of international, national, and local utilization of HTA that the focus, scope, and methodology differ. In many cases international collaboration organizations rely on evidence-based practices to develop the tools they implement in order to maximize the effectiveness. In the US, HTA practices and use
appear to be rather scattershot at the national level, based on the needs of the particular institution utilizing the HTA. While the FDA has clearly outlined the strictest standards for evaluating effectiveness and safety, there are still strides to be made in addressing the organizational impact of technologies. Currently, the onus is on specific health systems and hospitals to determine whether a medical device, intervention, or pharmaceutical is beneficial. Some agencies do attempt in-depth HTA; however only a limited number of technologies are assessed; and there is no single repository where this information is collected and made available to the public. Local hospitals are often utilizing what they have at hand, which could be anything from an ad hoc committee to a single professional or standing committee. There is some question as to whether the methodologies used at the local level are rigorous and reliable.159

As a result of examining the function of HTA at various levels, several observations can be drawn. One is the concept of developing HTA that is sensitive to the context of the health care system needs; a second is the development of another orientation, the decision-oriented HTA, to accompany the other dominant orientations (e.g. technology oriented, problem oriented, and project oriented).

One way for HTA to become more inclusive is to be more specific about the precise technologies that are being assessed and why they are being assessed. For example, the technologies that first come to mind are pharmaceuticals, medical devices, and interventions. These are essentially technologies within the healthcare system. Garrido et al expands on these categories, in the article Develop Health Technology Assessment to address health care system needs, and suggests two additional categories that can assist in the selection of methodologies to provide clarity. One of the categories
proposed is technologies and interventions applied to the healthcare system. This category would include the structural and organizational needs necessary to carry out the implementation of the new technology. This could include new policies or new physical space. They deal with the overall process and healthcare outcomes. The second category identified includes those technologies and interventions that exist outside of the healthcare system. These promote and protect how health technologies impact other sectors such as educational services, social services and the like. The authors suggest that clarity can be provided around what is expected from the HTA, and that by using these categories there will be greater focus on the goal and even a possible expansion of methodological approaches. This is because a number of different methodologies can be applied in each of these categories as opposed to trying to apply a single methodology to all.

The authors make the case that if HTA is truly going to develop and expand in order to meet the growing needs in healthcare more attention will need to be paid to other categories about technology assessments mainly increasing focus on regulatory policy measures organizations and health systems. They also contend that it will likely become important for individual hospitals and hospital systems to begin engaging in their own research in order to appropriately address all contexts of an issue, as opposed to relying upon data produced at the national or international level that is not context dependent. The authors argue that while hospitals may need to engage in research, which does not mean that they should do so in a vacuum, or on an island. They should do so working collaboratively with national and international organizations. Across the globe,
countries at all different levels of HTA development and utilization; thus, the diversity of this collaborative opportunity should be fully utilized.

The proposal of a new orientation to HTA is the result of a thorough analysis and the combination of two specific methodologies into one coherent method. Ritrovato et al have suggested a decision oriented HTA. The aim is to bridge the gap that still exists between “the world of research” and “the world of decision-making.” After extensive research, most of which focused on the core model proposed by EUnetHTA, these authors have suggested the combination of multi-criteria decision analysis (MCDA) and analytic hierarchy process (AHP). This new method consists of six steps. The first is defining the problem. The second is conducting a literature review. The third is the creation of a hierarchy construction, which ought to be based on key performance indicators in alignment with the AHP method. The fourth step is to conduct a priority analysis. Step five includes the evaluation of alternative technologies. The final step is a results presentation. This new orientation has already been utilized and tested. This began in 2009 in the Bambino Gesú Children’s Hospital. The results show that this Italian hospital was able to supply more precise and more structured output as well as contextualized evidence of specific technology, making it possible to obtain data that are more relevant and easier to interpret, and therefore more useful for the decision-makers to make investment choices with greater awareness.

2.4 Conclusion

This chapter reviewed current HTA practices as well as agencies, institutions, and governments that are charged or are voluntarily conducting HTA. The predominant
orientations—technology oriented, problem oriented, and project oriented—were addressed along with the three pillars: comparative effectiveness, economic evaluation, and organizational impact. It is abundantly evident that HTA is not highly regulated or standardized. The manner in which HTA is used, and when and how it is engaged, varies greatly across nations and agencies. The information produced is utilized and interpreted in different ways. The orientations differ depending upon the context. The assessment of each pillar is not required. In many cases, organizational impact is ignored altogether. The methodologies utilized vary greatly; and best practices are still being developed. HTA is unwieldy and it is very difficult to get a clear picture as the majority of aspects have very low levels of consensus developed around them. Given that HTA started in the 1970s, one must wonder whether these issues—the lack of standards, agreed upon methodologies, and dissemination of information—are ultimately reflective of the social and political contexts on which local, national, and international healthcare decisions rest.

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Chapter 3: Ethics and Health Technology Assessment

3.1 Introduction

Chapter Three will examine ethics in HTA. Particular emphasis will be placed on identifying how ethics is presently integrated into those processes, and on evaluating the role of ethics in HTA. The value-laden nature of technology justifies the integration of ethics and social considerations, which is lacking in many current HTA models. The chapter begins with a brief introduction to the task at hand and identifies a number of important aspects surrounding ethics and HTA, including: the role of ethics in HTA, appraisal of current HTA tools and methods, identification of gaps or deficiencies in ethics assessment, and finally the ramifications of these gaps.

This chapter will show that, while most professionals involved in HTA believe that ethical assessments and considerations in HTA are critical and necessary, this largely appears to be lip-service, given the general lack of integration. Many contend that ethics is neglected due to the practical limitations of implementing it.

3.2 The role of ethics and HTA

In this section, the role of ethics in HTA is reviewed from a theoretical perspective. Arguments for the inclusion of ethics in HTA will be explored. The implication surrounding the position of health technology as value-laden will also be explored in relationship to the inclusion of ethics in HTA. Ethical perspectives and aspects of HTA are considered in direct reference to the values and norms of the health
care context; in a way this is prescriptive. Ethics assessment offers guidance as to how to act or relate to the issue in question.

Over a decade ago, a survey was conducted by the International Network of Agencies for Health Technology Assessment (INAHTA), and they reported that 80% of HTA organizations and agencies considered ethics to be an “integral part of the assessment”.

As early as 2002, ethics assessments had already been included in a consensus statement about best practices in HTA. A more recent study by Arellano et al, from the Katholieke Universiteit Leuven, Belgium, in 2008, focused on attitudes towards ethics in HTA, from HTA experts themselves. They found that there is a general consensus that ethics assessment is important. For example, 90.1% of respondents in this survey disagreed with the statement that ethical implications should not be considered in HTA. Furthermore, 58.4% of respondents agreed that ethical issues should be an integral part of HTA and be performed by HTA experts. 60.8% believed that at least one, if not more, of the HTA experts working on a given project should have formal ethics training or education. In the absence of an ethics expert on the HTA team, 78.4% of respondents agreed that a professional ethicist should be hired in the role of a consultant.

In this study, the greatest consensus formed around the impact of technology on society. Ninety-three per cent of respondents considered this impact to be important, and believed that ethical analysis should play a role in HTA. The consequentialist argument is really quite simple. There are consequences for every action; this includes the implementation of new technologies. It is often the aim of society to maximize utility; this includes balancing the need for technological advancement and improvement in conjunction with its usefulness. Therefore, ethics assessment should not be minimized,
especially as it pertains to economic aspects of decision-making with regard to new technologies.\textsuperscript{5}

Armin Grunwald, a Dutch philosopher, argues that there are essentially two branches when it comes to how one acquires the knowledge necessary for decision-making surrounding new technologies. These two branches are the ethics of technology and technology assessment. He argues that these two branches have developed largely independent of one another and are grounded on different assumptions about how to orient knowledge for the advancement of technology and policy. The ethics of technology highlights philosophical ethics and analyzes the normative implications and potential moral conflicts. Technology assessment, on the other hand, is primarily descriptive of sociological or economic research.\textsuperscript{6} Since the publication of Grunwald’s article in 1999, there has been much discourse over the role and methodologies of each, and how they overlap and intersect. As a result of this discourse, suggestions of new orientations arose, including applying ethics through the lens of “technology as policy”.\textsuperscript{7}

M. Giacomini \textit{et al,} scholars from McMaster University, Canada, provide a theoretical contribution surrounding the notion of “technology as policy.” The authors argue that there are three important shifts that need to occur in the current thinking about HTA perspectives and approaches. First, there must be a shift from thinking of HTA as a research methodology and reframe it as a form of health technology policy analysis. This would view technology essentially as a form of policy, that in itself forms, shapes, and produces policy. Second, ethics must shift from a foundation in moral theory to focusing on only those values and norms most relevant to policymaking. The final shift must be from the view of evidence as scientific research to viewing it as “intelligence sources”
that necessarily include experts, stakeholders, and public policy makers.\textsuperscript{8} The authors argue that understanding HTA as policy steers analysis away from philosophical questions, ethical principles, and theories. Rather, ethical analysis should be geared toward practical and pragmatic questions. The authors contend that given a pluralistic global society, it is easier to generate consensus around “superficial and pragmatically express norms,” as opposed to “deep ideological commitments.”\textsuperscript{9}

One important question remains—can one justify technology development without the need for any ethical reflection. Grunwald asks whether there are certain conditions that can be fulfilled that would constitute an “ethics-free” space in technological development.\textsuperscript{10} He proposes a principle and framework by which to determine these ethics-free spaces. The principle states: “steps, decisions and processes in technological development are free from the demand or necessity for ethical reflection if, and only if, there is a comprehensive, clear, commonly accepted and factual acknowledged normative framework which has to be and factually is followed in technology development.”\textsuperscript{11}

From this section, one can discern three ways ethics can play a role in HTA. Ethics can be all-encompassing and integrated at the very core of HTA. It can be rebuilt on procedure, which is what primarily exists now, as will become evident in subsequent sections. Or, ethics can be ignored. Ethics can be neglected and remain unengaged; that is, of course, until a moral or ethical crisis hits.

Within these three levels of integration, ethics can be usefully applied to HTA in two ways. Ethics can operate within the existing framework of a given technology and also transcend a specific framework and address the technology itself. When moral
issues, questions, or problems arise as the result of a particular technology they already exist within a framework of the given situation. This framework accepts technology as value-neutral and attempts to identify what responsible and proper use should be. A traditional or classical approach to this includes the four general principles put forth by Tom Beauchamp and James Childress: autonomy, nonmaleficence, beneficence, and justice. From these general principles, rules and guidelines are extrapolated to determine appropriate use of a given technology. This includes both empirical and normative components. Quantitative data is necessary to determine risk, benefit, and financial cost. The normative principles are needed to identify which facts, supplied by the quantitative data, require consideration from an ethical and social perspective. This is useful because the framework can determine which facts require further consideration and sets the stage for additional assessment.

The second way ethics can contribute to health technology assessment, Henk ten Have, Director of the Center for Healthcare Ethics at Duquesne University, argues, is through an evaluation of the technology itself. Technology in this case is not considered to be value-neutral but rather value-laden; that is, the technology incorporates value in itself. This type of inquiry aims at uncovering the entrenched or pre-existing values in a given technology. As a result, a diachronic and synchronic perspective is produced. Ten Have writes: “values embodied in current technologies are explained in connection to similar values in history, but they are also clarified in connection to developments in other scientific disciplines, thus looking beyond the framework of present times and existing disciplines.” This type of ethics research attempts to demonstrate how humans understand their existence in the world, by evaluating what is acceptable and
unacceptable. In addition to these macro-considerations, this type of research should also focus on the values of stakeholders who will be affected if the technology is adopted.14

3.2.1 Justification for ethics in HTA

This section provides a number of arguments that justify the role of ethics in HTA, including arguments based on the value-laden nature of technology and the moral issues surrounding risk and uncertainty, theoretical arguments, and practical arguments.

Ethics should be an integral part of health technology assessment. Many concerns that arise under the categories of benefit, risk, and cost effectiveness are inextricably linked to moral concerns. Health is valued by almost everyone. Emerging health technologies directly impact health; so a variety of perspectives must be taken into account in technology assessment due to their relevance. Furthermore, especially in health care, when new technologies are introduced they create new care or therapeutic options that will impact those already in existence.

Social value impacts the development, evaluation, and use of health technologies. Health technologies reflect interactions between multiple social groups with various social values. Social values impact which technologies will be developed as well as how the development will progress. One example of the impact of technology on society and society shaping technology rests within the definition of death. Margaret Lock argues that without the technological development and adoption of the artificial ventilator there would not have been a reason to create the brain death criteria for the determination of death. Furthermore, it was judged by both the legal and medical communities in the United States that the determination of death is strictly a medical issue. Lock ties this
technological development and results with the introduction of organ transplantation to demonstrate how death determination criteria are inextricably linked to technological developments in organ transplantation.\textsuperscript{15} A significant challenge to considering and assessing social impact and effects is that they may be directly correlated to, or the result of, other social effects, which are the result of still others and so forth.\textsuperscript{16} The questions that arise are inextricably linked with moral considerations, particularly when assessing the benefits and risks of technology.\textsuperscript{17}

Ten Have argues that the gap between ethics and HTA stems from the dominance of the physician-scientist perspective which emphasizes efficacy and cost-effectiveness. He also cites two other equally important reasons. First, technology is often viewed as value-neutral; and thus it is established outside of, or away from, ethical issues. The second reason pertains to the fact that bioethics is a technology in and of itself. It is viewed as a tool to determine and, if possible, resolve the moral consequences of technology.\textsuperscript{18} Despite these dominant perspectives, he argues that ethics should play an integral role in health technology assessment.

3.2.1.1 Value-laden nature of technology and moral issues in risk and uncertainty

Health is valuable because it is a social good. This is why many scholars argue that ethics should be an integral part of health technology assessment. Emerging health technologies directly impact health in a number of ways including access or allocation of resources, delivery, and so on. Therefore, a variety of perspectives must be taken into account in technology assessment because it is relevant for everyone. Furthermore, especially in healthcare, when new technologies are introduced they create new care or
therapeutic options that will impact those already in existence. Health technologies reflect interactions between multiple social groups with various social values. Social values impact which technologies will be developed and adopted, as well as how the development progresses.¹⁹

One of the most persuasive arguments for integrating ethics in HTA is that health technology and its consequences or outcomes are morally relevant and have ethical ramifications. The argument is as follows. Society considers the promotion of health, the absence of pain, or improved health to be a moral good. Technology is a means to that intended end. Therefore, when assessing risks and benefits, and engaging in comparative effectiveness evaluations and economic analysis, the underlying presupposition is that this is being done to achieve a moral good. These normative implications provide justification for including ethics and HTA.²⁰ Given the focus and emphasis on the outcomes and consequences of the adoption of new technologies, this appears to encourage a strictly consequentialist utilitarian framework. Consequentialist frameworks are also one of the primary theories central to economic evaluation. This utilitarian framework, while relevant, is not necessarily the only or the most beneficial overarching framework for ethics assessments and HTA. Recall the fear articulated by Heidegger surrounding the joining of human ontology and efficiency.

Given the close connection between technology and society one might argue that it is just as important to consider the political aspects and applications of adopting new technology as it is the ethical consequences. Some scholars, including Hofmann, argue that political, legal, and social applications should be included as well. He even suggests that the political ramifications might appear to be “from more pressing for decision-
makers than other normative issues.”

These arguments, while closely related and similar in structure, are outside the scope of this dissertation. Yet, it is important to be aware and recognize similar arguments in related fields as they may become relevant.

Technology can also challenge society’s moral principles, practices and beliefs. For example, depending on the adaptation of the health technology, patient autonomy, integrity, or dignity might be impacted. There are many examples of these types of technologies, including cochlear implants, genetic testing, in vitro fertilization (IVF), and prenatal genetic diagnosis (PGD). Cochlear implants are controversial for a number of reasons one of which challenged the accepted understanding of the malady. The deaf community does not necessarily see deafness as a malady; and therefore cochlear implants in young children will dramatically impact their community. The other genetic-based technologies mentioned challenge how humans understand themselves: the rights of embryos, handling predictive information, and considerations surrounding risks and outcomes, just to list a few. Therefore, conducting an ethics assessment becomes critical in understanding the ethical challenges presented by a given technology to entire populations as well as specific communities, and ideally even those who are marginalized or vulnerable.

Every new technology does not pose a major moral challenge. However, this does not mean that the ethics assessment should be overlooked or eliminated. There could be implications for health policy regulations, which impact moral considerations as a result of adopting new technologies setting up those major ethical challenges. One of the difficulties is determining whether or not a new technology will be controversial or
present as significant moral challenge.\textsuperscript{24} This could result from any number of reasons, including functional creep or repurposing.

Health technology is value-laden, as there are normative underpinnings to health technology. Hofmann argues that “technology is given its purposes (promoting health, preventing disease) and its systems (procedures and organizations), which are given by values, making ethics, or at least axiology, relevant for addressing evaluative issues related to technology.”\textsuperscript{25} Addressing the value-laden nature of a technology, while informative, may be inadequate. This is largely due to function creep, which is the repurposing or adaptation of technology for unintended uses. It can be borderline impossible to anticipate these unintended applications.

Hofmann concludes that engaging in health care is not only a practical necessity but also a moral one. Ethics is the vehicle for reflection of this moral obligation. Technology compounds and enhances moral issues in healthcare, thus, technology assessment that does not take this moral dimension into account is lacking as it misses a critical aspect. Furthermore, Hofmann goes on to argue, that technology provides a direct improvement in human life. As a result, this raises questions surrounding what a good life is, and therefore elicits ethical issues and concerns. Eliminating ethics from assessment or neglecting it can lead to actions and adoptions of technology that directly conflict with the primary goal of healthcare, which is to help others.\textsuperscript{26}

Annette Braunack-Mayer, a professor at the University of Adelaide, provides an important distinction to help clarify this point—that is the distinction between ethics of HTA and ethics in HTA. The ethics of HTA examines organizational structure, relationships, value systems, and “functions of HTA as a system of behavior.” HTA is
regarded as its own normative discipline “subject to the same norms and values as the
technologies it addresses.” When the considering the ethics of HTA, it becomes evident
that there are ethical issues at the very center of HTA, particularly surrounding safety,
efficacy, effectiveness, and efficiency. Questions of how one defines safety and what
acceptable amounts of risk are raise moral concerns. Developing criteria to examine
effectiveness or new models to address efficiency also raise moral concerns surrounding
the threshold and limits of each. Ethics assessment is critical in determining these
thresholds and endpoints.

Theoretical critiques of technology appeal to the sweeping assessments of
technology and society by philosophers such as Heidegger, Adorno, Foucault and many
others. These theories and concepts are vital to understanding the value-laden nature of
technology. Ethics in HTA focuses on the technology or intervention itself and assesses
ethical problems and implication produced by the new technology. The technology is
often assessed for safety and efficacy while taking into consideration the wider social
context and ethical implications. This type of assessment typically extends from
analytical philosophy, particularly a principlist approach. Principles are applied to moral
problems presented by a new technology with the aim of clarifying and potentially
resolving the moral problem. Thus, on one level ethicists are working with HTA teams
to comprehensively assess a new technology; and on another level, outside of HTA
studies, ethicists are evaluating HTA as a whole to determine what is ethically legitimate
in HTA. These two approaches complement one another and provide a more
comprehensive assessment of and in HTA. Both are important undertakings.

There are several strong arguments that justify these applications of ethics in
HTA. These arguments are tied directly to recognizing how technology is value-laden and a social good. Ethics can provide two useful contributions. It can identify and address moral issues that arise as a result of a particular technology in an existing framework. Second, it can go beyond an existing framework and assess the value-laden nature of the technology as such. It demonstrates that HTA is value-laden. Moreover, it highlights the importance of, and gives a role to, community and public consultation. It is recognized that the inclusion of ethics in HTA is important; but it has not been fully integrated.\textsuperscript{31}

### 3.2.2 How ethics fits in HTA

Ethics can be conceptually applied in HTA in two ways. It can operate within the existing framework of a given technology and also transcend a specific framework and address the technology in itself. When moral issues, questions, or problems arise as the result of a particular technology, they already exist within a framework of the given situation. The second way ethics can contribute to health technology assessment is through an evaluation of the technology as such. This type of inquiry aims at uncovering the entrenched or pre-existing values in a given technology. As a result, a diachronic and synchronic perspective is produced. This type of ethics research attempts to demonstrate how we as humans understand our existence in the world, by evaluating what is acceptable and unacceptable.

One argument made by Hofmann is that integrating ethics in HTA has the potential to make HTA more efficient. This is largely due to the fact that traditional HTA's, in many cases, leave out important aspects of implementing new health
technologies. Ethics provides a framework whereby one understands some of these other important aspects. This speaks primarily to the dissemination of HCA reports. Many organizations and agencies use these reports for different purposes and understand them in different ways, as seen in Chapter Two. However, the outlooks assessments could provide the common linkage and rationale for either adopting or choosing not to adopt the new technology. Hofmann makes an important caveat—ethics integration may not make HTA reports easier to implement; and in a practical sense it may not make HTA processes easier to execute.\textsuperscript{32}

3.3 Appraisal of current methods that include ethics

This section will examine what the formal introduction of ethics into HTA processes actually accomplishes. This will be done by exploring the integration of ethics into HTA conducted in the United States. More importantly, this section examines current approaches, frameworks, and methodologies utilized in the application or integration of ethics, depending upon the organization.

3.3.1 Brief history of ethics integration in the USA

An ethics working group, in which sixteen agencies from across the globe were represented, was established in 2010 to address ethical issues in HTA. They attempted to develop a framework to assist HTA teams in dealing with ethical issues. The work of this group was published in an article, \textit{Tackling ethical issues in health technology assessment: A proposed framework}, in 2011. After considering many methodologies they decided that an “axiological” approach would be the most effective. This approach
“aims to elicit ethical reflection by highlighting overt and covert value issues though a non-exhaustive selection of targeted questions.”33 Thirteen questions were proposed to flesh out the value issues of process, technology, its implementation and use, its assessment, and stakeholder consideration. This type of assessment tool focuses only on ethics in HTA. It is devised to stimulate debate and bring ethical concerns the fore. However, it provides no systematic way to handle ethical problems when they arise; it only identifies an ethical or moral problem. The authors note that this is the first step towards developing a framework.

It is interesting to note that this first step of suggesting discussion questions appears to have taken place in the 1970s with the OTA’s proposal of questions.34 To operationalize it, the OTA suggest the discussion of ethics issues “with the relevant decision makers at the topic refinement phase of each HTA, having first mapped out who the stakeholders are, including those who are not immediately apparent.”35 The proposed operational mechanism, to some extent, already exists.

The AHRQ, which falls under the United States Department of Health and Human Services (USDHHS), conducts multiple in-depth technology assessments each year. One, already completed earlier in 2015, focused on the topic of cardiovascular procedures and subsequent cognitive function.36 Such assessments provide a forum for public review and public participation, and provide recommendations on evidence-based practice. Yet ethics is not integrated into the reports or procedures. This is interesting as their mission states: “AHRQ’s mission is to produce evidence to make healthcare safer, higher quality, more accessible, and affordable….”37 These aims, while admirable, carry
moral weight. Yet, this work is being done with little to no explicit connection to ethics and social considerations.

Outside of the AHRQ, the Presidential Commission for the Study of Bioethical Issues addresses number of high-level ethical assessments of emerging and existing technologies and processes. However, they are not an HTA body, meaning they do not engage in any HTA processes. Rather, they review ethical issues surrounding emerging technologies, which is valuable and similar to what should be occurring and HTA.\textsuperscript{38}

The FDA is a licensure agency focused on safety and cost effectiveness. While they have an immense responsibility and do a fairly good job executing that responsibility they do not engage in holistic HTA, either.\textsuperscript{39}

The Center for Evidence-based Practice (CEP), much like the AHRQ, is charged with collecting research and conducting original research necessary for state and federal decision-makers to arrive at informed decisions surrounding drug effectiveness and Medicaid. Two major initiatives in which they are engaged include the Drug Effectiveness Review Project (DERP) and Medicaid Evidence-based Decisions Project (MED).\textsuperscript{40} Again, it is interesting that a national organization that focuses on evidence-based practice, safety, and decision-making at the national level does not make explicit reference to ethical considerations on their website or in their publications.

There appeared to be no consistent standards or guidelines when it comes to the evaluation of technology, at the national level, in the US. However, some organizations, private and abroad, utilize coherent and integrated ethics assessments; these will be explored in the following sections.
3.3.2 Current methods

A recent study conducted by N. Assasi et al focuses on conducting systematic review of ethics methodologies and applications in HTA. The authors identified 43 conceptual frameworks comprising practical guidelines. Each of these used a different philosophical approach and structure, and had varying degrees of robustness and comprehensiveness. Furthermore they were designed to take place at very different points in the HTA process. The following are a number of ways the authors characterized the results of their finding. Of the 1,474 potential citations only 128 met the initial criteria. An additional 85 were removed from the list after further review, leaving the research team with twenty-one articles and twenty-two sets of guidelines included in the study. Six of the twenty-two guidelines included in Assisi et al’s study were developed by international or multinational organizations and agencies including the World Health Organization (WHO) and EUnetHTA. The rest, 16 in total, all had their origins in European countries. Interestingly, all ethics articles and guidelines were published in the English language.

One common characteristic that the frameworks and models possessed was that they were based on multiple ethical theories. It appears that—among ethics experts—there is consensus that a holistic approach must be adopted if the framework is going to apply across emerging health technologies. The reviewed frameworks included a number of wide-ranging ethical considerations that might be relevant in HTA. Primary ethical domains that the authors synthesized from their data collection include benefit and harm (safety), autonomy, equity (fairness or distributive justice), stake-holder values, utility, acceptability, psychological impact, impact on family and care givers, quality of
life, efficiency, opportunity cost, and ethical issues related to appropriateness of methods chosen for economic evaluations.\textsuperscript{44}

With regard to practical and procedural guidelines the authors discerned roughly four general approaches. These include what they termed as “classical methods” which rely on ethical reflection informed by well-founded ethical principles and theories. The second category includes the integration methods with participatory and interactive approaches, including the wide-reflective equilibrium. A third category centers about tools that enhance the synthesis of ethical data. The final category includes those frameworks that discuss ethical data to inform HTA decision-making.\textsuperscript{45}

The following sections will address the dominant ethics methodologies, including interactive and participatory approaches, social construction approaches, the wide-reflective equilibrium, integrated approaches, principlism and casuistry, as well as practical approaches.

3.3.2.1 Interactive, participatory HTA approaches

Interactive or participatory approaches engage stakeholders in meaningful and honest discourse in an effort to limit bias in HTA.\textsuperscript{46} Participatory TA and HTA are qualitative methods. The aim is to determine the attitudes, concerns, interests, understanding, and patterns of thinking of laypersons. Interactive approaches, in some cases, also assess the reasoning and arguments used by the public in relation to technology and policy. This information is used to inform policy makers. There are a number of different mechanisms proposed and utilized for participatory approaches, since the aim is to collect data on stakeholders. In many cases, the stakeholders must be
educated through awareness initiatives, which is one technique available. Other
techniques include social experiments, discussions and focus groups, workshops, and
consensus conferences.47

One analysis model is the axiological-based value analysis model. This is
proposed by Burls et al. Hofmann offers a similar participatory model.48 It centers on
public attitudes, values, beliefs, including a wide range from economic to social. It
emphasizes the origins of the values, the relationship between them, and the resulting
social dynamics. To map these values, Burls et al suggest a value analysis.49

Another model that invites wide participation is the triangular model. This model
suggests that there are three data points: facts, anthropology, and ethics. Sacchini et al
suggest that through data synthesis and reflection, informative data can be gleaned for the
evaluation of health technologies.50

Chantale Lessard, a Canadian scholar at the University of Montreal, developed a
conceptual framework to specifically integrate ethical considerations into economic
evaluation. The framework is grounded in complexity theory. The aim is to take into
consideration a large number of technical, contextual, and environmental factors. These
should be viewed as interrelated and evaluated in light of each other, as one vision.
Stakeholders are involved in the process, providing information on the environmental
factors, including social and ethical considerations. One emphasis is the sensitivity to
uncertainty, namely the unanticipated interactions or reactions between health
technologies and a given environment.51

In the study conducted by Assisi et al, fourteen frameworks emphasized the
necessity and importance of stakeholder perspectives and participation. In many of the
participatory models reviewed, stakeholders were utilized to gain insights into personal and social values and norms pertaining to the technology. The underlying assumption of these approaches is that the relationship between technology and society is not fixed or static. They influence and shape one another. Those scholars who champion participatory approaches often advocate for stakeholder engagement and involvement to occur early in the HTA process.\textsuperscript{52}

3.3.2.2 Social shaping of technology (SCOT)

The social shaping of technology frameworks take up the same assumptions and arguments articulated in Chapter One. Social shaping of technology (SCOT) approaches address the interaction between technology and society and assess ways to shape technology so that it benefits society. Deliberation on the influence of technology on society and vice versa is central to the enterprise. Social issues pertaining to societal norms and values as well as ethics are specifically addressed.\textsuperscript{53}

K. F. Douma \textit{et al} propose a constructivist framework, in the article \textit{Methodology of constructive technology assessment in health care}. The proposed constructive technology assessment framework (CTA) emphasizes both the technological facts and questions at hand as well as the environment in which the technology will be situated. The continuous change and interaction of the technology and environment are monitored as the technology continues to develop and diffuse throughout the environment over time. The endpoint of the measurement is when the quality of the new technology is optimized or stable. This means that it has stopped evolving and has a stable function, and application to society.\textsuperscript{54}
There are many additional approaches and frameworks similarly structured and based on the same philosophical and sociological foundations. Most notable are those forwarded by Grunwald and Clausen and Yoshinaka.\textsuperscript{55} Both of these frameworks contain elements of participation, and were mentioned in the previous section.

Bijker introduces a wide interpretation of the “technological frame.” Recall from Chapter One that Bijker claims a technological frame is “a combination of current theories, tacit knowledge, engineering practice such as design methods and criteria, specialized testing procedures, goals, and also handling and using practice.”\textsuperscript{56} This is important because the concept must include laypersons and non-experts, such as non-engineers and non-scientists. A wide audience is necessary in order to recognize and connect different problems and available solutions. This concept describes the interaction between all the relevant actors and stakeholder. The technological frame is not simply a collection of the perspectives of relevant individuals or system as a whole; rather, the important aspect is interaction between the actors, not the actors themselves.\textsuperscript{57} Technological development is a two-sided coin, one side is social impact and the other is social shaping. Bijker uses the concept of technological frame to demonstrate this. The technological frame of a social group is shaped by an artifact’s development and stabilization within that social group. This demonstrates social impact, which is observable. On the other hand, technological frames also influence and, to differing degrees, determine the design process within a specific group. This demonstrates social shaping. This holistic approach forms the concept of the technological frame.\textsuperscript{58} The identification of these shifts can provide useful information to HTA teams.

SCOT is not just a combination of different social and technical aspects shoved
together; nor is it simply applying an existing sociology model to technology. What Bijker has laid out is a mechanism for analysis that engages a “sociotechnical ensemble.” He argues that this approach allows one to find the socially-constructed character of an artifact while simultaneously being able to determine what constitutes a stable set-up. This approach amounts to three important theoretical activities. First is the sociological deconstruction of the technology in an effort to understand its interpretive flexibility. Second is describing the technology’s social construction. The final activity is to explain the social construction process in light of the technological frame, which is informed by relevant stakeholders.59

Overall, the key difference between SCOT approaches and participatory approaches is the level to which participants are engaged, and the way the data gleaned from the participants is used. In SCOT approaches, much more social surveillance and observation occurs, whereas in participatory approaches the majority of the data is informed by stakeholder and public responses.

3.3.2.3 Wide reflective equilibrium and Integrated approaches

Wide reflective equilibrium approaches attempt to arrive at consensus regarding ethical judgments of technology through a process of reflection.60 Through a thorough review of ethics methodologies it was found that the wide reflective equilibrium is not often used on its own, but rather in conjunction with other applications or methodologies. It usually functions as a decision-making mechanism. The wide reflective equilibrium is a method that emphasizes stakeholder and layperson involvement in a reflection process. Deliberation occurs among a wide set of societal perspectives, beliefs, and values. This
method seeks to balance normative claims and other judgments through reflection to arrive at a consensus on an issue.⁶¹

One of the most robust frameworks utilizing the wide reflective equilibrium is an integrated approach. Integrated approaches put forth a holistic assessment that actively integrates social and ethical considerations into health technology assessment by combining two or more approaches described above. Interactive evaluation is one integrated approach that utilizes elements of social constructivism, stakeholder participation, and the wide reflective equilibrium. It is designed to be a holistic approach and help avoid normative bias by considering multiple perspectives to yield an evaluation and decision-making process that is effective in assessing controversial issues.⁶²

Reuzel puts forth a holistic assessment that actively integrates social and ethical considerations into health technology assessment.⁶³ Reuzel argues that a useful framework or paradigm can be constructed by combining social constructivism and Michael Scriven’s evaluation theory; he terms this approach “interactive evaluation.”⁶⁴ Scriven, known for his contributions to the theory of practice and evaluation, asserted that evaluation is the “science of valuing;” it is the determination of merit or worth. Generally there are four steps: (1) establishing the criteria of merit; (2) constructing standards; (3) measuring performance and comparing with standards; and (4) synthesizing and integrating data into a judgment of merit or worth.⁶⁵ The force of this evaluation strategy is strengthened when coupled with social constructivism.

Constructivism asserts that the truth about something or its perceived merit is constructed. This means that the technology in question resulted from directed choice (not haphazard chance) reflecting what is desirable and useful. Therefore, when
constructivism is applied to health technology it asserts that—as the technology was being developed—decisions were constantly made regarding form, function, or use. Reuzel arrives at the conclusion that health technology can be, to some extent, directed. Thus, social scientists and ethicists have a role in evaluation research. They are charged with aiding in “constructing alternatives for a better society, which is based on insight into the social embedding of the things being evaluated.” Reuzel states that this paradigm aims at evaluating the interactions between relevant persons and parties involved with the interaction resulting in deliberation and harmonization. In the end questions must be answered and decisions must be reached.

There are three essential axioms of this approach. First, facts are contextual. They are given meaning through the norms and values of the individuals operating in a particular framework. Second, it is impossible to circumvent this subjectivity, and arguably undesirable as well. Therefore, what interactive evaluation attempts to accomplish is to explain the different frameworks, including norms and values, of the relevant social groups and stakeholders. Problems and issues are identified and clarified as each framework is explored and considered alongside the others. The most important tool in this process is interviewing.

It has been successfully argued that ethics should play a role in health technology assessment. When one asks questions such as “what values are at stake?” or “what happens when different groups or individuals assign various or even conflicting values to the same technology?” moral considerations are already being made. Reuzel recognizes this and places a substantial emphasis on the necessity for ethical consideration in interactive evaluation. He lays out the role for ethics as it fits in his framework quite
clearly. In controversial cases, ethics can provide precise clarification of the matter and issues at hand, as well as guide deliberation to avoid or escape the controversy. He does not believe that traditional approaches, like the four principles approach of Beauchamp and Childress, will be useful because the goal of that framework is to assess moral right or wrong. In the interactive evaluation framework the goal is to design alternative solutions and thus escape moral controversy, not solve moral issues or pass judgment. He employs the ethical tool of casuistic analysis as a mechanism for clarification, because it has the potential to find “a widely endorsed solution to aspects of a technology-in-context that make up the controversy.”\textsuperscript{70} In addition to that, he utilizes a wide reflective equilibrium to promote legitimacy and fairness. The equilibrium must be agreed to by all participants, eliminate power relationships, and should be a newly established equilibrium that reflects the current context.\textsuperscript{71}

Agreement or a temporary consensus is the goal. While feasibility of agreement can be an issue, a more pertinent question is whether the agreement is justified. Reuzel \textit{et al} argue that yes, agreement can be justified if it is regarded as a wide reflective equilibrium.\textsuperscript{72} The wide reflective equilibrium is based on John Rawls initial conception of the reflective equilibrium; however, to be applicable here it must meet three criteria. It must be inter-subjective; achieved by all individuals involved; and, finally, a new equilibrium must be produced as opposed to forcing individuals into an established ethical measure.\textsuperscript{73} Interactive evaluation can also reduce normative bias. This is important because HTA is not always an objective enterprise. For example, cochlear implants were being used in pre-lingual deaf children and this posed a threat to the deaf community. Many physicians and proponents of the cochlear implant perceived deafness
as a handicap since having the capacity to hear is the norm. However, many in the deaf community do not agree. In this example, it was assumed that deafness should be eradicated and the considerations of the deaf community were not taken into account. By taking into account three major axioms mentioned above it becomes possible to reduce normative bias. For Reuzel, the role of ethics in health technology assessment is to address moral controversy. By clarifying the issues, the goal of finding an escape from the controversy can begin. The issues and values at stake, as well as moral beliefs, entail social constructions. Therefore, by creating and designing acceptable alternatives participants have the ability to modify their values and perspectives.

Reuzel’s approach is both feasible and productive. He succinctly demonstrates this in his assessment of cochlear implantation. It is a comprehensive, labor intensive approach that merits serious consideration. However, this framework only addresses ethics within the context of an existing technology that bring about some form of controversy. Therefore, it only addresses one of the ways ethics can be employed in HTA. Reuzel does not explicitly assess the ethics of HTA; it is only assessed in relation to the social impact and controversy. The role he gives to ethics and social construction suggest that this could be a very useful paradigm.

Several other frameworks utilize the same tools, similar logic and philosophical arguments, but arrive at different configurations of integrated approaches. One such example, from Johnson et al, originated in Canada. It is a framework that uses multi-criteria methodologies, with special attention to ethics. The framework is based on four criteria for HTA assessments, including clinical benefit, consistency with ethical and social values, cost–effectiveness, and feasibility of implementation. The authors call
for systematic research including literature reviews, public participation, and stakeholder deliberation. After this, policymakers may consider a recommendation or decision regarding the health technology. Rather than utilizing the wide reflective equilibrium, this framework relies on a decision-making rubric developed by Goetghebeur et al, which is a structured decision-making process that takes all dimensions—ethical, social, technological, economic, safety, etc.—into consideration. The information is transcribed into a matrix where it can be processed and scored by experts. The goal is to provide a ranking for the best overall outcomes as well as the best overall alternatives among health technologies.77

3.3.2.4 Principlism and Casuistry

Principlism applies overarching ethical principles, which mirror a given society’s common morality, to ethical problems. Casuistry is the practice of applying analogous logic; cases in question are compared to similar cases that have been undisputedly resolved. These two are often practiced together.78

Beauchamp and Childress identify and utilize four key principles which, when properly applied to the field of biomedical ethics, can provide a justified guide for action. It must be noted the Beauchamp and Childress are only addressing the field of biomedical ethics; they are not providing or attempting to explicate a general moral theory. They do not start with abstract principles; rather, they begin with middle principles in conjunction with case specifics. These four principles are considered to be prima facie principles, which mean that the principle must be fulfilled or adhered to, unless there is a conflict.
The first principle is autonomy, which is respect for the human person. This means that each autonomous agent has the right, and others acknowledge that right, to have specific opinions, make choices, and act according to their own volition. This principle demands not only a respectful attitude but also respectful action. Respect for autonomy requires more than noninterference with others’ lives. At times action is obligatory, such as helping others maintain their autonomy and help eliminate conditions that could disrupt autonomous action.79 The second principle is beneficence. This principle is twofold; individuals must refrain from hurting one another, and furthermore must contribute to the welfare of others. Beauchamp and Childress identify two key aspects of beneficence—positive beneficence and utility. Positive beneficence stipulates that individuals provide benefits to others. Utility requires that individuals “balance benefits, risks, and costs to produce the best overall results.”80 Third is the principle of nonmaleficence; this is the do no harm principle. The principle of nonmaleficence imposes an obligation to not intentionally inflict harm on others. In medical ethics it has been closely associated with the maxim Primum non nocere: “Above all [or first] do no harm.”81 The fourth and final principle is justice. Beauchamp and Childress do not endorse any specific theory of justice. However, the concept of justice provides a foundation by which to analyze the other three principles. For example, if one is an egalitarian the individual will appropriate these principles much differently than someone who is a libertarian. However, which ever concept of justice is employed, it must be ethically justified.

The relevance and roles these principles play depends upon which one is emphasized or given more weight. This obviously effects the consequential conclusion
and decision. This will be briefly demonstrated through the example organ donation after cardiac death (DCD). It can be argued that DCD fulfills the principle of beneficence because this act benefits the donor, as their wishes are being carried out, and the recipient, who needs this organ to live. On the other hand, the principle of nonmaleficence could be used to argue that just because there is a lack of evidence that the patient is being harmed does not mean that the patient is not being harmed by using a two to five minute interval for the determination of death. The exact time of death is unknown, hence organ procurement could happen before death, which would harm the patient. 

Taking on a different perspective, if beneficence is championed, one could go as far as to argue that it is a moral duty to contribute organs to others. Individuals have the moral obligation to allow their organs to be used in order to save the lives of others. On the other hand, if one emphasizes autonomy and nonmaleficence, it is arguable that organ donation is certainly not a duty and furthermore some methods of procurement directly violate or harm the patient. The goal of this example is not to show that one principle can trump another, because ordering is not the intention when it comes to these four principles. Rather, the complexity rests in finding the proper balance of these four principles. In the example above, it is not that one principle is perhaps more important or overarching than another; instead it is about finding the proper application.

From this, it is clear that several different arguments, with vastly different outcomes, can be justified through these principles. It is the account of justice that needs explanation. Justice does not seem like a middle principle at all. In fact, in their theory it seems to be the guiding principle. However justice, for Beauchamp and Childress, does not balance other principles; rather, it balances theories of justice that are applied to these
principles such as libertarianism, egalitarianism, utilitarianism, communitarianism, and so on. The methodology of ethical justification is the overarching aspect that allows for any sort of justification. They maintain that “no single theory of justice or system of distributing health care is necessary, or sufficient, for constructive reflection on health policy.” While all of the general theories mentioned above provide a valuable perspective on morality they “only partially capture the rich diversity of that life.” Yet, Beauchamp and Childress tell us that although there are several viable and, at times, conflicting theories, this does not justify a piecemeal approach to health care. They claim that this piecemeal approach, currently used in the United States, is simply a way to avoid the larger complex questions about justice. The exact role of justice in Beauchamp and Childress’s theory is that justice not only balances differently theories of justice but it is also “a group of moral norms for fairly distributing benefits, risks, and costs.” The purpose of this structured theory of biomedical ethics is to explicate principles that are derived from considered judgments that stem from common morality. We will consider the problem of conflicting norms in the next section.

For Beauchamp and Childress, principles are the most general and comprehensive norms. Although there is a loose distinction between rules and principles, both are general norms of obligation. The key difference is that rules are more specific in content and more restricted in scope than principles. Principles do not function as precise guides to action that direct society in each circumstance in the way that more detailed rules and judgments do. However, *prima facie* principles alone “do not contain sufficient content to address the nuances of moral problems.” This means that *prima facie* principles do not possess the specificity to deal with the complex issues of biomedical ethics.
Beauchamp and Childress employ the process of specification in order to reduce the indeterminacy of abstract moral norms. That is, the specification adds content. Some specifications go as far as to prohibit certain actions, for example, prohibitions of cruelty. Weighing and balancing principles and rules is often a necessity. Balancing is the process of finding reasons to support beliefs about which moral norms should be utilized; it also considers the relative weights, strengths, and weaknesses of different moral norms.

Beauchamp and Childress’s analysis of conflicting moral norms relies heavily on W. D. Ross’s distinction between prima facie and actual obligations. “A prima facie obligation is one that must be fulfilled unless it conflicts, on a particular occasion, with an equal or stronger obligation.” This means that the obligation is absolute or binding unless another moral obligation outweighs it. The actual obligations result from examining the competing prima facie obligations and deciding what ought to be done. There is no moral theory or system that is free from conflicting norms and thus exceptions. For Beauchamp and Childress there are six conditions that must be met in order to justify infringing one prima facie norm to another: 1) good reasons can be offered to act on the overriding norm rather than on the infringed norm; 2) the moral objective justifying the infringement has a realistic prospect of achievement; 3) no morally preferable alternative actions are available; 4) the lowest level of infringement, commensurate with achieving the primary goal of the action, has been selected; 5) and negative effects of the infringement have been minimized; and 6) all affected parities have been treated impartially.
Beauchamp and Childress offer three methods for ethical justification: top-down, bottom-up and an integrated approach. Top-down models are similar to deductive logic. This is the model that Rawls employs; except he does not advocate for balancing principles. Principism begins with a set of principles or premises that collectively form normative precepts that result in justified moral judgments. Simply put, a general principle is being applied to a specific case and that general principle informs individuals how to act or respond to that specific case. The argument structure would like this: 1) Action X is morally obligatory, 2) Action Z is the same as action X, then 3) Action Z is morally obligatory. Many moral aspects of human life fit this model quite nicely. However, this model, while useful, can at times be insufficient. This model requires that theories, principles, and rules take priority to traditional practices, institutional rules, and case judgments. The difficulty is that principles often are so abstract that it becomes incredibly difficult to determine an exact course of action for a specific case. At times, when trying to achieve a stable balance, some principles must be specified and emphasized over others in order to make proper judgments. In order to balance principles, the particulars from specific cases are taken into account to inform judgment. In difficult cases there is a complex interplay between principles and facts, rather than simply principles informing the actions of the individual involved.

The second type of ethical justification is the bottom-up model. Casuistry is the most well-known bottom-up model. Bottom-up models are similar to methods of inductive logic. Essentially, the justification begins from a specific set of particular instances and progresses to generalities, rules, and norms. Principles and rules are not prior, epistemologically speaking, but rather derivative. The starting point for decision-
making in particular cases includes preexisting social practices, precedent cases, the study of new cases, and comparative case analysis. Inductivists argue that this model is actually more allied with how human beings reason and problem solve on a daily basis. It reflects human experience and allows morality to evolve. Simply put, a set of ethical rules are developed from a social consensus shaped directly by particular cases. There are some concerns that should be highlighted regarding this type of model. First, there is no clear methodological resource; this means it is a highly subjective process. As with any subjective process, it remains difficult to prevent destructive biases and is easy to ignore morally relevant aspects when they do not produce the desired end result. Another concern is the issue of conflicting analogies. The bottom-up model, for it to have any success, must result in cases being properly resolved. If a case is improperly resolved and subsequently used as an analogy or precedent to address other cases, there will be a continuous chain of improperly resolved cases. Hence, it will be incredibly difficult to break and correct that cycle. Despite these challenges, this method is still a very useful tool. Casuistry is one form of bottom-up reasoning, it will be addressed later in this section.

There is a third method of justification put forth by Beauchamp and Childress. As frequently happens, when faced with two opposing models a researcher inevitably combines the two in order to create a more palatable one. This is exactly what Beauchamp and Childress have done; they suggest an integrated model that utilizes Rawls’s concept of the reflective equilibrium. The key to Rawls’s notion of the reflective equilibrium is that when some aspect of moral theory, held by an individual, conflicts with their considered judgments, they are required to adjust one or the other to restore the
equilibrium. This means that the process of revising and reevaluating our moral beliefs, in order to adhere with the moral principles we hold, will allow the individual to continually develop a consistent network of moral beliefs. This is precisely what Beauchamp and Childress call for in the field of biomedical ethics. Of course, it would be foolish to think that the achievement of a completely stable equilibrium is realistic. However, by continually waxing and waning through a network moral beliefs, in light of the goal of stability, the individual will move closer to that stable equilibrium.\textsuperscript{101} If accepted and properly applied, the reflective equilibrium is a sufficient methodology for justification.

According to Beauchamp and Childress, an individual’s initial norms are informed by common morality. They explain that morality refers to a set of norms that dictate the right and wrong qualities of human action. When these norms are widely accepted, a stable social agreement is formed. Common morality applies to everyone in all places. It provides the foundation to judge all humans and their conduct by the standards of common morality. The point of emphasis is that common morality has normative force. By establishing a set of standards by which all are judged, common morality creates a way to mediate human interaction by rendering some actions unethical.\textsuperscript{102} Common morality relies on shared moral belief as its starting point; however customary moral beliefs deriving from a specific culture do not qualify as part of common morality. Common morality also maintains that when an ethical position is inconsistent with pre-theoretical moral values it is highly suspect and should come under scrutiny.\textsuperscript{103} Finally, common morality is pluralistic. In sum, Beauchamp and Childress
are advocating for reflective equilibrium as a methodology working in tandem with a common morality approach to considered judgments.\textsuperscript{104}

Casuistry is a case-based reasoning method. The basic logic is that similar cases ought to be treated similarly. This assists in building coherence and consistency within systems. Typically, this is done by describing the case in question and comparing the ethical considerations and or problems surrounding this case with examples of ethical considerations related to similar cases. This helps to identify the paradigm that best fits the case.\textsuperscript{105}

There is an element of coherency that must be addressed when using principlism or casuistry. Coherence analysis, as it is sometimes called, can be employed to ensure the consistency of an application and analysis of ethical reasoning and judgments. Beauchamp and Childress attempt to address this coherency through the reflective equilibrium. This includes assessment of the use of theories, principles, and value judgments. Assessment does not indicate whether some arguments are stronger than others, it simply attempts to ensure consistency and application.\textsuperscript{106}

3.3.2.5 Practical Applications

Some frameworks go beyond the basic methodology and attempt to provide a practical skill set or toolbox for HTA processes. This allows individuals or groups to conduct ethical assessments in a coherent, structured way. Many of these tools include checklists and sets of questions. Consensus is that ethical reflection on context-sensitive details that entertain different perspectives and apply multiple ethical theories or principles can be synthesized into usable information. Three of these proposed tools will
be briefly described, including the frameworks proposed by Droste et al, Hofmann et al, and Culyer et al.\textsuperscript{107}

There are times when it is incredibly difficult to even locate relevant ethics materials, which can dash any desire to perform a thorough assessment. There should be a systematic way to search for relevant ethics data. Sigrid Droste et al, in the article \textit{Information on Ethical Issues in Health Technology Assessment: How and Where to Find Them}, proposed a framework to make this more accessible, based on a similar tool used in the assessment of clinical benefits.\textsuperscript{108} Their framework specified key search terms and databases for ethics and HTA. Along with this information, they introduced some relevant search strategies for ethics related content. The framework also suggests the utilization of consultation from an expert ethicist. Their eight-step process included: (1) translation of the search question using the PICO scheme [Patient/Problem, Intervention, Comparator, Outcome] and additional components; (2) concept building by modeling and linking search components; (3) identification of synonyms in all relevant languages; (4) selection of relevant information sources; (5) design of search strategies for bibliographic databases; (6) execution of search strategies and information seeking, including hand-searching; (7) saving of retrieval results and standardized reporting of the process and results; (8) final quality check and calculation of precision and recall.\textsuperscript{109}

Bjørn Hofmann published a series of thirty-three ethical, or morally relevant, questions, called the Socratic approach, related to the development and use of healthcare technologies in 2005. The questions are broken into seven groups: (1) the morally relevant issues related to the disease and patient group; (2) the ethical, social, cultural, legal, and religious challenges related to the health technology; (3) moral challenges with
structural changes related to the health technology; (4) issues related to the characteristics of the health technology; (5) the moral issues related stakeholders; (6) the moral issues related to the assessments of the health technology; and, (7) additional moral concerns. Over the past decade this method has been implemented and incorporated into several methods. It has been used in multiple HTA projects including human papilloma virus vaccination, neonatal screening for inborn metabolic disorders, stem cell transplantation, bariatric surgery, and many others. While the method has been useful, a number of working groups have come together to determine how to adapt the Socratic approach in HTA. The goal is to increase the transferability of information.

There are a number of limitations within this approach. One of the largest is the fact that it is a checklist of questions; and, as with most checklists, it is not exhaustive. This means that there is the possibility that some important ethical issues might be neglected. An expert group assembled to assess the limitations of the Socratic approach identified fourteen limitations. They also made additional recommendations to increase the impact and value of the methodology. The revised approach now only has six steps as opposed to the seven listed above. They include: (1) identify the intended purpose of the health technology and revealed the background for the assessment; (2) identify involved persons, groups, and stakeholders; (3) identify relevant moral questions from a list questions and justify the selection; (4) perform literature search in accordance with the identified moral questions; (5) analyze and discuss the moral questions identified in step three on the basis of existing literature and hearings or statements have involved parties qualitative studies; and, (6) wrap up and summarize the process. It is important to articulate these six steps in order to draw an important comparison between the old and
the new versions. There is a significant advantage to this new six-step approach as opposed to the previous set of thirty-three questions. However one element that is missing from both of these is the final evaluative step, which is to evaluate the process and make recommendations on improving the process for further use.

Another tool, in checklist format, was proposed by Anthony Culyer and Yvonne Bombard, both scholars at University of York. These authors provide a comprehensive checklist for specifically addressing the issues of equity. It can be adapted to different stages of the HTA process. For example, it could be used to identify technology priorities; yet it could also be utilized to discuss equity considerations in the final recommendation and decision-making phases. The authors maintain that there are two issues that are hindering the development of a holistic HTA. The first is the fact that there is no consensus on the significance or the scope of equity. The second issue is that there is no consensus on a process or mechanism that allows for the systematic and comprehensive treatment of equity along with cost-effectiveness. Based on these issues, the authors developed a framework to address equity issues in HTA. A common understanding or consensus about equity in HTA is critical in moving the discourse forward. This ensures that assessments treat similar cases similarly, and one can begin to resolve the discrepancies nationwide and globally of differing HTA results and adoptions, both appropriate and inappropriate, of technology.

3.3.3 Analysis

Some scholars argue that multiple ethics methodologies can be applied simultaneously; and this provides the benefit of multiple perspectives. On the other hand,
however, there are the scholars who argue that there are underlying fundamental contradictions between some of these methodologies and this requires the use of one theory to ensure consistency.\textsuperscript{116}

Several issues have been raised with the SCOT approaches. Klein and Kleinman claim that the two problematic areas lie in method and explanation. They call the “snowball method” into question. The snowball method is how relevant social groups are identified. They claim that this is inadequate because “identifying unrecognized and missing participants, while its emphasis on groups overlooks social structures that might account for such absences.”\textsuperscript{117} Social constructivism also struggles to explain success and failure in the creation of new technologies. Bijker relies on the concepts of closure and consensus, but does not explain how consensus is reached.

Klein and Kleinman argue that too little attention is paid to the power of the relevant groups. Perhaps group power dynamics would explain why some groups’ meaning and interpretations carry more weight and ultimately become the consensus.\textsuperscript{118} A final criticism of this theory rests on Bijker’s notion that “modern society must be analyzed as a seamless web.”\textsuperscript{119} Klein and Kleinman argue that this view of society makes the determination of cause and effect impossible; and thus, the proposed analysis also become impossible.\textsuperscript{120} This point may be off target. Bijker’s notion is that technology and society are constantly shaping each other; it does not appear that proving cause and effect for one over the other is a primary concern in Bijker’s framework.

In order to conduct ethics analysis there is a need for ethical knowledge and ethics expertise. In Assasi et al’s appraisal of ethics methods, they noted that six frameworks specifically highlighted the need for ethics expertise. Specifically, ethics expertise is
necessary in preparing search strategies, making and assessing normative judgments, and providing the requisite ethical knowledge and education required for analysis, discourse, and decision-making.\textsuperscript{121} A recent study in Canada revealed that there was a general lack of available ethics experts. However, they interestingly reported that it is “unlikely to be a barrier to conducting ethics analysis in HTA in the Canadian context.”\textsuperscript{122} Furthermore, Bond \textit{et al}, in the article \textit{Ethics Expertise for Health Technology Assessment: A Canadian National Survey}, cautioned against the employment or utilization of ethics experts, since there is not a currently reliable credential for ethics expertise.

A very interesting distinction is made by Sandman and Heintz, two Swedish HTA scholars, in the article \textit{Assessment vs. appraisal of ethical aspects of health technology assessment: can the distinction be upheld?} They suggest that the distinction between assessment and appraisal is very tenuous and in many cases difficult to support. This is relevant for ethics assessment and HTA because HTA are limited to the assessment aspect of it while other individuals or decision-makers are responsible for the appraisal and recommendation aspect of HTA. Appraisals and recommendations carry the force of either accepting technology, possibly requiring mandatory adoption other technology, or eliminating the possibility of adoption of the technology due to ethical issues and or norms that we are expected to follow. For example, if there is an incredibly positive appraisal within the ethics portion of an HTA, and it follows that the rest of the HTA is consistent with a positive appraisal, this could ultimately result in the recommendation that it is mandatory to implement this technology. One can even go so far as to conclude there is a moral obligation to do so if the benefit is great enough. The authors argue that as long as the ethics assessment portion is presented transparently it is an obligation of
ethics experts to disclose “well-founded conclusions are and or whether they're power alternative conclusions, the HTA agencies should not avoid taking the ethical analysis as close as possible to the definite conclusion.” What the authors conclude is that if experts engage ethics analysis honestly and as objectively as possible, they should not stop short of drawing conclusions and making recommendations. They believe that these two elements—assessment and appraisal—can work hand-in-hand.

Some arguments posit that ethics is not necessary to address the question of whether a technology is “efficacious, effective and efficient, it is crucial to answer the question of whether it is right or not to implement and use the technology. Although this is relevant for health technology appraisal, it is not for assessment, where the issue of whether it is right or not to implement technology is declared to be beyond its scope. Accordingly, there would be no need for integrating ethics.” This position maintains that technology and HTA is value-free, or at the very least value-neutral.

3.4 Deficiencies and Gaps

This section addresses the deficiencies and gaps of current methods of HTA; they are noticeable in the theoretical and practical roles of ethics. These include priority setting and completion rates, the narrowness of ethics in HTA, and the lack of oversight and general standards.

3.4.1. Ethics is not a priority

The word “priority” can have multiple meanings in different contexts. Here the focus will be on two meanings of the word. First, in the common use of the term, ethics
is not a priority in HTA. Very few national HTA programs have a quality integration of ethics. Ethical guidelines are often developed by multinational organizations with time and endowments to support operations, as well as a strong commitment to collaboration and inclusion. When committed to these, ethical and social sensitivities are required.

The second use of the term “priority,” deals with a specific function in HTA; that is priority setting. Ethics, thus far, has had a limited role in priority setting in HTA’s. Few countries and organizations engage in meaningful and intentional priority setting processes. Yet, the suggested benefits of ethics inclusion in priority setting have been articulated for the last fifteen years.¹²⁵

There is inconsistency regarding the types of technologies selected, as it is typically the purview of specific agencies which technologies they choose or are expected to review. When a technology is assessed, there are also issues with completion rates.¹²⁶ Mitton and Donaldson, in the article Health Care Priority Setting: Principles, Practice and Challenges, conclude that applying an ethical framework to priority setting in HTA assists in the identification of organizational behavior. This is important when developing a comprehensive priority-setting approach.¹²⁷ A study of priority setting, conducted by Hussein Noorani et al. concludes that developing methods in priority-setting is not necessarily a true priority.¹²⁸ The authors identified fifty-nine unique priority-setting criteria in the eleven agencies examined. There is immense variability among priority setting techniques; in addition, quantitative rating methods that include cost-benefit considerations were not often utilized. Priority setting methods are really only being developed in those countries with well-established HTA bodies. The impact of having a sound priority setting technique is that it will increase the timeliness and
relevance of topics, it will improve technology tracking, and will also allow for the identification of new criteria and the refining of existing criteria.129

Here is a specific example of completion rates as they pertain to randomized controlled trials (RCTs). Through March 2011, there were 98 RCTs published in the Health Technology Assessment journal. These were the results surrounding the completeness of the reports:

Components of the intervention description were missing in 68/98 (69.4%) reports. Baseline characteristics and descriptions of settings had the highest levels of completeness with over 90% of reports complete. Reports were less complete on patient information with 58.2% of the journals having an adequate description. When looking at individual intervention types, drug intervention descriptions were more complete than non-drug interventions with 33.3% and 30.6% levels of completeness, respectively, although this was not significant statistically. Only 27.3% of RCTs with psychological interventions were deemed to be complete, although again these differences were not significant statistically.130

These results, complied by Douet et al, have some dramatic implications. They call into question the replicability of the studies reviewed. Douet et al were very careful to address the replicability of their study, and the authors conclude that their methods are transparent and easy to replicate. They also raise questions as to whether the studies reviewed were transparent, complete, and ethical.131 They note that these are important aspects, however, ethics was only mentioned at one minor point in Douet et al’s entire article, and it was to note that this research did not require or solicit and ethics approval.132

As ten Have points out, ethics can play a critical role in identifying those technologies that should be prioritized.133 This was demonstrated in the Dutch study conducted by Marc Berg et al, in the article Technology Assessment, Priority Setting, and
Appropriate Care in Dutch Health Care. The study commented on the appropriateness of HTA agendas, and the potential impact of calling into question the legitimacy of health professionals in determining prioritization, rationing, and resource allocation. These are questions of ethics. The authors note: “in priority-setting debates and attempts, political and ethical considerations are discussed openly; any attempt to delete an intervention or service from the insurance package has always been met with an avalanche of moral, political, economical, and other reasons why it should or should not be included.”

Through the assessment of emerging or new technologies recommendations can be made based on the observations and outcomes of current HTA's. Given the priority of social impact and values, and considering the norms at stake, stakeholder involvement becomes crucial. Stakeholder involvement puts ethics assessment in a prime position to make calculated and informed decisions about which technologies require immediate attention. In essence, this should play a role in priority setting.

Hofmann suggests that this could be due to the fact that practicing ethics or bioethics is significantly different from practicing HTA. There are very few ethics experts who also have expertise in HTA. Ethics does not usually fit in a nice tidy box or as a step in the process, which is counterintuitive to the way HTA processes are run.

3.4.2 Ethics in HTA is too narrow

The second deficiency is that both theoretical and practical aspects of ethics in HTA are too narrow in multiple senses of the term. They are too narrow because the questions asked and investigated are in some cases too specific. Questions must be asked about the true goals of ethics integration with HTA. Interdisciplinary approaches, while
recognized as vital, are often inadequate; and there are only a limited number of
technologies addressed with HTA and even less so with ethics and HTA. This relates
directly back to the previous discussion about the role of ethics in HTA. Since there is no
defined role, and there are challenges to implementation, it becomes more convenient to
neglect the endeavor altogether.\textsuperscript{137}

Ethical assessment often occurs late in technology development, which is
problematic. When reviewing HTA processes, if ethical assessment occurs at all it is
often in one of the final phases. Some examples will be explored where technology
would have greatly benefited from early ethics assessment. SCOT methodologies and
participatory approaches call for this, but are not frequently adopted.\textsuperscript{138} The timing is
problematic, because if ethics assessment is relegated to the end, there is potential for the
assessment to be rushed or neglected altogether.

\textbf{3.4.3 There is a lack of oversight and consistency in standards}

The final deficiency to be addressed here is directly linked to and amplifies the
first two; there are no standards, requirements, or oversights, outside of Institutional
Review Boards, for research involving human participants. There are only guidelines,
proposed frameworks, and checklists. This means that when ethics assessments is
engaged in HTA process—if it is engaged at all-- it is done so with varying
methodologies and scope. Furthermore, HTA generally suffers from this problem. The
argument is not for regulation in the sense of government statutes or laws. Regulation of
HTA would be most helpful and beneficial if it came in the form of benchmarks and
identification of best practices. Evidence-based practices have been articulated for
economic evaluation and comparative analysis; however they are far from finalized. There are very limited evidence-based practices for measuring organizational impact and ethics assessment.

There are a number of examples where lack of structure produced negative consequences. One example of this is the drug mebeverine. Mebeverine is a drug used in the treatment of abdominal cramping and irritable bowel control. Moret-Hartman, Van der Wilt, and Grin conducted a case study around this drug. The HTA conducted was not sufficient because the problem was not defined correctly. Therefore the decision rendered and defended by clinicians and policymakers had the potential to be problematic. Through a rigorous analysis using the theory of argumentative policy analysis, the authors concluded that the usage problem relating to this drug was not properly structured. In reality, there was disagreement about norms at stake and the information needed to address problem. For example, physicians were concerned with maintaining a positive relationship with the patient and patient satisfaction, while policy makers were concerned with the cost of the drug and reimbursement. This means that the experts conducting the HTA did not respond to the perceived problems of the target population. The authors concluded that in the future, if HTA and participatory approaches are to be useful, they must accurately characterize all accounts and perspectives.

The lack of oversight, standards, and evidence-based practices is the direct result of having no consensus surrounding methodology. Furthermore, many methodologies are deficient or flawed in some way. There have been attempts to develop consensus
among multinational organizations such as workshops conducted by the INAHTA, HTAi, and EUnetHTA. However, consensus has not been reached in the HTA community.\textsuperscript{142}

### 3.5 Challenges and why the deficiencies probably exist

This section addresses the two largest categories of obstacles or challenges to the integration of ethics in HTA. These challenges also likely account for existing deficiencies; although there are always difficulties in determining and proving causal relationships. Two categories of issues will be addressed. First are the practical issues of time, fiscal resources, and other factors. The second major challenge, again, returns to the relationship between society and technology, medicine and values. This is the issue of the technological imperative and how it is expressed in healthcare.

#### 3.5.1 Time, fiscal resources, and other factors

The first obstacle is time and money. Technological assessments are lengthy and expensive because they are interdisciplinary, requiring experts from an array of fields. Assessments are important because they can reveal information about intrinsic risk and therefore redirect research to mitigate such risks. They can identify the need for new or additional controls and regulation, reveal the consequences of a particular technology, or even prevent potential abuses by evaluating potential risks. Meeting these goals requires going beyond examining efficacy and cost-effectiveness. There is no question about the value and necessity of health technology assessment or the inclusion of ethics in that assessment.
Timely execution of HTA is very important. HTA is meant to inform key decision-makers and policymakers on the use of health technologies; this means that the information has to be available before a decision must be made. For this to occur, those who engage in HTA must conduct their studies in a timely manner. The decision to utilize HTA must include careful consideration of timing. The goal is to find the balance between allowing reimbursement decisions to be made as quickly as possible while at the same time minimizing risks should the technology turn out to be of little or no value, or in the worst case scenario, dangerous.143

HTA is not a one-and-done process. For many agencies and organizations it might appear that way, because they carry it out in that fashion. More advanced countries and organizations review decisions after a certain period of time; still they is few and far between. For example, the DERP evaluates and updates its evidence-based medicine reviews once every two years. Another example is NICE’s practice of reviewing recommendations every three years. There are situations when review is required sooner; this occurs when new information becomes available or major adjustments have been made to the technology.144

The importance of time is made clear by the recent flurry of publications surrounding the benefit and implementation of rapid reviews and mini-HTAs.145 CADTH has established the Rapid Response Service in response to the high demand for timely HTA. This new service allows them to conduct HTA in approximately five to six months. The service includes providing reference lists, summaries of abstracts, summaries of critical appraisals, peer-reviewed summaries with critical appraisals, systematic reviews and meta-analysis, and the final review resulting in a Rapid HTA.146
However, expedited processes can also have severe ramifications. To rush through the HTA process does not allow for the closing of the assessment loop; that is, reflection on the process as a whole and implementing action steps to improve the process. This potentially impacts both priority setting and determining benefits. Furthermore, this can be linked to the general neglect of ethics and most HTA functions. If there is little time to conduct HTA that means little reflection on processes and procedures as well.

Ethical assessment require time and money, both of which are often in short supply; experts generally do not work for free. Until additional funding sources such as grants or expanded budgets become available and include provisions for ethical assessment, the participation of ethicists and other social scientists may be limited. It is fiscally and temporally impossibly to do thorough technology assessments on every health technology. Limitations in funding bring up additional ethical questions such as “should assessments only be carried out on selected projects, if so, which ones?” Ethical and social examination of health technologies may be able to assist in answering these questions or developing creative solutions. Fiscal consideration and budgetary allocations are necessary for ethics assessments. If such assessments do not appear as a line item on a budget, it will likely not happen. Furthermore, physical limitations impact each of the three deficiencies already identified here.

One final factor to consider is whether or not the integration of ethics is worth the efforts. Hofmann summarizes this point by stating “it has taken so long to try to integrate ethics in HTA and so many resources has been spent; it obviously cannot be worth the effort.” He goes on to support this by acknowledging that there is no concrete
evidence of increased effectiveness or efficiency due to ethics integration. Furthermore, it is difficult to demonstrate any concrete outcomes from the integration of ethics. He suggests that including ethical considerations in HTA muddies the decision-making process, and ethicists tend to complicate issues rather than clarify them. He says, anecdotally, “Letting one ethicist into the room is the same as letting in a pile of incoherent opinions.”149 Beyond, anecdotes, Hofmann argues that HTA professions believe they are capable of carrying out ethics assessments, and, thus, there is no need for the inclusion of ethics experts.150

From a strictly logistical and pragmatic position this may seem to be a very persuasive argument. However, given the importance of moral considerations relating to human quality of life and health, ethical considerations must be assessed. Hofmann succinctly articulates the three options for ethics: no integration at all—in fact, remove the term ethics from HTA definitions; take current definitions seriously and integrate ethics to the same extent as economic evaluation and comparative effectiveness; finally, adjust the very nature of HTA so ethics assessments and be authentically carried out.151

3.5.2 The technological imperative

The second major obstacle is somewhat philosophical in nature, and that is the overuse of technology in medicine, which dramatically increases healthcare costs and can at times put the patient at unnecessary risk. One driving factor of medical technology is the physician’s desire to provide good care of their patients; thus the most thorough tests are ordered. Also fear of malpractice suits, because the US is a notoriously litigious society, causes many physicians to call for a litany of tests and be overly thorough as
opposed to discriminating in their selection of tests given to their patients. This is an obstacle for technological assessment and, by extension, ethics. Ethics, in this case, may have the capacity to help contend with this issue. If ethics is able to explore the value-laden nature of technology as such, the results may shed light on this overreliance and overuse of technology in medicine.\(^{152}\)

Hofmann notes that there are many different conceptions and characterizations of the technological imperative, especially as it is applied to health. It was a significant topic of discussion in the 1980s when observations were being made that there seemed to be a reliance on technology to the extent that “medical technology has grown from being a tool to becoming a companion and, in some cases, the master of physicians.”\(^{153}\) Those scholars who were part of the discussion then apparently held a positive outlook and thought that in the coming decades there would be a more rational integration of medical technologies. Hofmann observes, however, that there does not seem to be any reason to believe that the application of technology in healthcare is any more rational today than it was in 1980s. In fact, he writes that there seems to be a “pathological reliance on technology” and that “technology has become the bias of our culture.”\(^{154}\) He asks the appropriate questions about our understanding of technological imperative. “How is it possible that although we develop and apply technology in healthcare ourselves, we can still feel that we are controlled by it?”\(^{155}\)

There are a number of reasons why society adapts and integrates existing technologies and new technologies in healthcare. When addressing patient concerns, running additional tests that may be outside of the necessary scope can relieve anxiety. From the physician’s perspective, running additional tests can assist in the avoidance of
malpractice suits. Outside of relieving anxiety and avoiding malpractice, sometimes patients demand to have certain procedures; and they are obliged by physicians who do not wish to argue the finer points of necessity. This partially harkens back to respecting patient autonomy. Some may argue that there is a moral imperative to the use of technology, and that it helps in some way to advance patient autonomy. An observation that takes a slightly more cynical turn is that new technology is integrated to retain some level of paternalism. By rendering the technology so difficult to understand, it becomes nearly impossible for patients not familiar with medicine to fully comprehend the technologies themselves and the implications of treatment. That puts the onus of understanding and application on the physician.

It is very difficult to determine whether a technological imperative truly exists in healthcare. This relies completely on the characterization of the technological imperative. An important observation is that regardless of the characterization, the technological imperative somehow impacts human responsibility in healthcare. It can reduce responsibility or increase responsibility. For example, the application of technology in healthcare has been very powerful and allowing experts to more precisely diagnose and respond to health maladies. If it is argued that society ought to do everything possible to help the patient, then it might be conceivable to view the technological imperative as both an imperative and a moral obligation. Conversely, the adaptation of technology can be seen to reduce the human responsibility in medicine. This is because the human element is to some degree taken out of it and the responsibility is placed on technology's ability to function properly.\textsuperscript{156}
3.6 Conclusion

This chapter covered landscape of ethics and HTA. First, the role of HTA was considered in light of the value laden nature of technology and the relationship between technology and society. Arguments were presented that supported health as a social good, and confirmed the conclusion that ethics should be an integral part of HTA processes. This was followed by a brief survey of how ethics assessments can theoretically and practically fit in, or not fit in, current HTA processes.

Several existing methodologies and theoretical approaches were reviewed. These ranged from highly theoretical methodologies, such as the SCOT approach, to very practical approaches such as the Socratic approach. Each methodology reflected the underlying vision and understanding of the role of ethics in HTA.

The remainder of the chapter surveyed current frameworks and approaches to deliver HTA. It was concluded that while these efforts are portable, there are some remaining gaps and deficiencies. They are: (1) ethics as a priority; (2) the timing and narrowness of ethics assessment; and (3) the lack of standards, guidelines, and consensus surrounding methodology. In addition to these deficiencies and gaps there are a number of obstacles that must be overcome as well. The obstacles include limitations and restrictions around time limitations and fiscal resources. Furthermore, questions surrounding the philosophical positions posed in response to the technological imperative must be addressed.

When considering the integration of ethics in HTA there are three definitions that become incredibly important: integration, ethics, and HTA. It is clear from the global overview provided that the HTA community and experts have no consensus on any of
these. Hence, the level of ethics in HTA is dependent upon the answers to what HTA is and what HTA should strive to become. Thus HTA experts may see ethics as a threat or burden to the current assessment nature of HTA or possibly as a mechanism for further development and enhancement of current processes.

It is unreasonable and naïve to think that a single dissertation can solve, or even adequately address, any one of these deficiencies or gaps in HTA. What this dissertation does attempt to accomplish is to solidify the role of ethics in HTA, specifically in emerging genetics health technologies, and alleviate some of the practical problems identified in this chapter. This is accomplished by recognizing the reality of the landscape for what it is, and embrace the inconsistencies, flux, and chaotic nature of implementation.

The nonlinear approach will be fully outlined in the following chapter, and attempts to take the strengths of ethics methodology and combine them with sound methodologies from other disciplines to increase the validity of this approach. The goal is to find a way to have meaningful ethics assessment occur throughout the process of new technological development.

ENDNOTES


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7 Grunwald, *Technology Assessment or Ethics of Technology?* 170 - 171.


13 ten Have, *Ethical Perspectives on Health Technology Assessment*, 73.

14 ten Have, *Ethical Perspectives on Health Technology Assessment*, 74-75.


17 ten Have, *Ethical Perspectives on Health Technology Assessment*, 72.

18 ten Have, *Ethical Perspectives on Health Technology Assessment*, 73.


22 R. P. B. Reuzel, "Health Technology Assessment and Interactive Evaluation: Different Perspectives" (PhD, University of Nijmegen).


26 Hofmann, Why Ethics Should Be Part of Health Technology Assessment, 425-7.


29 Braunack-Mayer, Ethics and Health Technology Assessment: Handmaiden and/or Critic? 308-310.

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35 Burls et al., Tackling Ethical Issues in Health Technology Assessment: A Proposed Framework, 235.


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43 Assasi et al., Methodological Guidance Documents for Evaluation of Ethical Considerations in Health Technology Assessment: A Systematic Review, 204-205.

45 Assasi et al., *Methodological Guidance Documents for Evaluation of Ethical Considerations in Health Technology Assessment: A Systematic Review*, 205-211.


54 Douma et al., *Methodology of Constructive Technology Assessment in Health Care*, 162-8.


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135 Marc Berg, Tom Van Der Grinten and Niek Klazinga, *Technology Assessment, Priority Setting, and Appropriate Care in Dutch Health Care*, 42.


Hofmann, *Is There a Technological Imperative in Health Care?* 675.

Hofmann, *Is There a Technological Imperative in Health Care?* 680.

Hofmann, *Is There a Technological Imperative in Health Care?* 684-687.
4.1 Rethinking ethics in HTA

Chapter Three identified a number of deficiencies and gaps in current ethics methodologies and approaches applied to HTA. This chapter will address these deficiencies by proposing an approach that rethinks and broadens the integration of ethics in HTA. In addition to addressing the deficiencies, this chapter will also provide a response to the obstacles in HTA, and how this new approach can have a positive impact. The approach specifically addresses time on task, fiscal concerns, and the technological imperative. Additional benefits and limitations outside of those addressed in Chapter Three will be discussed at the end of this chapter. Many of these observations are not new; however, the argument to incorporate them into a nonlinear approach is unique and original. The contribution of this dissertation is to provide a methodologically sound and valid ethics approach with the appropriate corresponding tools.

To accomplish all of this, the first section of this chapter will provide a brief overview of the deficiencies, outlined in Chapter Three, to frame the introduction of the non-linear approach. The following sections will introduce and fully detail the nonlinear approach. Throughout the delineation of the nonlinear approach, methodological justification and evidence of validity will be presented and discussed. A description of how the nonlinear approach addresses the deficiencies, gaps, and obstacles, as well as an articulation of expected benefits and limitations, will be provided. The chapter will close with some remarks on how the nonlinear approach does and does not fit with current HTA practices and processes.
4.1.1 Priority and priority setting

From the analysis provided in Chapter Three, it is clear that, for most HTA processes, ethics is not a priority. This is despite the general consensus around its integral role in HTA. The United States, one of the most developed countries in the world, does not have a coherent ethics framework by which to address HTA. Most of the existing and more well developed ethics methodologies and frameworks have originated in Europe or in multinational organizations such as the WHO, INAHTA, and EUnetHTA.

Priority setting is currently becoming a major concern in the HTA community. This is due to the seemingly exponential increase of emerging health technologies, which increases the demand for HTA. There must be a way to prioritize these technologies to ensure that those posing the greatest risks, both normative and practical, are being immediately addressed. However, there are no evidence-based practices or best practices available as this is still a newly emerging issue. Ethics assessments, which have the capacity to identify those important norms and values of greatest concern to stakeholders and society at large, is currently not part of the priority setting discourse in any meaningful way. Some scholars maintain ethics has insights and valid methods to contribute to priority setting; but these have yet to be systematically explored.

4.1.2 Ethics assessment occurs late in the process and is too narrowly focused

If ethics is employed in HTA, it is typically relegated to a specific point in the process. Many of the models articulated in the previous section do not function properly.
as a cog in machine, or in this case a step in a process. Ethics methodologies and approaches that take broader ethical considerations seriously include SCOT methods, participatory approaches, and integrated approaches.\(^4\) These are very challenging to integrate into existing HTA frameworks. Many of the practical approaches have been built to function as a step in a process. For example, Hofmann’s 33-question framework, known as the Socratic approach, fulfills this role. This is meant as a systematic framework that can be executed within a known timeframe. That is a great benefit to HTA planning and execution. In fact, Hofmann’s approach has been successfully integrated into many HTA processes and reports.\(^5\) This indicates the willingness to integrate methodologies that are low-maintenance and flexible. There is nothing inherently wrong with this, as it makes sense from a logistical perspective. However, the trade-off of depth, breadth, and inclusion are not to be taken lightly. This has been noted in recent assessments of the Socratic approach.

### 4.1.3 Limited oversight and guidelines

Limited oversight, lack of standards, and lack of regulations have a profound impact on the integration of ethics in HTA.\(^6\) Since there is no professional consensus around guidelines, and limited consensus about the role of ethics, including appropriate integration of methodologies, it is challenging for HTA agencies and organizations to make coherent progress. Furthermore, there does not appear to be an overwhelming demand from national or global bodies for the integration of ethics. There is, however, a call for greater transparency.\(^7\) Simply because there is a lack of oversight does not mean that everything should be regulated or subject to external review. Rather, a good first
step would be to formulate best practices based on evidence. This falls more in line with the ethics of HTA as opposed to the ethics in HTA, which is not the focus here. It is legitimate to question the benefit of conducting ethics assessment at all. Currently, there is no clear data on return on investment, cost-savings, or life-saving interventions on the part of ethical recommendations. Despite the lack of concrete evidence, though, there are still arguments to be made. The answer is part philosophical and part practical. The philosophical arguments have been addressed in Chapter Three. The practical argument for the integration of a nonlinear approach will be fully delineated in Chapter Five. The following section details the phases of the nonlinear approach. The analysis will return to these deficiencies and gaps after the approach has been explained.

4.2 A nonlinear approach

4.2.1 Explanation of the approach

This section details the components of the nonlinear approach; it is based on foundations laid in Chapters One through Three, and shapes a model of ethics integration in HTA. The model provides a way to make ethics relevant and meaningful in HTA. The theoretical foundation is grounded in the conclusions drawn in Chapter One surrounding the relationship of society and technology and the value-laden nature of technology. It is nonlinear in the sense that it does not function as a point in a process, and is cyclical in nature. Also, it emphasizes finding an optimal solution among multiple alternatives, because that is the best possible answer when addressing emerging technologies. This is grounded in methods of nonlinear programming.
This approach has a number of primary aims: (1) begin ethics assessments earlier, (2) provide a flexible framework whereby ethics experts and non-experts can coherently work together; (3) support, not stymie, scientific progress; (4) provide meaningful discourse and recommendations; and, (5) continually improve by assessing the ethics assessment mechanism itself. All of these elements are embodied in this approach. These overarching aims assist the approach in addressing a number of the deficiencies and gaps introduced in Chapter Three.

4.2.2 Scope

The nonlinear approach is developed specifically for emerging genetic health technologies. Emerging genetic technologies are of a unique variety, as the very nature of the technology calls into question some of our most foundational normative principles. As such, at this point in time, a practical methodology is needed to address emerging genetic technologies specifically. The reasoning and justification for selecting genetic technologies will be provided in Chapter Five. Initial arguments will be provided in the analysis of the nonlinear approach in this chapter.

The aim of the approach is to be flexible, accessible, and inclusive. This means that it is flexible based on the context of technology. It can be adapted to meet the needs and scope of the project, as it is based on specific research questions. It is an accessible methodology in that it is easily understood. However, experts are needed to undertake some of the data analysis and project design aspects. Scientists, researchers, and for that matter any person involved in the development of a given emerging genetic technology, can use this approach.
This assessment tool should be employed while the technology is still in the research and design phase. This takes the nonlinear approach out of the restrictive HTA timelines and processes. It is more akin to a TA process, in this respect. It can be engaged from the very start of a new research project or shortly after a study is undertaken. As the project reaches certain benchmarks for major breakthroughs the process will continually be reengaged. The ethics assessment will continue to grow with the emerging technology.

4.2.3 Overview of the nonlinear approach

There are five overarching phases in the nonlinear approach. They include: (1) identification and inquiry; (2) research and data analysis; (3) concept mapping; (4) evaluation; and, (5) closing the loop. The visual below represents the intention of this approach to be continually utilized, engaged, and reengaged at critical points in the development of emerging genetic health technologies.
The nonlinear approach is nonlinear in two overarching ways. First, it is nonlinear in the sense that it moves through multiple cycles and it does not function as one point in an HTA process. Second, within the approach itself there are elements of nonlinearity, including the flexibility to transition back and forth between phases, reflect on the entirety of the approach at any point, and the inclusion of elements that are unknown or unconstrained (this will be addressed in Phase 3). The nonlinear approach retains a structure, and this structure at points requires certain things to happen. However, this must be done for purposes of coherence.

The rest of this chapter will fully detail the intended activities in each phase of the nonlinear approach. The methodological strength of each phase will be presented and discussed. Finally, a coherent picture of how each phase fits in the larger context on the nonlinear approach, as well as in broader HTA processes, will be presented and discussed along with the projected benefits and limitations of this approach.
4.2.3.1 Phase one: Identification and inquiry

The first phase identifies the scope of the technology and all intended and potential uses. There are two activities in this phase that must be completed. First one must identify research benchmarks and construct a rough timeline. Second, the facilitators or research team must identify the values associated with these intended uses, and construct a research question.

As previously stated, this methodology is developed for emerging genetic health technology. Ideally, this approach would be adopted at the onset of new research or integrated into research soon after scientific results are available. There are a number of ways to identify technology in need of assessment; one such methodology is horizon scanning. The technique of horizon scanning is a process that systematically examines emerging technologies for early signs of potential threats or opportunities. The emphasis on new technologies surrounds the uncertainties in risk prediction. It takes seriously the trends in technological developments, explores unexpected issues that arise in existing technology, and evaluates persistent problems. This is all done in an effort to predict what technologies will present opportunities or threats in the future. A recent horizon scanning study surrounding health-related genetic tests conducted by Gwinn et al, in the article *Evidence on Genomic Tests at the Crossroads of Translation*, reported that:

After the pilot phase, our scan detected approximately two to three new genomic tests per week. Nearly two thirds of all tests (122/188, 65%) were related to cancer; only 6% were related to hereditary disorders. Although 88 (47%) of the tests, including 2 marketed directly to consumers, were commercially available, only 12 (6%) claimed United States Food and Drug Administration licensure.
The contribution of engaging in horizon scanning is the positive impact it has on priority setting for other emerging genetic health technologies. Utilizing the work that has been conducted is central to anticipating future developments. It will also help to identify whether there are similar technologies being developed that could be included or benefit from being included in this research. A recommended activity, although not required, is that researchers consult recent horizon scans to determine similar technologies or research being conducted or developed.

This approach will likely not work well if utilized by an outside agency or body assessing a research firm or team’s work. This approach is meant to adapt and grow as a technology is developed. Therefore the perspective of an outsider observing the research is not as useful as this approach being integrated with the work of the scientific research team. For meaningful ethics assessment the approach must be integrated with the research. Thus, to attain meaningful results, the inclusion of the research team is paramount. The important point is that this is not an appropriate methodology for oversight or regulatory bodies. This is an internal mechanism by which a research team or research firm can conduct ethics assessment in a meaningful way. The benefit of this is twofold. The data can be directly transferred to any formal HTA processes. Second, it will alleviate some of the societal skepticism that usually accompanies emerging genetic technologies. Further explanation and arguments surrounding the reasons why emerging genetic technologies hold a special place, at this point in human history, will be articulated in Chapter Five.

If a research team is curious whether or not this approach is appropriate to engage, they need to consider several points. First, will this technology at any point
perceivably impact human health in any way, whether it be as a direct medical device, treatment or intervention or something that will address human health in other ways such as environmental improvements? Second, is the foundation of this research dealing with genomics or genetics? If the research will impact human health or quality of life and is based in genomics or genetics, then this approach is appropriate for that technology.

After a research team engages this approach, phase one can officially commence by formulating a research question for assessment. Basic inquiry and question-framing is critical to this process. The formulation of the question will impact how it is answered. Each cycle starts with a research question that relations directly to ethical considerations. That question can be massaged and reframed throughout the process. Questions will be different depending upon the stage of development of the technology. For example, technology in the very early stages of development may ask questions of general population perceptions of values or morality towards the potential uses and benefits of the technology. Questions can also be as open-ended as asking what the potential ethical or social problems, issues, or controversies in this technology might include. Technologies in more advanced stages of development may ask more specific questions to elicit results that guide education or advocacy plans. For example, questions might surround whether a given population will utilize this technology, or how adoption of this technology might impact current health system structure or other existing policies.

4.2.3.2 Phase two: Research and data synthesis

There are two actions that need to be completed in this phase: the literature review and analysis; and outcomes setting. It is important to gather as much information
as possible about the scholarship already completed pertaining to the new technology or any similar technologies. To accomplish this, a literature review should be conducted that directly engages both the technology and the research question. This research should be compiled and a brief analysis developed. All participating researchers should familiarize themselves with this material. There are three recommended methods to go about conducting a successful literature review, these include the methodology proposed by Droste et al, outsourcing the work, and conducting a literature review based on sound research practices. It is also important that after the literature is collected that it be synthesized and disseminated to the research team.

First, is to utilize Sigrid Droste et al’s research methodology, which is specifically developed for locating ethics information for HTA. The benefit of utilizing this approach is that it allows research teams that do not have a strong foundation in research methodology conduct a literature review on their own. The authors provide a robust eight-step framework. The steps include:


This useful and user-friendly methodology was discussed in Chapter Three. The second option is to outsource the research. This can be accomplished in a number of ways, including partnering with a research university or college, or other organization such as a rapid report service or private HTA firm. For example, Canada has developed a rapid
report service that provides concise and semi-synthesized data on HTA related topics and technologies. Furthermore, they allow clients to specify research parameters. Given the need for expedited HTA, it is likely other organizations will soon offer similar options. The Canadian rapid report system can provide reliable research in a little as five to six months. Depending on the timeline of the research, this may or may not be an appropriate selection. If the two options recommended above are not practicable, the third option includes conducting the research and literature review internally using other reliable research methods.

From this research, the information collected must be synthetized and disseminated. The synthetics should provide a summary of information collected, this can take the form of an annotated bibliography or a white paper. These materials should be circulated to the research team, and they should familiarize themselves with it.

In some cases, information may be limited or non-existent given the newness of the technology. This is acceptable, as this process will be repeated; therefore, literature reviews may yield more results after the technology has existed for some time. The final action in this phase is to set research objectives or intended outcomes. Based on the research question and the information gathered the following questions should be answered: (1) what is the knowledge to be gained?; (2) in what way is this knowledge going to be useful?; and, (3) who can help to gain it?

4.2.3.3 Phase three: Concept mapping

Concept mapping is a means by which to visualize the connections between, ideas and concepts from a wide range of perspectives. Concept mapping has sound
mythological foundations in the social sciences since its inception more than two decades ago. There is an impressive body of technical literature supporting the process. Concept mapping has also been applied to a broad range of disciplines and projects, including some in health care. The methodology continues to be developed, refined, and adapted. HTA literature surrounding the application of ethics methodologies contain multiple frameworks that mention mapping or finding a coherent way to link concepts, ideas, facts, and perspectives. In effect, this is seeking social patterns of values and coherency in them. Concept mapping is a tool that can accomplish this in a comprehensive way with a very high level of validity.

Groups utilizing concept mapping draw on both qualitative and quantitative research. This information is then translated into a visual, which helps simplify the complex task of balancing and connecting multiple stakeholder perspectives. A concept is an element or component of a larger theory—in this application, the nonlinear approach. Kane and Trochim state that, “fundamentally, concept mapping facilitates the identification of common themes to enable theory development, decision-making, action, or assessment.” Groups that participate in any sort of public planning must address the challenge of finding a way to coherently work together. Not only is the challenge of communication and collaboration daunting, but it can also be difficult to find a common framework that can guide the group work. The use of concept maps provides a flexible, inclusive framework that can be fit to any group, because concept mapping is contextually specific and naturally inclusive.

Concept mapping has been used in healthcare as an education tool, specifically in nursing. It has been shown to improve organizational skills, critical thinking, and has a
tremendous impact on how students understand and create care plans. Concept mapping has also been used in very practical ways, including as a mechanism to improve decision-making in health care. Concept mapping has been used to collect data and evaluate diverse stakeholder opinions on primary health care services. It has been utilized to explore how patients cope with disease or illness in a given health system. The challenges faced by individuals with traumatic brain injury have been assessed using concept mapping. Concept mapping has also been used in public health and many other areas. The application of concept mapping to healthcare is not new. There are well-established examples; and it has been integrated in many university curricula.

This method has even been suggested as a possible methodology in HTA. Donna Southern et al, an Australian scholar at Monash University, suggested concept mapping as an alternative to discussion or focus groups. The suggestion was made as a way to remedy issues in face-to-face meetings and audit group dynamics. The concept map would allow all to express their views in a safe, stress-free environment period. The authors also found the use of both qualitative and quantitative data very appealing. They suggested the creation of multiple maps to establish cross cutting links and issues. They expressed the desire for participant engagement via feedback in an effort to solidify the validity of participant responses.

William Trochim and Rhoda Linton also provide some very useful observations. One is the relevance this method has for priority setting. Additionally, it is a useful decision-making tool, and can collect group opinions in a methodologically sound manner. Trochim and Linton also note other methodological benefits. These include the fact that researchers have little control over the outcomes of the data sets and results.
Thus, there is less room for tampering or manipulation of data, and other unethical conduct in the ethics assessment. Like Southern et al, they praise the ability to validate participant responses, which lends an increased validity to the entire method. However, Trochim and Linton state that this process can be both time-consuming and expensive. It should be noted that this comment was taken from an article written in the mid-1980s. Given the technological advances in both communication and the computing of large data sets, the cost can likely be significantly reduced with the application of appropriate technologies and software.

Outside of these very limited instances—using it as a mechanism to collect and evaluate public opinions—concept mapping, as it is being described and used in the nonlinear approach, has not been applied in HTA. However, many HTA methodologies do have some elements of mapping in them. For example, SCOT approaches map development over time; and participatory approaches attempt to map stakeholder perspectives and attitudes.

Concept mapping is theoretically grounded in structured conceptualization. This means that the resulting model represents part of the theory. The model allows for the comprehension and description of relationships between concepts within the theory. There are three major components in structured conceptualization. First are the process steps. Stakeholders and relevant parties must generate ideas and set the parameters of the domain. The structure emerges by connecting all the ideas and facts that are related. This can be done in words, through pictures or mathematical symbols. The second component is perspective. There are three broad perspectives desired, including that of individuals, groups, and the assessment mechanism or algorithm. The third major
component is the representational forms. Any conceptualization with multiple perspectives can be represented in multiple ways. For example, it can be represented as a list with descriptions, as a pictorial representation such as a map or chart, or even as a symbolic representation such as a mathematic equation.29

Concept mapping has a number of concrete principles that ground it as a sound methodology. The first is that it values individual knowledge. An expert with the requisite knowledge can provide individual contributions. So, while multiple experts are engaged, this means that the concept mapping aggregates individual knowledge of all the experts. It takes it in conjunction across disciplines and sources. The key to properly utilizing this principle is that the appropriate areas of expertise must be included. The second principle of concept mapping is that it provides the rules for building and recognizing emergent relationships of meaning among concepts. The activity that is occurring in this process is that participants link ideas, concepts, facts, and observations to discern relationships between them. The third principle is that concept mapping produces a conceptual model. The accuracy of the model is based on the inputs from those involved in the process. Again, it is crucial that the relevant experts be available to provide additional input. The inclusion of both experts and laypeople increases the diversity of perspectives. The emerging visual framework provides a unique representation of the issue. Concept mapping explicitly includes disparate units of existing knowledge in a unified conceptual framework. Finally, concept mapping should be applied within a specific context. This means that when applying concept mapping to the issues of emerging genetic health technologies the content of the concepts map should be highly reflective of the realistic or real-world context.30
There is a wide number of concept mapping approaches including idea maps, mind maps, mental maps, cognitive maps and so on.\textsuperscript{31} As discussed by Kane and Trochim, these correspond to different traditions within the social sciences. For this endeavor, the most appropriate mapping approach is collaborative group concept mapping. Group concept mapping is recognized as an applied research methodology, and has its foundations in a number of social science traditions. For example, discussion and facilitation methods are linked to the Delphi methodology; and the computation of results, depending on the system used, may be grounded in multivariate statistics or multidimensional scaling.\textsuperscript{32}

The creation of a concept map in the research and development phase of a technology may appear to be simply another bolt-on ethics approach to HTA. If implemented cynically or inauthentically, that could be an accurate description. However, the very nature of concept mapping lends itself to a high level of authenticity, because it is not a checklist or one-and-done approach. Furthermore, it illuminates those ethical and social considerations that may not be obvious, and draws connections between existing ethical issues and concerns so a more complete picture and understanding of the landscape can be gathered.

The following section addresses the practical steps for creating a concept map for planning and evaluation of ethics. Before launching into the concept mapping, consideration of the results from step one and two must be addressed. First, one must gather the information collected for step one and step two, and then reevaluate step one in light of the information collected in step two. Step three begins with conceptualization of the project. This should be based on the information from steps one and two, and
broadened to include thoughts, ideas, or even hunches. If there are no adjustments that need to be made to the research question, proceed to step three. If adjustments need to be made, make them before proceeding to step three. Any adjustments should directly reflect the research gathered in the literature review and the intended outcomes.

4.2.3.3.1 Practical Concept Mapping Steps

The process of group concept mapping, including basic rules and practical steps, follows the method established by Kane and Trochim in the *SAGE Handbook of Applied Social Research Methods*. Again, it is important to note the recognized validity of this methodology. This is a highly relevant methodology for ethical assessment for a number of reasons. Concept mapping identifies ethical and social issues, connects these concepts and issues, and identifies particular issues among specific populations or sub-groups. In addition, concept mapping fits well in the overall structure of the nonlinear approach in that step six of the concept map lends itself quite well to the development of action steps in phase five of the nonlinear approach. Concept mapping alone will not resolve ethical problems, but it will provide valid data for the justification of future action steps. It is in phases four and five of the nonlinear approach where there is an opportunity to address ethical issues themselves in more depth. There are six steps: (1) preparing for concept mapping; (2) generating ideas; (3) structuring statements; (4) concept mapping analysis; (5) interpreting the maps; and, (6) utilization.33

Step one, preparing for concept mappings, revolves around identifying two key knowledge sources. The first is the facts of the problem or issue at hand; and the second is the participants or stakeholders. To identify the knowledge contained in the
participants and stakeholders oftentimes requires a wider discussion takes place or a more structured set of questions and answers can be applied. For example, a prompt or open-ended question that will focus participants and elicit the appropriate knowledge sources might look like “we know that this new technology is successful when…” or “a specific issue that affects patients receive predictive information as a result of genetic testing is…. Intentional and careful consideration must be given to construction of questions, prompts, or open-ended statements. They must elicit the appropriate breadth and depth of responses. Also, the answer is often determined by the way the question is asked; careful attention to existing biases must be given. Additional considerations in this step that must be made include the selection of participants and stakeholders as well as the appropriate number.  

Step two, generating ideas, involves generating responses to the prompt and collecting those responses. Kane and Trochim suggest using a form of structured brainstorming articulated by A. P. M. Coxon, a professor of social sciences from the UK. This builds on the intentional structuring of the prompts and open-ended statements in step one. To generate these brainstormed responses there are number of mechanisms by which to engage participants. These can include face-to-face meetings, web-based meetings (e.g. webinars, Skype, Adobe Connect and so on), and emailed surveys or traditional mail-based surveys. Either during or immediately after the generation of the responses, there are a number of other options by which researchers can gain additional ideas and information. These include but are not limited to excerpts or conclusions from documents resulting from a literature review or interviews with experts in the field.
This step concludes with a synthesis of information. The researchers review all ideas generated and collected and organize them into rational sets. The goal is to reduce or eliminate any redundancies as well as determine if any ideas fall outside the scope of the current project or are simply not relevant to this research. There are methods by which a formal content analysis can be used to synthesize the collection of statements, one of which is proposed by Klaus Krippendorf, who is the Gregory Bateson professor for Cybernetics, Language, and Culture at the Annenberg School for Communication, University of Pennsylvania. For example, if more than 600 statements are collected, there will be overlapping and irrelevant statements. Kane and Trochim suggest that ideally, after engaging idea synthesis, this number would be reduced to approximately 100 - 120.

Step three centers around the structuring of statements. In this step there are three tasks that must be performed by the participants and stakeholders. The first task consists of participants sorting the statements. Then, in the second task, they must rank the statements, and, finally, in the third task, provide some basic demographic and characterization information. The former consists of an unstructured sorting of the statements resulting from step two. Each individual is responsible for sorting the statements into groups in any way that makes sense for them. Kane and Trochim articulate a number of guidelines to assist in this sorting. First, there cannot be the same number of ideas as groups, this means that participants actually have to engage in the sorting process. They cannot establish every idea as separate from another, thereby having the same number of groups as ideas. All the statements cannot be put in the same group, because this provides no distinctions. There should be no miscellaneous group. If
the statement is wholly unique it should be separated out. The benefits of using this type of sorting are that it can accommodate large number of statements or ideas. The most important benefit is analyzing the connections individual participants have made between the different statements. For example how participant sorts and connects ideas will be different from other participants; and this will reveal the nature of relationships and connections on multiple levels.\(^{39}\)

The second task participants and stakeholders must complete is rating the statements. The statements can be rated by a number of measures; these will be specific to the context of the project. The statements could be rated on level of importance or priority, feasibility, or any other relevant characteristic. A Likert scale is a useful mechanism for rating. This will reveal the most relevant concerns to specific participants. This allows for a very rich data analysis. In the final task, participants must provide some basic personal and demographic information. Demographics or characteristics of participants can be viewed in relation to the information gleaned from statement ratings. This allows correspondence to be grouped into subgroups or focus groups if need be or for detailed analysis.\(^{40}\)

Collecting responses, organizing and ranking those responses, and collecting participant information are all fairly standard and routine practices in qualitative group research. Step four is what separates concept mapping from other similar qualitative group research methods. Kane and Trochim advocate for a combination of analysis methods that integrate two key components, qualitative input and quantitative analysis. The aggregation of this information allows for the creation of a concept map. The image below is an example of a pictorial concept map.
Pictorial concept maps, like the example above, are very useful in visualizing connections and maintaining a coherent vision of the entire project. It is recommended that in the first cycle of the nonlinear approach, that a pictorial concept map is developed to coherently demonstrate crosscutting concerns and themes. These connections are not always as explicit in other visual representations. In the example above, there is coherence both in the organization of the concepts as well as the connections between them.

Depending upon the size of the focus group, it may or may not be appropriate to move beyond a pictorial representation. In the initial cycles of the nonlinear approach, when focus groups may only include the research team and relevant experts, the pictorial concept map is likely the most appropriate. As broader participation becomes necessary,
the more likely the need becomes to transition to representative models outside of the pictorial representation. These other concept representations have great capacity to aggregate and display data. When moving through the multiple cycles of the nonlinear approach, options exist to build upon the concept map originally created in prior cycles. Or create a new concept map more appropriate and reflective of the participants may be created. Then, integrate the prior work with the new.

The other types of concept mapping that are more adept at handling large numbers of participants are also more systematic in nature due to the fact that the input is identical to the information gathered. Computers are required to complete this analysis. Specifically they identify the basic analysis as the combination of three methodologies including sort aggregation, multi-dimensional scaling (MDS), and hierarchical cluster analysis.42 Concept maps can be represented in many different ways. This involves placing the rankings, in their numeric form, into a matrix that is then represented in a plot-chart or point map to display, visually, the proximity of related issues. The result of this input reveals clusters of ideas and statements on a highly conceptual level.43 This requires the use of computer software.

Depending upon the depth of analysis in the given cycle there are a variety of software options. For pictorial concept mapping available software includes, MindMaple, Cmap, Freemind, VUE (visual understanding environment), iMindMap, MindMangager, NovaMind, and several more. Many of these are free and include both a web-based version and an application. For more advanced mapping and data collection software, options include Microsoft Excel (although this is typically not the most user friendly), NCSS10 Data Analysis, SigmaPlot, and Thinkmap. This type of software can
range from anywhere from free to $1,500. Flexibility exists based on the needs and skillsets of the research team. Selection of software should be appropriate to the scope of the current cycle. A brief example of how to utilize these more complex statistical tools will be provided in Chapter Five.

In step five the maps are interpreted. Since this is based in stakeholder and expert participation, it is useful to include both in the analysis. A simple rule to follow is that all participants who provided responses should be presented with the visual product and be given the opportunity for further feedback. Inclusion increases transparency and lends itself to additional participant buy-in and joint authorship. Kane and Trochim also note that it yields “richness” to the results, as well as increases the value for both the participants and the researchers.

Evaluating and interpreting the maps—whether a point map, cluster map, or pictorial map—can occur in several different ways. Pictorial maps, point maps, and cluster maps (the more basic configurations of concept maps) can be read in a way that informs further analysis. This means that based on the finding there is now a more clear direction and indication for additional research necessary to address the research question. The data can also be formulated in different ways to reveal crosscutting issues between different sub-groups identified in the participant sample. This information can be used to identify areas where problems exist. For example, in the case of evaluating a large number of participant responses, if there is a huge difference or gap between the ranking of importance of a given social value between the subgroup included in the research and a non-expert subgroup, that indicates that this is an issues that should be given particular attention. If a certain group is ignoring a specific aspect, while another
group finds it very important, further examination is essential. This divergence can yield some very insightful information and guide future action steps.

The question becomes, what actions are appropriate to take based on data? Obviously, to some extent that depends on the data. Step six involves using the evaluation of information in step five to inform action. Collecting data lacks purpose if it is not going to be utilized. The information yielded in the research should provide the foundation for future action. This also means that the action should be consistent with the findings. Connections have been identified, crosscutting links have been established, and this can inform a wide range of actions surrounding emerging technologies.

Actions can range from pursuing further, more focused, research. Education initiatives can be initiated or those in existence can benefit from being properly informed. Social change programs can also be initiated or better-informed, such as advocacy groups. One example of concept mapping informing social change is the evaluation of the Centers for Disease Control and Prevention Research Centers Program, conducted by L. A. Anderson et al. Concept mapping was used to take a very large and diverse set of participant and stakeholder perspectives into account. A logic model was developed and used to evaluate the centers. Valuable information surrounding the perception of the center and understanding of the center’s function and outcomes was gathered and analyzed from stakeholders and program partners. As a result of this research, important program expectations were established.
4.2.3.3.2 Linear vs Non-linear HTA

HTA practices have not been traditionally thought of as nonlinear. HTA processes typically occur in a step-by-step process, where the former step triggers the next. This is linear. This process is acceptable for safety and cost-effectiveness evaluations, but not for ethics. This is because ethical issues, questions, and problems are not structured the same way, and thus do not lend themselves to fitting nicely in a rigid framework or process.

Linear and nonlinear programming are problem solving processes in the subfield of mathematical optimization. Optimization problems can be either linear or nonlinear. An optimization problem is one in which a single solution is not sought, but rather the best solution among many solutions is discerned. Optimization problems have existed since ancient times. Optimization is easily observed in nature; and as a result, “many laws of physics are formulated as principles of minimum or maximum of some scalar characteristics of observed objects or systems, like energy or entropy.”48 The most important application of linear and nonlinear programming is to solve optimization problems surrounding human activities. For example, it might be beneficial to figure out what the most cost-effective means are to reach a certain goal. Likewise in cases where resources are scarce or limited, it is important to consider how to maximize those resources.

Linear programming is a mathematical technique that attempts to find the best possible solutions. This can be applied to real-world situations such as allocating limited resources, including output surrounding energy, machines, human power, time, and cost.49 Linear programming can only be used when all constraints and all functions are
themselves linear—having one dimension and, when graphed, resembling a straight line. Essentially, a linear equation is an equation, which forms a straight line when it is plotted on a two-dimensional graph. Another characteristic is that linear equations and their variables only appear to the first power. This differs from nonlinear equation in which dependent variables can exist to different powers or even in other mathematical forms.\(^{50}\)

Linear programming allows one to take multiple independent variables into consideration simultaneously. These are called linear relationships.

Nonlinear programming is primarily used for those problems that have unknown variables, equalities and inequalities, and undefined constraints. The focus remains on optimization, a concept well rooted in many decision-making mechanisms.\(^{51}\) This is typically addressed in mathematics, where the object or solution is portrayed as an integer, graph, or equation. Nonlinear programming has taken on a vital role in many disciplines including management science, engineering, systems analysis, economics, and computer science.\(^{52}\) It is a mechanism, which one can use for decision-making.

There are three general stages when utilizing nonlinear programming. The first stage surrounds the development of a mathematical model that identifies and accurately represents the problem. This includes identification of all the variables, retrieving data relevant to those variables, determining which function is to be optimized (minimized or maximized), and organizing these variables and the corresponding data into mathematical relationships. These mathematical relationships are called restraints and are represented as equations or any qualities.\(^{53}\) The second stage entails the analysis of the mathematical model produced by the first stage. It must be determined what the appropriate numerical technique is for finding the optimal solution. It is at this stage where one can determine
whether or not the problem is in fact linear or nonlinear. For example, if one or more of the constraints is nonlinear the model becomes nonlinear; also if the objective function is nonlinear than the entire optimization problem can be said to be nonlinear. The third stage aims at finding the optimal solution. In the vast majority of cases computers are used to do the mathematical computations. In some cases, a new code must even be written to address the multiple variables. The numerical solutions provided by the computation must be reinterpreted and analyzed; these are then evaluated and utilized to make decisions. Mordecai Avriel, in his book *Nonlinear Programming* states, “analysis of a nonlinear program provides valuable insights into the structure of the problem and answers questions about the existence and characterization of feasible and optimal decisions.” This sums up what ethical and social research, in many cases, is attempting to do; that is, make optimal decisions or arrive at a justified conclusion among unknown and unconstrained variables. However, this is not to say that the sole focus of ethics assessment is arriving at a justified conclusion. Rather, the focus is on the whole process, which includes identifying the problem or ethical issue, analyzing the substance of the issues in order to understand the potential social impact, and then arriving at the conclusion or decision. There is no justified conclusion without careful attention to and analysis of the specific ethical issues.

Nonlinear programming has been applied to many specific real-world phenomena and problems including sports, chemistry, weather prediction, war, and disease, just to name a few. In sports, nonlinear programming is critical in understanding the aerodynamics of sports balls. For example, it would be incredibly beneficial to understand how to bend the soccer ball like David Beckham or Wayne Rooney, throw a
major league curveball, understand the ball trajectory, or even the implications of using a traditional bow as opposed to a compound bow.57

In the book, *Political Complexity: nonlinear models of politics*, each chapter focuses on utilizing a nonlinear model to understand politics. One of the chapters was written by Walter Mebane, and focused on campaign funds. The primary question was how incumbent congressmen/congresswoman are able to amass substantial campaign funds.58 Through nonlinear programming and analysis, Mebane determined that there was a nonlinear relationship between campaign contributions, district service, quality of the challenger, and election outcomes. He concluded, as a result of this analysis, that “voter preferences only partially determine election outcomes.”59

A final example of how nonlinear programming is applied is in the understanding of disease transmission, including both the spread and growth of diseases. The analysis provided by Richard Enns, in his book *It’s a Nonlinear World*, focuses primarily on infectious diseases such as influenza. Each year in the United States and across the world there are fears of an influenza epidemic whether it is the strain of the horrific Spanish influenza (H1N1) of 1918, bird flu (H5N1), or any of the other dangerous strains. Is estimated that as many as 22 - 40 million people died in a ten month period as a result of the Spanish flu.60 Based on the danger posed by influenza, it is imperative to understand disease spread and transmission. In an effort to understand disease transmission, Enns considered a number of models including the SIR model with and without the dynamics, as well as different constraints such as herd immunity and vaccination and geographic location. Furthermore, he has applied these models to various infectious diseases including mad cow disease and the Black Death. The result of these models indicates the
minimum speed of transmission for the spread of Black Death and other contagious
diseases.⁶¹

There have been some attempts to utilize nonlinear programming in TA and HTA.
An early example of nonlinear programming being applied to emerging technologies
dates back to 1976. An article by Alan Manne, *ETA: a Model for Energy Technology
Assessment*, argues that nonlinear modeling could predict own- and cross-price elasticity
of demand and energy conservation of different fuel sources (e.g. coal, synthetic fuels,
nuclear energy, water, hydrogen and solar).⁶² One of the possible outcomes, based on the
interpretation of data is characterized by the following:

As of 1970, virtually the entire U.S. electricity supply was provided by
fossil-fired and hydroelectric units. During subsequent years, it appears
optimal to install nuclear facilities at a rapid rate. According to Figure 3,
the energy output of LWR’s will overtake that of hydroelectric by the late
1970's and will overtake fossil plants during the 1990's. LWR capacity
reaches a maximum of 1200 GW in 2015, and then begins to drop as old
units are retired at the end of their 30-year service life. The LWR is in turn
replaced-first by the FBR and later by the ADV technology. By 2030, only
a small proportion of the electrical energy is generated by fossil or
hydroelectric plants. Adaptations of both linear and nonlinear programing
have been employed throughout the decades.⁶³

According to the U.S. energy information administration about 67% of the electricity
used in the United States was from fossil fuels in 2013.⁶⁴ 19% is derived from nuclear
energy, 7% from hydropower, and 6% from other renewable sources.⁶⁵ While these
predictions might have been pragmatic considering the data, social and political
constraints were likely not successfully taken into accounts. A few modern examples
include photochemical air pollution control and proposed modeling for
pharmacoeconomics.⁶⁶
It should be noted that the utilization of linear and nonlinear programming in emerging technologies and health technologies can provide valuable information in the HTA process but it does not substitute for the HTA process. The benefit of using this line of reasoning is that the aim of nonlinear programing is to fully represent complexities of interactions that have many variables, including unknowns, defined and undefined constraints, and appropriate objectives when aiming to arrive at a decision in a complex problem. Applying the general philosophy of nonlinear programing, here termed nonlinear thinking, is a qualitative not an empirical analysis. Therefore, nonlinear programming is not strictly applied; only the overarching conceptual framework is applied to ethics in HTA.

The application of key concepts from nonlinear programing, such as optimization and the inclusion of unanticipated or unconstrained problems, have informed aspects of the nonlinear approach presented in this section. First is the notion of optimization—that finding a singular solution to a problem is not only unlikely but impossible given the polarity of society. Rather the focus is to find the best solution among many possible solutions. It is similar reasoning when choosing which technologies to fund, develop, and so on. Similarly, with ethical considerations, there are often many possible justifications and reasoning to support a conclusion; the aim is to find the strongest solution among many.

The second connection is in the language and the way nonlinear programing deals with uncertainties and unconstrained variables. In emerging technologies, there are, at times, immense uncertainties and well as unknowns. Having a meaningful way to incorporate these concepts in the nonlinear programing suggests that it can be
analogous to the nonlinear approach. All the ethical questions will not be answered. There are unknowns. By recognizing the uncertainties exist and unknown consequences are possible, they can be accounted for through placeholders. It is critical not to dismiss uncertainty or to deny the potential for unanticipated or unknown consequences. The mathematical model of nonlinear programing provides insights for including these into a coherent decision-making model. The adaptation of the nonlinear approach as applied to ethics requires that these uncertainties and unknowns be coherently accounted for and discussed without stymieing scientific progress. Part of this was addressed in Chapter Two, surrounding the discussion of risk, uncertainties, and the ethical acceptability of risks. That is the contribution of nonlinear programing to the nonlinear approach. It allows for the frank conversations surrounding these very issues concerning the ethical acceptability of risk.

4.2.3.4 Phase four: Evaluation

In the fourth phase, the results of the concept map are taken into context with the larger research project. There is one central activity in this phase and that is answering the question: “were the outcomes, set in phase two, met?” Three additional follow-up questions should also be answered: (1) “How was the outcome(s) met?”, (2) “What do these finding indicate about the research?”; and, (3) “What does this mean moving forward?” Recall that the outcomes from phase two articulate the expected gains from the concept mapping exercise. This brief evaluation phase is setting the foundation for phase five, which calls for action based on the results of the concept mapping exercise.
4.2.3.5 Phase five: Closing the loop

This phase is the most crucial and distinctive in this approach. First, reflection must occur on the process as a whole; and an honest appraisal of the results must be given. The nonlinear approach stems from the collision of four areas: mathematics, bioethics, emerging health technologies, and higher education assessment. The inspiration for phase five, however, can be credited to assessment in higher education.

Assessment in higher education occurs at two levels, institutional effectiveness and student learning. Here the emphasis will be on those processes utilized in student learning assessment. The same logic applies; but rather than asking questions of emerging technologies, questions are being asked of student learning. Outcomes are created, often labeled student learning outcomes (SLO) or simply learning outcomes (LOs). Assessment takes the form of measures by which one can determine whether the outcome have been met, evaluate the results, and then make adjustments that impact student learning so they are better prepared to meet the outcome. The final phase, closing the loop, is the most critical. This methodology has been demonstrated, and is supported by national agencies such as the American Association of Colleges and Universities.\textsuperscript{68} It is a step phase that is, at times, overlooked because it is difficult. Yet, it is absolutely critical when it comes to analyzing and attempting to create positive change. Without reflecting and determining what needs to be improved or adjusted—teaching, advising, student services, or learning—in order to continually improve student learning, students will not improve and the assessments have been completely devalued as the information was not appropriately utilized.\textsuperscript{69}
Overall, the goal of student learning assessment in higher education is to produce credible evidence of student learning. Then, use the data to continuously improve programs and services. This allows institutions to demonstrate and maintain accountability. Furthermore, it creates a culture where outcomes assessment is a continuous process and not cobbled together by a small portion of the faculty. Finally, the evaluation aspect of assessments allows for reflection and improvement upon the assessment mechanism and process itself. Having a mechanism for continual improvement is important, but equally, if not more so, is having the capacity to assess the assessment mechanism. This is a key step toward increasing the effectiveness of any assessment program, mechanism, and protocol. One of the most important questions does not involve the quality of the assessment measures themselves but rather, whether the data or information that has been gathered is the right information. The right information consists of information that can lead to action steps toward meaningful and positive change.

The most appealing aspect of learning assessments is that they represent an internally driven, formative process. This means they can be undertaken and adapted to each institution’s specific needs. It is this element that is most beneficial when reflecting on and attempting to improve ethics assessment in HTA.

The connection between student learning assessments and ethics assessment, outside of the word “assessment,” is the fact that both processes are aimed at gaining new knowledge and insight, and then utilizing that information to affect positive change for the future. The only way to determine whether or not positive change has occurred is to continue the assessment process by closing the loop and re-engaging the assessment cycle. It is evident from the literature and analysis provided in Chapter Three that many
scholars and institutions are reflecting on the use of ethics in HTA, and critiquing the various models and frameworks; but the question becomes how those reflections move the discourse forward.

The final phase of the nonlinear approach requires reflection and action. Reflection should occur on two levels. First, reflections surrounding the methodological aspects of the process should be conducted. Questions to be asked include: What worked? What did not work? What helped progress? What hindered progress? Did the implementation tools work correctly (e.g. meetings, technology, data analysis)? What can be done to improve the process?

The second level of reflection occurs when the approach needs to be reengaged. This approach is not meant to run through a single cycle. It is meant to have as many cycles as needed to shed light on the relevant issues, frame the question properly, and provide insights for decision-makers and policymakers. It is unlikely this will be completely attained in one cycle. Since this approach is engaging emerging technologies very early in the research and development phases, they are likely to be substantial breakthroughs benchmarks that are met throughout the research process. As these benchmarks are met and major breakthroughs occur, the approach should be reengaged. This is a cyclical approach; and the process should begin again, building on the work of prior cycles.

4.3 Discussion and analysis of benefits and limitations

This section will provide an assessment of the non-linear approach. This will be accomplished by addressing the overarching benefits and limitations. The gaps and
deficiencies identified in Chapter Three will also be specifically addressed, along with the practical obstacles also presented in Chapter Three.

4.3.1 Benefits

By adhering to the overarching aims—(1) begin ethics assessments earlier than formal HTA assessments; (2) provide a flexible framework whereby ethics experts and non-experts can coherently work together; (3) support, not stymie, scientific progress; (4) provide meaningful discourse and recommendations; and, (5) continually improve by assessing the ethics assessment mechanism itself—the nonlinear approach produces some benefits. The benefits include increased time, sound methodologies, increased inter- and multi-disciplinary collaboration, the inclusion of wider ethical and social issues including socioeconomic issues, improved transferability of information, and finally as a step closer toward creating consistency in ethics assessment while not stymieing scientific progress. This approach is cyclical in nature, meaning that it is not a one-and-done process nor is it a single point in general HTA process. It is ongoing and happens concurrently with technical development. This approach is accessible to scientists and non-ethics experts due to its interdisciplinary methodology. However, ethics expertise is still needed in the research and evaluation portions of the approach.

4.3.1.1 Increased time

Increased time for reflection and evaluation is one of the most distinct and important advantages. Time is gained by moving the ethics assessment outside of the traditional HTA process. That elevates ethics to a more integral position for
technological development as a whole, as it is now embedded from the very onset of scientific research. This rejects the notion that scientific development and technical innovation occur in a value-free or value-neutral space. When concerning emerging genetic health technologies, those positions are simply not tenable. With the benefit of added time, thoughtful reflection can occur.

In addition, the cyclical nature of the approach means that one does not have to “get it all right the first time.” That allows for researchers to continually build on and add to the robust understanding of ethical issues. It also increases checks and balances, because results can be compared between the cycles. It was evident from Chapter Three that ethics assessment in HTA is, at times, a nearly static function in the overall HTA process. Thus, if the assessment is not accurate the first time, researchers are not moving forward with inconsistent or invalid data and recommendations. Multiple cycles allow for confirmation of validity, which is all made possible by increased time.

4.3.1.2 Methodological strength and collaboration

The approach is accessible as it is based on best practices from a range of disciplines that offer structured and organized methods to conduct intellectual inquiry. The methodologies utilized are also fairly simple in concept, despite some of the labor-intensive aspects. Scientists may find the adaptation of concepts from nonlinear programming to make very good sense as an analogy to ethics analysis.

The nonlinear approach helps researchers and policymakers make decisions about new technologies in two ways. First, it highlights potential pitfalls, which can directly impact the ways technologies are introduced to the public. Many genetic health
technologies will have similar characteristics when it comes to uncertainties, surrounding dual use, unintended, unanticipated, and unknown outcomes. Starting and continuing the discourse will help assist policymakers in understanding public perception of the acceptability of risk. Ideally it will also help society to arrive closer to some consensus about what is and what is absolutely not acceptable.

The potential, and arguably necessity, for increased inclusion of different perspectives is a benefit of this model. The nonlinear approach does not function properly without multidisciplinary collaboration, public participation, and stakeholder engagement. In order to create an accurate concept map, there must be inclusion and engagement of the relevant parties and experts in discourse through interdisciplinary collaboration.

4.3.1.3 Wider ethical considerations

In current HTA models, including those used by NICE and EUnetHTA, ethics assessment occurs at one point—if it happens at all—and then is often left untouched, unless substantial changes are made to the technology. A strength of the nonlinear approach is that it is iterative; that is, it is applied repeatedly. By moving ethical assessments into the research and design phases of technologies that are likely to be applied to human health, it becomes possible to conduct ethics assessment multiple times throughout the development of the technology, thereby allowing time for an iterative process to take place. As multiple ethics assessments occur they build very much like a spiral, continually refining, aligning, with the ultimate aim, in case of HTA ethics assessment, of building consensus and developing direction and recommendations for
As a result of nonlinear thinking, this model can more easily address a wider range of ethical considerations and stakeholder perspectives, thereby adding depth and breadth.

When addressing emerging genetic health technologies this becomes more important, as the implications of these technologies are still widely speculative. A few examples of the wider ethical considerations surrounding emerging genetic health technologies include: what does it mean to be human? what is life? how does one understand autonomy in relation to future generations and future research? It is not unreasonable for there to be an acknowledgment of these issues as emerging genetic health technologies become a realization. For example, biobanking has become incredibly important. A biobank is a location where blood samples or tissue samples are stored. Depending upon the level of consents and the nature of the biobank, patient information may or may not be attached to the samples. This obviously presents issues of privacy and confidentiality. But a more subtle ethical issue that has come to the fore is the question of future research and the role informed consent, as well as how the underlying principle of autonomy may play in this. Often when tissue samples or blood samples are collected it is done so with the knowledge that the samples will be used in future research. Because the research is in the future, it is impossible to know what the research might actually entail. If a patient gives consent, they are giving blanket consent to any research, whether they may find that research acceptable or not. These wider ethical issues will be examined in greater detail in Chapter Five.
4.3.1.3.1 Ethical and socio-economic considerations

Given the type of data collected and the method by which it is collected, the nonlinear approach can yield some very rich analysis surrounding socio-economic concerns and perspectives. The nonlinear approach has the capacity to address socioeconomic issues in the sense that it can take seriously the concerns of individuals and subgroups representative of various economic classes. That being said, this is possible only if the participant selection reflects this diversity. The richness of the data, and breadth of the social issues depends greatly on the diversity of participants. If there is representation of various socioeconomic classes, then the nonlinear approach has the capacity to not only reveal the difference in perspectives, but also take each group's perspective as seriously as the other. This means that no additional weight will be given to preferred or special groups of individuals. This dramatically widens the opportunity for many other ethics assessments. These wider considerations are necessary when addressing equity and socio-economic factors; they are critical to producing meaningful results.

4.3.1.4 Dissemination and transferability of findings

The nonlinear approach can begin to address what some scholars have started calling the “moving target problem.” This is problematic in HTA for a number of reasons. The “moving target problem” arises when changes in the way a given technology is used, applied, or upgraded happen before the dissemination of information for the HTA process. This dramatically affects the currency and relevance of the findings. The nonlinear approach directly addresses this problem. This is an approach
that is built to be repeated continually until the technology is stabilized and there is
general public consensus and education surrounding it. Thus, as technologies hit major
benchmarks or breakthroughs, methodology can be stopped at any point and started back
at the beginning; after one cycle has completed, another cycle can begin as soon as there
is a shift in research, a major break through, or an update in the application of
technology. This is not a one-and-done approach; this is not a checklist approach. It is
meant to be fluid; it is meant to function simultaneously with the ongoing development of
the technology. Even after the technology has gained market approval, this approach can
be employed to monitor shifts in it as well as provide a wealth of data to inform the
assessment of future emerging technologies.

Another way the nonlinear approach can address the transferability and
dissemination of information challenges that current HTA creates, is the manner in which
the results are presented. As a result of the nonlinear approach, a graphic will be
produced. Graphics, especially the pictorial concept map, allow for clarity in
understanding because the conventions and crosscutting links are visually available.
Since the links are available, different organizations and agencies can utilize the concept
maps as a foundation and add their unique dimensions and considerations. This is much
easier to promote collaboration and build understanding around, as opposed to a highly
technical, dense document.

4.3.1.5 Creating consistency in ethics assessment

The aim of this approach is not to have every single organization apply the
approach in the exact same way; in fact, it is the opposite. Flexibility was built into this
approach with the recognition that agencies and organizations of different scope, size, and needs would be integrating it. This may seem as though it introduces anarchy into a fairly stable system, however just the opposite occurs. Flexibility allows the increased ability to take contextual features into account. This embraces the plurality of society as well as reflects the interdisciplinary nature of HTA.

The built-in flexibilities also allow for broader discourse to take place as each new cycle is started. For example, if a technology is so new that there is little to no literature on the subject, then it may make sense for the first cycle of the nonlinear approach to include on the research team a selection of highly-qualified experts. As the technology develops and reaches certain benchmarks, the time comes for the cycle to re-engage. In the second iteration it may be appropriate to extend the participant pool in concept mapping phase to a wider range of stakeholders and other interested parties. As the technology becomes more mainstream, insofar as the layperson might recognize its existence, it is likely appropriate to engage the wider public, including non-experts as well as other interested parties. In another example, for a technology that is somewhat established, or perhaps based on an existing technology or process, it may be appropriate to engage the wider public from the onset. In short, the level of technological development and stability of the technology directly contribute to the context and level to which the nonlinear approach is used.

It would be legitimate to ask how this builds consistency, especially if every organization is using the tool as they deem appropriate. The consistency is in the methodology. If a sound methodology exists, it should produce valid results regardless
of the context. In addition, the validity of the raw data yielded in the concept-mapping phase can always be assessed by external experts.

4.3.2 Limitations

The limitations of the nonlinear approach include the status quo of ethics assessment, the sum of the parts problem, the way in which this approach was generated, and the required need of ethics expertise. The final issue to address is that ethics assessment does not necessarily solve ethics issues, problems, or controversies.

The first limitation surrounds the current status quo of ethics assessments. That is, the assessment is recognized and accepted, but no actions are taken. The second issue, the sum of the parts problem, surrounds the seemingly cobbled together methodologies suggested in this approach. Methodologies from the social sciences, bioethics, mathematics, and higher education assessments have been integrated to produce the nonlinear approach. Simply because all the phases in the approach are methodologically sound, does not mean that the sum of the phases is methodologically sound. Although, it is argued in this dissertation that it is methodologically sound; without hard data, it is difficult to present a concrete case. This will be explored in Chapter Five. The third limitation is similar in nature to the second. The nonlinear approach, to date, has been developed in something of a vacuum, albeit a very well informed vacuum. This is important to recognize because it can call into question some of the conclusions that will be drawn in Chapter Five. However, it is equally important to note that the aim of this dissertation was to provide a sound methodological foundation; an aspect which can be established. The final limitation is that this process still relies, to some extent, on ethics
experts. It has been noted by a number of scholars that there is a practical limitation based simply on the number of qualified individuals.\textsuperscript{78}

It should also be noted that ethics assessment cannot fix all the issue encountered in HTA; furthermore, it is unlikely that any one approach will successfully surmount all the practical issues surrounding the integration of ethics in HTA.\textsuperscript{79} Ethics assessment in HTA will not solve all ethical problems. Rather, it positions stakeholders and policymakers to better anticipate ethical and social issues that are likely to arise through a thorough process that can address the complexities of these issues. It is important to keep in mind that ethics is but one component of HTA. Yet, it is one component that should pervade all aspects of HTA. For example, when engaging in economic evaluations one should be keeping an eye on justice and fairness. When engaging in comparative effectiveness, considerations of individual and social benefits are essential.

### 4.3.3 Addressing the deficiencies

This section addresses each of the deficiencies and gaps identified in Chapter Three. In doing so, a clear justification for the nonlinear approach to ethics in HTA emerges. The first deficiency surrounds priority setting, as well as the initiation and completion of HTA studies. Since institutions conducting HTA set HTA priorities, this would likely require vast institutional organization as well as global cooperation. These considerations are beyond the scope of this dissertation. However, it is important to note the efforts currently taking place to coordinate efforts, such as those by the EUnetHTA, as well as argue for continued efforts in this area.\textsuperscript{80} The nonlinear approach begins to address issues of priority setting in a very subtle way. This particular approach is created
specifically for emerging genetic health technologies; the narrowness on this focus indicates a very specific priority set by the author of this dissertation, which is informed by current advances in health technologies, the bioeconomy, and current bioethics literature. The application of this approach to emerging genetic technologies is the focus of Chapter Five. Also, in Chapter Five additional arguments and justifications will be provided surrounding the specific selection of emerging genetic health technologies as a priority ethics in HTA.

The second deficiency is narrowness, first of HTA in general and then of ethics in HTA. Typically, HTA focuses on cost-effectiveness and efficiency. Ethics in HTA is typically employed through one methodology. There is a range of methodologies available. This approach offers a coherent way to employ multiple methodologies simultaneously in an effort to maximize time, resources, and ethical considerations. Elements from the dominant methodologies are integrated in such a way to bring three key aspects to the fore. Based on the plurality of perspectives that concept mapping can include in one visual, there is increased breadth.

Ethics assessment in current HTA occurs late in the research and design process and it is too narrowly conducted in many circumstances. Typically, formal HTA occurs when a medical device or intervention is ready for human application. Portions of HTA can be completed, specifically ethical considerations, before research and development reaches this critical threshold. By conducting ethical assessment sooner, key issues can be anticipated and given adequate time for expert and public discourse. This is similar to what is done in TA. Ethical, social, and the resulting policy considerations should be forethought not an afterthought. Ethical assessments should not be reactionary; they
should be anticipatory and proactive. The crux of this approach lies in the timeliness of its application. This methodology is not intended to be applied to help technologies that are getting ready to hit the market or seeking market approval. Although the methodologies are sound, it is simply not the intent here. The ability to conduct this approach multiple times requires significant time in which to do so.

The third gap is the clear lack of standards, benchmarks, and regulations. The nonlinear approach does not make significant contributions in this particular gap. The benchmark and standards have yet to be established for this type of methodology. The only reasonable expectations are appropriate application of the methodology, and honesty in the reporting of data. Yet there is one area where this approach could make a positive impact, and that surrounds the transferability of information and dissemination of information. Since part of the final product will be a visual—a pictorial concept map—it will be easier to recognize and understand by both the researchers and laypeople alike; this is part of the strength of using a concept map, as noted in the description above. It has the capacity to absorb wide sets of perspectives, ideas, and facts and show there into relatedness. The following sections address some of the additional benefits mentioned above.

4.3.4 Addressing the Obstacles

There are a host of practical obstacles surrounding ethics in HTA, three of which were addressed in Chapter Three. This section will address three: financial limitations, time, and the technological imperative.82
4.3.4.1 Financial limitations and time

This approach cannot adequately address this obstacle at this time. There is very limited research addressing the fiscal impact of ethics assessment. It is unknown if there were will be a tangible return on investment. However, there is precedent for integrating ethics into the research and design phases of emerging technologies. In one significant example, ethical, legal, and social issues (ELSI) were given significant attention in the Human Genome Project. Five per cent of the annual budget was allocated to the study of ELSI. This amounted to approximately $18 million per year.\(^\text{83}\)

There is no denying that ethical assessment takes thought and time. Time is an issue. For example, NICE reports that it takes at least 54 weeks to complete a thorough HTA report in the UK.\(^\text{84}\) Canada has developed the Rapid Report system takes upwards for five to six months. The time to conduct appropriate ethical assessments in HTA is largely unknown. This is likely due the sporadic integration of ethics and lack of tracking. Only in the last five years have systematic reports been generated about ethics methodologies; hopefully in the next five years systematic reviews of fiscal impact, both in cost to implement and run, as well as the cost savings gained by utilizing ethics assessment, will be determined. While this could be persuasive evidence, it would be a mistake to reduce the value of ethics assessments to cost savings.

4.3.4.2 The technological imperative

In Chapter Three, it was argued that based on the value laden nature of technology and the social good produced by it, there is an obligation to consider the impact of these technologies on societal values and norms. In essence, this not only
justifies ethics assessment but also makes it an obligation. Following this argument to its logical end, technology is a social good, social good should be enhanced, thus an obligation exists to continue to produce technology toward socially good ends. In sum, it can be argued that a moral obligation exists to continue the advancement of technology for social good.

This approach takes a well-founded stance on the issue of the technological imperative. Technological progress will not stall or discontinue. Nor should it. It does not make sense to reduce the progress of technological innovation when it is aimed at producing a social good even if there is the risk of dual use or negative outcomes. Society has the obligation to ensure that the technologies applied to human health are safe and can exist within current societal norms. That is not to say that just because a certain technology, such as emerging genetic health technologies, pushes the bounds of societal values and norms that scientific and technological progress in those areas should cease. Many do not agree with this position. Bio-conservatives such as Leon Kass and Francis Fukuyama would heartily disagree with this, especially surrounding emerging genetic health technologies that push the bounds of the enhancements and trans-humanist enterprises.85

One of the primary reasons for focusing this approach on emerging genetic health technologies is that these technologies are currently challenging social values, norms, and, in some cases, our very ontology, and they will continue to push the bounds of normative positions and ethical paradigms. For example, the conception of autonomy in the United States is that it should be upheld. Most federal legislation seeks to enhance autonomy as opposed to limit it. The concept of autonomy, as most often expressed in
healthcare, is embodied in the idea of informed consent. Yet this notion of informed consent seems to crumble or at the very least appear inadequate in upholding the economy when it comes to holding and maintaining blood and tissue samples in biobanks. One must wonder how an individual can consent to future research when they do not know what that future research will be. This question alone gives pause, as it requires everyone to reconsider informed consent. Every individual who donates tissue or blood to biobanks signs an informed consent document. Many consent to future research without knowing what the research will be; can it be concluded that is that truly the full embodiment of autonomy or the complete abuse of it? The individual is clearly not informed; but at the same time they are making an autonomous decision not to be informed. These issues will be dealt with fully in Chapter Five.

In the United States, the FDA does a fairly good job at determining the safety of medical interventions; however, ethical and social considerations are greatly lacking. In this case, oversight does not entail regulation. Oversight and regulation considerations must be non-restrictive, with research supporting oversight with the intent of guiding investigators and scientists to take seriously ethical and social considerations while they are conducting research, not after the research is completed.86

4.4 Using ethics effectively and efficiently

Two additional considerations are addressed in this section, which are key aspects of the nonlinear approach, including using ethics assessment efficiently and effectively as, well as having reasonable expectations for ethical contributions. Ethics assessment should provide basic direction for stakeholders, policy makers, and the public.87
The primary aim of this approach is to support scientific developments and innovation, not stymie progress. Therefore, ethics should be employed effectively and efficiently. The nonlinear approach can be efficient when the appropriate tools are used, including software, solicitation of expertise, outsourcing some work when possible. The nonlinear approach is effective when it provides useful information that can inform researchers during the research and design process, and, in turn, assist decision-makers and policymakers. This means that the language used in assessment must be accessible to ordinary people not just the experts. One advantage to the nonlinear approach, which enhances its efficiency and effectiveness, is its ability to produce data that can be used by a wide range of individuals and organizations. For example, the information can inform HTA processes if the emerging technology is enrolled in a formal HTA process, this advantage will be addressed specifically in the following section. Licensure bodies and policy-makers can also use the information yielded in this approach. The benefit of this approach is that by removing it from the formal HTA process, but keeping it consistent with current ethics methodologies in HTA, the nonlinear approach becomes far more flexible and adaptable.

4.4.1 Formal HTA processes and the nonlinear approach

Since many technologies are not subject to formal HTA processes, and there are not very many HTA processes that include ethics assessments, it can be concluded that very few technologies are actually receiving ethics assessments in the form of HTA projects. If possible, the nonlinear approach should be directly linked to an existing HTA processes. If an ethics component already exists in HTA processes, much groundwork
has already been laid. If there is no ethics assessment mechanism in the HTA process, then the nonlinear approach does provide valid data for consideration. Furthermore, for its full strength to be realized, the information generated by the non-linear approach should directly feed into and inform existing ethics methodologies.

Logically, the nonlinear approach pairs best with participatory-based ethics assessments. Also, given the deliberative nature of concept mapping it could easily be paired with a wide reflective equilibrium. Although, that is not to say that it would be at odds with other established ethics methodologies in HTA. In an ideal setting the nonlinear approach provides the foundation for integrated approaches such as that suggested by Reuzel. A participatory-based reflective equilibrium is the mechanism by which ethical assessments will be continually refined in order to build consensus around conclusions and recommendations. Reuzel et al argues that agreement can be justified if it is regarded as a wide reflective equilibrium. The wide reflective equilibrium is based on John Rawls’s initial conception of the reflective equilibrium; however, to be applicable here it must meet three criteria. It must be inter-subjective, achieved by all individuals involved and, finally, a new equilibrium must be produced as opposed to forcing individuals into an established ethical measure. The participatory-based reflective equilibrium will closely reflect Reuzel’s work surrounding a wide-reflective equilibrium.88

The integrated model utilizes John Rawls’s concept of the reflective equilibrium. In this model, the starting point is a particular individual’s considered judgments. Considered judgments are judgments that display one’s moral capacities or competence with the least distortion.89 The key to Rawls’s notion of the reflexive equilibrium is that
when some aspect of moral theory, held by an individual, conflicts with their considered judgments, they are required to adjust one or the other to restore the equilibrium. For Rawls, “it is an equilibrium because at last our principles and judgments coincide; and it is reflective since we know to what principles our judgments conform and the premises of their derivation.”90 This means that the process of revising and reevaluating one’s moral beliefs, in order to adhere with the moral principles society holds, will allow the individual to continually develop a consistent network of moral beliefs. This is precisely what Beauchamp and Childress call for in the field of biomedical ethics. Of course it would be foolish to think that the achievement of a completely stable equilibrium is realistic. However, by continually navigating a network of moral beliefs, in light of the goal of stability, there will be a move closer to that stable equilibrium.91 If accepted and properly applied, the reflexive equilibrium is a sufficient methodology for justification.

This would provide an ethics assessment with depth and breadth. The strengths include validity of results, inclusion, transparency, and comprehensible results. This would be invaluable for policymakers and health decision-makers. In sum, the nonlinear approach can stand on its own to present ethical conclusions and recommendations of action steps to inform HTA processes that lack an ethics element, or it can greatly inform any ethics assessment that is already integrated in an HTA process.

4.5 Conclusion

This chapter established the methodological foundations as well as the practical phases for the nonlinear approach. Methodologically, this is grounded in well-documented sociological and mathematical and ethics disciplines. Concept mapping has
a long-established history as well as recognized validity. Nonlinear programming has been applied to multiple disciplines; and the basic tenants, applied here, lend additional validity to the nonlinear approach. The ethics methodologies employed are recognized as valuable and consistent with current ethics assessments in HTA. SCOT methodologies and participatory approaches both utilize stakeholder and public participants in discerning public values and norms surrounding technologies. The nonlinear approach also integrates best practices in assessment. By drawing parallels between assessment methods in other disciplines, in this case student-learning assessment, additional strength is attributed to the model.

There are five practical phases to this approach. They are: (1) identification and inquiry; (2) research and data synthesis; (3) concept mapping; (4) evaluation; and, (5) closing the loop. The nonlinear approach was developed to be continual process, whereby assessments can continue as technologies continue to develop, stabilize, evolve and possibly repurposed. In phase one there are two actions. The first is to identify a technology and become involved with research team, if possible. The second action is to identify a research question surrounding ethical and social concerns. The second phase of the nonlinear approach, research and data analysis, requires the completion of a literature review and analysis of the results. This information should be used to inform the initial research questions. Adjustments should be made if necessary. The third phase, concept mapping, is the labor-intensive phase. It requires six individual steps including (1) preparing for concept mapping; (2) generating ideas; (3) structuring statements; (4) concept mapping analysis; (5) interpreting the maps; and, (6) utilization. After the data has been collected the results should be shared with the participant pool for any
additional feedback. Phase four includes an evaluation of the entire process. The primary activity is to reflect on the outcomes established in phase two. The final phase of the approach, closing the loop, includes two primary actions. The first is to develop action steps based on the data and interpretation of the data in previous phases. The second is to reflect upon when it is appropriate to reengage the nonlinear approach.

There are several intended benefits, including increased time, sound methodologies, increased inter- and multi-disciplinary collaboration, the inclusions of wider ethical and social issues including socioeconomic issues, improved transferability of information, and finally creating consistency in ethics assessment while not stymieing
scientific progress. In addition to benefits there are limitations as well. They include the status quo of ethics assessment, the sum of the parts problem, the manner in which this approach was generated, the required need of ethics expertise, and the fact that ethics assessment does not necessarily solve ethics issues, problems, or controversies.

The nonlinear approach cannot address the fiscal concerns relating to HTA or biotechnology research in general. If anything, this model will likely put an additional strain on fiscal considerations given the expected continuous duration of the approach. There is precedent for allocating significant portions of the budget for ethical considerations in emerging genetic health technologies; and it is hoped that scientists would continue to build on this precedent. Perhaps in the future, after the approach is utilized, there may be some way to calculate return on investment.

The following chapter will apply the nonlinear approach to emerging genetic health technologies. This application will be conducted theoretically as the primary aim of this dissertation is to provide the foundational methodology to support the use of the nonlinear approach.

ENDNOTES


50 Enns, It’s a Nonlinear World, 4.

51 Avriel, Nonlinear Programming, xiii- xv.

52 Enns, It’s a Nonlinear World, 1-10.


54 Avriel, Nonlinear Programming, xiii – xv.


56 Avriel, Nonlinear Programming, xiii.

57 Enns, It’s a Nonlinear World, 73-87.


59 Enns, It’s a Nonlinear World, 323.


61 Enns, It’s a Nonlinear World, 281-300.


63 Manne. ETA: A Model for Energy Technology Assessment, 390.


75 Duthie and Bond, Improving Ethics Analysis in Health Technology Assessment, 64-70.


87 Callahan, Health Technology Assessment Implementation: The Politics of Ethics, E14-E19.; Duthie and Bond, Improving Ethics Analysis in Health Technology Assessment, 64-70.


90 Rawls, Theory of Justice, 42.

91 Tom L. Beauchamp and James F. Childress, Principles of Biomedical Ethics, 6th ed. (New York: Oxford University Press, 2009), 382.
Chapter Five: Applying the non-linear approach to emerging genetic health technologies

5.1 Introduction to emerging genetic health technologies

Chapter Five will apply the nonlinear approach to an emerging genetic health technologies; specifically it will address a technology that has significant implications for the cultivation of protocells, gene therapy, and other emerging genetic technologies. The technology is the recent breakthrough in expanding the genomic code. This qualification is deliberate for two important reasons. First, emerging genetic health technologies have applications and implications across a range of other emerging genetic health technologies. Second, emerging genetic health technologies raise some crucial ethical concerns that challenge existing ethical paradigms.

To accomplish this, the chapter will begin with a brief introduction to genetics as the future of medicine. This will include identifying some ethically problematic existing technologies, as well as some ethically problematic emerging technologies. This will be followed by a review of TA and HTA in this area. Then the nonlinear approach will be applied to the expanded genome. This chapter will conclude with discussion and analysis of the application.

5.1.1 Examples of existing and emerging genetic health technologies

Genetics is the future of medicine, and brings with it a new set of ethical questions and concerns. This is evident given the number of clinical trials surrounding genetic interventions, research prioritization, research that is being funded, and the
emergency of personalized or precision medicine. President Barack Obama brought precision medicine to the national stage in his recent Precision Medicine Initiative.\(^1\) This section will address the ramifications of some existing genetic technologies, specifically using whole genome sequencing as a diagnostic tool in clinical medicine and biobanking. It will also address the implications and potential ramifications of emerging genetic technologies, specifically protocells and gene therapy.

There are already plenty of examples that show how the introduction of genetic technologies and data into clinical care has forced clinicians to ask new questions about values and ethics.\(^2\) Using whole genome sequencing as a diagnostic tool in medicine is quickly becoming a reality. An in-depth look at some of the looming ethical issues induced by utilizing whole genome sequencing as a diagnostic tool in medicine and biobanking is revealing. Before examining emerging ethical and social issues in genetic health technologies it is helpful to understand some of the current predicaments in which society finds itself. When ethics assessments are not conducted, society is even less prepared to address the questions posed by these technologies.

5.1.1.1 Whole genome sequencing as a diagnostic tool in clinical medicine

Examining how specific genes are expressed in plant, animal, and human genomes has a number of vital applications in healthcare. Genetic screenings can help classify some conditions that play an important role in diagnostics. It also opens the whole new world of pharmacogenomics and precision medicine. Pharmacogenomics is the process of tailoring pharmaceuticals to specific patients, usually based on genomic indicators.\(^3\) In short, the drugs are based on the needs identified in the individual’s DNA.
One of the best examples of this is revealed in chemotherapy choices. Understanding the cancers or the tumors genetic makeup physicians can best determine which chemotherapy choices are most likely to be effective. Genetic information can also tell much about the prognosis and prevention of some genetic disorders. For example, this information can indicate how aggressive a cancer might be, which impacts the prognosis. In addition, genetic information can also help identify individuals with specific gene mutations that increase the likelihood developing cancer, heart disease, diabetes, or other health issues later in life. When considering the use of whole genome sequencing as a diagnostic tool in clinical medicine, the key ethical issues can fall into four broad categories: limited therapies, uncertainties in risk prediction, third-party notification or unintended notification, and access to genetic information.

The first issue is limited therapies. There are currently no gene-transfer therapies to assist with many identifiable genetic disorders. The patient will be provided with information about their genetic health, which can be very useful in helping them to determine what type of life to lead. However, there are no medical therapies to address many genetic problems directly (e.g. Parkinson’s and Alzheimer’s); the most that can be offered is symptom management. Currently, there are no gene-transfer therapies adopted in the Western hemisphere. China has claimed success with Gendicine; but this therapy has not been adopted elsewhere. Absent gene-transfer therapies, patients will be provided with potentially devastating information and have no medical alternative. This can have profound psychological effects. Therefore, when the option of genome sequencing is presented to the patient it is imperative that they truly understand the implication of the results. Healthcare professionals already prescribe and carry out a
number of various genetic screenings on a regular basis, for example, newborn screening, carrier screening, gene therapy, and gene-based therapy.\textsuperscript{6}

Although, it should be noted that while many genetic diseases cannot be treated, whole genome sequencing is particularly helpful in cases such as identifying potential breast cancer candidates. This information is also helpful in guiding individuals toward better lifestyle practices. Currently, in the United States there are hundreds of clinical trials in various trial phases being conducted.\textsuperscript{7}

The second issue surrounds uncertainties in risk prediction and probabilities. Patients have difficulty understanding risk probabilities and they are often poorly communicated.\textsuperscript{8} One problem revolves around interpreting the information revealed by sequencing an individual’s genome. Take for example an individual who has their genome sequenced and is told they have a ten per cent chance of developing Alzheimer’s disease after the age of seventy. What does that figure actually mean? Is it an absolute one in ten chance; or is it a one in ten chance if a series of other genetic factors are expressed? The answer is unclear; even geneticists face challenges when describing the true value of genetic probabilities. Conveying this uncertainty in risk probabilities to patients is extremely difficult. From an ethical perspective, one must consider how such information would impact a patient’s life decisions. If an individual is given this information at age forty, will they then wonder and worry for the next thirty years about their prospects? As genome sequencing becomes widely available, the disclosure of relevant information must be considered as well as developing meaningful ways to present risk probabilities to patients without creating undue fear.\textsuperscript{9}
The third issue is unintended notification or third party notification. Third parties may be unintentionally affected by the patient’s genetic test results. An ethical consideration that requires immediate attention pertains to the biological relatives of those individuals having their genome sequenced. Families share genetic material and the results of one individual’s test will have implications for others in the family, particularly for biological siblings and children. When genetic information is being discussed, the familial implications must be considered as well as the privacy of both the patient and family members. A number of recommendations have emerged due to this ethical dilemma of healthcare professional’s moral obligation to third-party relatives. It has been suggested that these issues be addressed in the initial informed consent process.¹⁰ Health care professionals should discuss implications for the patient’s family and encourage patients to include close biologically-related relatives in some discussions. There should be a family-centered approach to informed consent with genome sequencing because the information affects not just patient but their immediate relatives.¹¹

The final problem addressed here, although others do exist, is access to genetic information. Direct to consumer genome sequencing allows individuals to purchase genetic tests without the ability to interpret the tests. Direct to consumer (DTC) marketing whole genome sequencing from companies such as 23andMe and deCODE genetics have a number of ethical implications.¹² In the United States, more than sixty companies currently offer DTC genetics tests via the Internet. Many states do not have any legislation governing or regulating DTC genetic test; but a few require that stores may only carry those over-the-counter tests approved by the Food and Drug
Administration (FDA). The FDA has successfully prevented the direct sale of kits in retail stores such as Wal-Mart. The FDA maintains that genetic tests should be sought through a doctor to avoid misinterpretations of the results. Moreover, many consumers are not equipped to address the complexities associated with understanding genetic test results. As a result, consumers take the test results to their primary care physician for interpretation. Many primary care physicians are not equipped to interpret genetic tests or provide genetic counseling. Issues surrounding the consumers understanding can result in frustration and confusion. It also has the potential to overload an already strained healthcare system, by requiring the physician to spend additional time with patients and potentially order more tests based on the result of a DTC scan. This, ethically speaking, is a double-edged sword; it is imperative to help people care about their health and take advantage of any information available. However, this must be balanced with the needs of both the individual and society.

The primary piece of legislation that protects individuals from being discriminated against by insurance agencies is the Genetic Information Nondiscrimination Act of 2008 (GINA). This allows individuals to take advantage of the useful information genetic tests can provide without fear of increased insurance premiums or cancelation of coverage. This provision falls under HIPAA. However, it still remains unclear what the ramifications will be for insurance companies when an increased number of the population begins to have genome sequencing tests as a part of their general healthcare.
It is clear from this glimpse into this singular application of genetic technology that the implications go far beyond the scope of safety, economic evaluation, and comparative effectiveness.

5.1.1.2 Biobanking

The second existing issue that will be addressed is biobanking. Biobanking has become a very interesting ethical conundrum. Biobanks seek to catalog individuals’ genetic material or tissue samples in order to create database or be used for future research. There is one central ethical issue which revolves around informed consent. Informed consent was developed to help protect the individual from paternalism or being coerced into a particular course of treatment. Informed consent is the practical expression of the principle of respect for autonomy. The goal is to ensure that individuals fully understand what it is they are agreeing to before they agree to do it. Patients or research participants express their consent by signing a document that details all relevant information. Informed consent should be voluntarily given; and coercion should always be avoided. In the case of biobanking it is not always known for what purpose the genetic data or tissue samples will be used. Therefore, the question becomes whether an individual can consent to research that will happen in the future with very limited or no knowledge of what that might include.16

Many articles and books have been published on this emerging issue. One of the most influential publications, edited by Jan Helge Solbakk, Søren Holm, and Bjørn Hofmann, is The Ethics of Research Biobanking.17 This book provides an excellent overview of the key ethical issues surrounding autonomy and consent. In addition,
Heather Widdows has advocated for rethinking our approach to informed consent as it relates to biobanking and genetic research. In their recent article, *The Ethics of Biobanking: Key Issues and Controversies*, Widdows and Cordell address these very issues.\(^{18}\) This builds on Widdows’ previous article, *Conceptualizing the Self in the Genetic Era*.\(^{19}\) The authors suggest that rather than consenting to a specific intervention, treatment, or research use, the participants would consented broadly to various forms of undisclosed research. This is called broad consent. Rethinking the very nature of informed consent has generated conversation surrounding the nature of autonomy in this new genetic era. Questions surrounding whether the current understanding of autonomy is appropriate are essential if a number of paradigmatic shifts occur in the current social and normative understanding of autonomy. Perhaps, as the authors suggest, autonomy may need to be removed as the primary ethical pillar of informed consent surrounding genetic data or material in research.\(^{20}\) A new understanding of autonomy and informed consent—as they relate to biobanking and other genetic research—is needed because the present understanding is not consistent with the practices of biobanking.

### 5.1.2 Emerging technologies

From the two examples addressed above, it is clear that ethicists, policy makers, and society as a whole do not have a firm grasp on how to address these technologies. This challenge is compounded when addressing emerging genetic health technologies. This section will address some of the highlights, including protocells and gene transfer therapy, as it is impossible to provide an exhaustive account of all emerging genetic
health technologies. The focus of this section will be the products of synthetic biology, specifically protocells, as well as gene therapy.

The products of synthetic biology have already started to yield health advances. One example of this is the anti-malarial drug artemisinin.\textsuperscript{21} Through a reengineering of a microorganism that produces artemisinin, scientists were able to create artemisinin artificially. As opposed to waiting for artemisinin to be produced naturally, and derive it from the plant parts of the Artemisia annua, which is the plant that artemisinin comes from. It can now be produced far more cheaply and efficiently. Most importantly it can potentially save thousands of lives. It is projected that approximately 700,000 to 1,000,000 deaths occur as a result of malaria and malaria-related complications each year. The marketing for the synthetic drug began in 2012. The manufacturing plant was built and production began in 2013.\textsuperscript{22} By August of 2014, Sanofi, the company responsible for production, had announced the release of the first batch of semi-synthetic artemisinin.

Techniques used in synthetic biology, specifically those surrounding DNA sequencing and computer modeling of the sequencing, may streamline vaccine development and delivery. In order to create new vaccines, a virus strain must first be identified. Each strain has its own unique genetic code; this code is used to generate the vaccine. Now that sequencing is faster and cheaper, this process is becoming more streamlined. Moreover, the ability to “bank” the genetic information of various diseases and viruses has reduced the time it takes to identify the virus.\textsuperscript{23}

Other products of synthetic biology include the development of renewable and clean bio-fuels. A recent topic of intense discussion has been the creation of genetically
modified organisms also called genetically manipulated organisms (GMOs), including both plants and animals. There are many examples of these products. One of the most well established GMOs in agriculture is the Gold Rice Project.24 Another example which has drawn national attention in the United States, creating a crisis of sorts, surrounds the release of genetically modified mosquitoes in the Florida Keys.25 While these are all interesting and compelling examples, the focus in this chapter is the application to health. In order to have a better understanding of the potential contributions of genetics and synthetic biology to human health two emerging technologies will be reviewed: protocells and gene therapy.

5.1.2.1 The creation and cultivation of protocells

Protocells are living organisms that are self-organizing, can replicate or reproduce, and have the capacity to evolve and adapt to their environment. They spontaneously assemble from both organic and inorganic material. These organisms, more simple than bacteria cells, consume raw materials and generate energy from them and their environment.26 There are two primary scientific methodologies used in protocell research—the top-down and the bottom-up approach. The top-down approach involves modifying existing organisms in an effort to create new ones. The bottom-up approach aims at using nonliving materials to create living organisms.27

Cultivating the first protocell is a scientific milestone. It represents the capacity to synthetize life in a laboratory. Furthermore, the creation of protocells is the first step toward the next major development of intelligent machines. Scholars predict that protocells will help bridge the gap between the living and nonliving.28 This would allow
scientists to dramatically increase the capacities of living and inanimate systems. If these technologies can be harnessed, there are an abundance of practical applications including environmental, pharmacological and medical diagnostic functions. For example, protocells might serve as vehicles to deliver and activate drugs in a very specific way and target particular tissues or organs. At present, only living organisms can self-repair or heal, and actively learn and adapt to unpredictable environmental changes.

Technological instruments alone are brittle, non-adaptive, and costly. If the gap between living and nonliving, organic and inorganic, can be bridged, the possibilities for technological advancement are dramatically increased. Protocells and gene therapies will be utilized hand-in-hand as protocells can provide the vehicle for successful gene therapies.29

There are many potential benefits and areas of application for protocell research. The production of biofuels could reduce the United States’ and the world’s dependence on fossil fuel. This in turn would reduce dangerous emissions as well as the political unpredictability surrounding existing fossil fuel consumption.30 With this promise of renewable energy come several risks. Contamination of the natural ecosystem or any biological system, either accidentally or intentionally, by the release of organisms is a risk.31 Uncontrolled release of new microorganisms is a serious concern because there is no way to predict how the new organism will impact the existing system. Moreover, this is compounded if the microorganism was not intended for that particular system.32

Another potential benefit is the advancement and improvement of human health. Improved drugs, vaccines, and their delivery method could be adapted to pharmacogenomics. This means that protocells could be used as vehicles for drugs
tailored to an individual’s genetic code to combat a specific disease or disorders such as immunodeficiency virus and cystic fibrosis. This type of scientific breakthrough would greatly assist research efforts in gene therapy. The use of protocells in medicine carries risks. The primary risk is to the humans into whom they are being inserted and the environment in which those individuals live. Unanticipated adverse health risks and other side effects may accompany the use of cell therapies. Moreover, the human germ line may be unintentionally, or intentionally, altered. Although this is a risk, it may not have negative outcomes or harms.

A third potential benefit is the ability to genetically alter crops and livestock. Currently some technologies have already enhanced agriculture; but protocells would provide increased potential. For example, plants could be genetically altered to yield higher levels of consumable proteins. Another promising agricultural application is the production of environmental biosensors for monitoring soil nutrients. In addition, the development of biosurfactants can bring needed bacteria and other agents to ecosystems as well as be tailored to clean and manage specific types of pollution. There are three primary risks associated with this type of research: uncontrolled release or escape that disrupts or destroys an ecosystem; the evolution of these organisms into dangerous strains that are difficult to control; and the potential for increased pesticide resistance.

Biosecurity is also a primary concern because there is the potential for protocell research to be used with pernicious intent for nefarious purposes. The dual-use of products from research must be carefully considered. However, the issue of dual-use is inherent in most emerging technologies. There are already examples of reengineering viruses such as the polio virus and the Spanish flu. Therefore, concerns pertaining to
biosecurity and the threat of bioterrorism should not cripple research efforts. Yet with the increasing availability of second hand equipment, and as DNA sequencing becomes easier and more accessible, danger rises from biohackers or garage biology. Tucker and Zilinskas maintain that government-level biological warfare programs currently pose the greatest threat for potential misuse. They also indicate that it is unlikely that new organisms will be developed and released; rather, it is more likely that a modified version of a preexisting organism like the polio virus will be developed. Whether new lethal components are created or existing ones are modified, the problem of abuse and misuse certainly exists. These fears are amplified by the fact that protocells evolve and their properties could change in unforeseeable ways. This in turn makes evaluating long-term consequences very difficult.

The consequences of creating artificial cells are unclear. Yet, policy makers will have to make difficult decisions regarding the acceptability of risk in research protocols, where to allow field trials, whether to allow commercial application, addressing liability issues of harms, and considerations regarding the accessibility to scientific information that can be misused or abused. One of the roles ethics plays is to help discern the acceptability of risk and how to mitigate certain harms.

5.1.2.2 Gene therapy

Gene transfer utilizes genetic material or genetically modified organisms to study and alter human genetics and biology. Gene transfer can be used for both therapeutic purposes and for human enhancement. For example, it can be used to treat cancer and cystic fibrosis or it can be used to create a new human trait or enhance an existing feature
in a healthy individual. There are also investigative gene transfer studies that aim at marking individual genes in healthy participants. Gene transfer is a growing field and comprises two-thirds of all phase one and phase two trials in the world. Currently, there are no commercial products available in North America, Japan, or Europe. China has approved a gene transfer treatment, called Gendicine, to treat head and neck cancer.

With any new technology or research initiative, particularly those involving human participants, many ethical considerations must be taken into account. Both protocells and gene transfer carry significant risks as well as an increased level of uncertainty relating to the magnitude and severity of risks.

Risk assessment in gene transfer technologies raises many concerns that overlap with clinical research ethics. Ethics should play a significant role in risk assessment because the ultimate questions are value-laden and require ethical consideration. For example, determining the acceptable amount of risk to a research participant is a value judgment that hinges on a number of factors including the social value of the protocol and potential benefits. The level of risk incurred by any participant must be justified.

Risks in gene transfer technologies can be divided into two categories. First, there is the technology itself, determining whether the hardware works and what physical or psychology risks the intervention(s) present to the participant. Second are the risks associated with the clinical research trial process. These risks include the blind ambition of science, financial conflicts of interests, pressure to execute the study quickly, and the list goes on. Risks are compounded by the involvement of human participants; and questions of using stable or even healthy patients in gene transfer studies have drawn a lot of attention. A prime example is the Gelsinger case. A teenage boy, Jesse
Gelsinger, was enrolled in a gene transfer experiment to treat ornithine transcarbamylase deficiency, at the University of Pennsylvania. His death was the first cause directly by gene transfer and raised many concerns regarding following research protocol, informed consent, and conflict of interest. But the aim of this dissertation is not to produce a laundry list of the inadequacies of current research ethics guidelines. Rather, the focus here will be on the technology itself and how to address the uncertainty of risk in gene transfer trials; in addition, a new comprehensive model for risk-benefit analysis in research trials will be highlighted.

The risks associated with gene transfer technologies present a challenge because, like protocells, they contain a high level of uncertainty. Jonathan Kimmelman, a professor in the Biomedical Ethics Unit at McGill University, makes the point that gene transfer research is not necessarily riskier than other types of research protocols; rather, the uncertainty of risk, both in severity and magnitude, is not as identifiable and predictable as in other medical interventions. Kimmelman notes several important risk factors in gene transfer. He divides them into two groups. The first group he calls “conceptual features,” which include: the use of active agents rather than chemicals, genetic material directly affects the individual’s genes, the drug functions both as the delivery vehicle and the therapy, gene therapy may have risks with long latencies, and there may be a risk to public health if certain viral vectors are present. When participants receive gene therapy or transfer, they typically must continue long-term treatment which can elevate risks as time passes; furthermore, many toxicities in gene transfer are immunologically based. The second classification of factors Kimmelman identifies are methodological risks, these include: there is limited number of animal
models that predict vector safety, meaning that it is difficult to predict toxicity; some vectors can produce a plethora of different human responses; and, gene vectors carry with them the possibility of “non-linear dose-response.”

Like protocell research, gene transfer can also challenge the conception of life, albeit, in a slightly different way. If or when gene transfer therapies are successful, humans will have the capacity not only to treat genetic disease but also to enhance themselves. Therefore, if one approaches ethical concerns in risk assessment comprehensively they must address the ethical concerns surrounding enhancement. That is, they must determine to what extent they are willing to alter their genetic make-up and what the implications for future generations might be. The possible human enhancements resulting from gene therapy research potentially include improving human health and extending life span, the eradication of disease, as well as elimination of unnecessary suffering. More dramatic enhancement measures include the augmentation and improvement of human intellectual, physical and emotional capacities. However much has to be accomplished before these technologies even stand the chance at becoming a reality.

Ronald Cole-Turner, from the Pittsburgh Theological Seminary, makes an important distinction. In the past, technology has been used to enhance humanity though the human changing the world around them. Now technology is being turned inward. The individual does not remain unchanged; they are changed to better suit the environment and compete in it. This is precisely what gene transfer technologies seek to accomplish; although their efforts are not necessarily geared toward human enhancement. Advancing biomedical enhancement for the sake of human enhancement
is the beginning element for the transhumanists’ position. According to the transhumanist position, the next stage of human evolution is rational evolution. In this concept, scientists attempt to give humanity the best opportunity to not only survive, but have the best possible lives in the present and foreseeable future. As gene transfer technologies advance these wider philosophical, ethical, and social considerations must be taken seriously.

5.2 Existing ethics assessments: TA/HTA currently being conducted

The second portion of Chapter Five deals with TA and HTA processes that have been completed or are currently underway, including the President’s Commission and a variety of scholarly publications. Bjørn Hofmann’s Socratic approach has been applied to a number of genetic technologies including neonatal and newborn screening, stem cell transplantation and a few others. However these reports are incredibly difficult to locate. These ethics assessments have occurred within existing HTA process. The FDA has assessed the genetic technologies that have been accepted into mainstream healthcare. This ensures a certain level of safety, comparative effectiveness evaluation, and economic evaluation. However, this does not include ethical or social assessments. Two types of publications will be addressed here, including comprehensive treatment of a particular technology or subset of technologies, and individual or singular publications on a specific issue or argument. There are many individual publications but not many comprehensive assessments.
5.2.1 The President’s Commission

In 2010, the President’s Commission for the Study of Bioethical Issues (PCSBI) published *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*. This was largely in response to J. Craig Venter’s work surrounding the synthetic cell, which was announced earlier that year. However, a vast array of products and potential products resulting from processes involving synthetic biology were addressed, including, bio-fuels, GMOs, as well as biosafety and biosecurity risks. President Obama commissioned this report to be forward-looking and anticipate ethical, social, and environmental issues that may arise. Risk encompasses social, ethical, economic, and scientific considerations. Certainly one principle or even a set a principles cannot adequately address all of these areas. Currently, there is no comprehensive systematic assessment tool available; although suggestions regarding important aspects, such as risk and ethics in HTA, are being discussed.

The PCSBI could be one such agency for oversight of emerging technologies; but federal oversight is often limited to those entities that are owned or funded by the US government. Despite this limitation in direct governance and regulation, the PCSBI makes several useful suggestions for ethical considerations in synthetic biology. They rely on the principles of public beneficence, responsible stewardship, intellectual freedom and responsibility, and democratic deliberation, as well as justice and fairness. These ethical principles are relevant to considering the social implications. These are excellent aims generally speaking; however, when attempting to systematically assess the technology it becomes difficult to see exactly how these principles ought to be used. It appears that these principles are to be applied in a similar manner as Beauchamp and
Childress’ four principle approach. Furthermore, there is no clear way to balance these principles or resolve conflicts and naturally existing controversies, as there is no decision-making mechanism proposed.⁵⁹

5.2.2 Existing publications

A variety of scholarship has emerged in recent decades regarding the ethical assessment of the products of synthetic biology; many of these publications emphasize issues in uncertainty, risk, and threats to the existing ethics paradigms.⁶⁰ This scholarship is published as standalone articles, books and collective anthologies. However, there are few comprehensive approaches to the assessment of the products of synthetic biology. Furthermore, outside of conjecture, speculation, and a few proposed frameworks, little has been done in the way of suggesting how to actually go about regulating or providing meaningful oversight in this field.⁶¹ Regulation is called for by many scholars; however, the mechanism to appropriately accomplish this is in question.⁶² One of very few comprehensive reports, outside of the PCSBI’s report, was published in October of 2007, by the J. Craig Venter Institute. The report was titled Synthetic Genomics: Options for Governance.⁶³ This document addressed the risks and benefits of creating new organisms or altering those in existence. Several governance, standardization, and regulation options were outlined including policies for commercial gene synthesis firms, policies for monitoring and controlling equipment and reagents, and policies for users and organization. Ethical considerations were only made insofar as to note that there are ethical concerns regarding the production of new organisms; although, specific ethical considerations were not addressed. The interesting aspect of this publication is that it
was a private institute who commissioned the report in an effort to get ahead of the curve. Rather than waiting for ethical or regulatory issues to emerge, likely during some crisis of public conscience, the Venter Institute was attempting to deal with these issues upfront. In light of Venter’s research, two themes have permeated the literature surrounding protocells and gene therapy, including how life is defined, and whether scientists are “playing God” when they experiment with plant, animal or human genomes. These will be addressed in the following section.

5.2.2.1 “What is life?” and “Playing God”

Two important ethical considerations flood this literature: what is the nature of life or the organisms scientists qualify as living, and whether building life in a laboratory is ethically permissible or simply “playing god” or “playing with fate.” An important ethical consideration is that the products of protocell research may transgress cultural and moral norms, and most notably the very conception of life.\textsuperscript{64} The very conception of life, its intrinsic value, is seemingly challenged. For anything to be described as living there first needs to be an understanding of what it means to be alive. The definition of life has been sought out by the greatest minds in history; and yet there is no definitive answer. Some philosophers offer no better suggestion than to stop trying. Mark Bedau in his article \textit{What is Life?}, suggests that life may not have a unified all-encompassing explanation.\textsuperscript{65} Furthermore, life may cease to be a basic category of natural occurrence. He asserts that there really is no single answer to the question or definition of life and the question is basically wide open.
Many critics suggest that pursuing protocell research is meddling in ideas beyond our control, violates nature’s sanctity, or is man’s attempt to “play God.” Mark Triant and Mark Bedau argue in *Social and Ethical Implications of Creating Artificial Cells* that, overall, these types of blanket arguments are vague, unsophisticated, and largely ill-conceived, thus presenting no founded reason to arrest the pursuit of this research.\(^\text{66}\) However, questions about the nature of life are appropriate. Creating life from inorganic materials elicits challenging philosophical questions about what it means to be alive; the distinction is now blurred. Even though these considerations can be successfully argued in many fashions, it is important to address them as they may impact public opinion.\(^\text{67}\)

5.2.3 Gaps of current genetic HTA projects

5.2.3.1 Ethics assessment is irregular and scatter-shot

As outlined in Chapters Three and Four, there are gaps in ethics assessment. These gaps exist in emerging genetic health technologies. This section will address these gaps. Formal ethics assessment among emerging health technologies that involve the use of protocells is irregular and virtually non-existent. For the purposes of clarity, formal ethics assessment takes place as part of an initiated HTA project; and informal ethics assessment refers to the scholarship published outside of initiated HTA projects. As a result of the literature review, it is evident that most scholarship explores the risks, benefits, and various ethical arguments; yet in very few instances is direction provided to scientists, policymakers, or the public. This scholarship is very important, but it is not ethics assessment; it is critical discourse surrounding ethical issues in this area, which could provide the foundation for ethics assessment. PCSBI’s report on synthetic biology
is an excellent starting point, but it remains only an overview of potential issues. Venter’s report on governance is quickly become outdated, as it is nearly a decade old at this point. Many of the singular publications are very insightful, but standing alone lack impact.

There are a number of private companies addressing the assessment of genetic health technologies. There are three prominent companies in the USA: ECRI Institute; Hayes, Inc.; and Blue Cross and Blue Shield Technology Evaluation Center. Private companies offer a range of services from HTA reports, horizon scanning, genetic test evaluations, and so on. Many also have specific areas of focus. For example, Blue Cross and Blue Shield Technology Evaluation Center emphasizes comparative effectiveness reports. While these private companies provide a very important function, many do not engage emerging technologies. Again, they are geared toward assessing those technologies that are seeking market approval or licensure. The same gaps that exist in the application of ethics to HTA in other health care contexts, ethics as a priority, narrowness and lateness of assessment, and general oversight and guidelines are the same for those applied to genetic technologies.

5.2.3.2 Ethics as a priority

Among emerging genetic health technologies there is abundance of acknowledgments that ethics is important; however there is no consensus on how to go about articulating that fact. Thus far in the chapter, a wide range of publications have been addressed. These publications are critical in developing and continuing the discourse; however many are not comprehensive in nature and hence they are just
standalone publications. It is unclear whether there is any impact at all, outside of identifying a problem. Given the justification for the integration of ethics in Chapter Three, and the relationship between society and technology provided in Chapter One, there is a strong case for the meaningful integration of ethics at the research and design phase of emerging genetic health technologies. However, this is not happening in a meaningful way; but that does not mean that it cannot.

5.2.3.3 Narrowness and lateness

Current ethics assessment is too narrow in the sense that many of the ethical considerations are considered in isolation from other variables and factors. For example, there are limited publications at the intersection of emerging genetic health technologies, ethics, and bioeconomy.\textsuperscript{70} As shown throughout this dissertation, most HTA assessments occur only when the technology is seeking market approval; and ethics is often neglected. Given the ethical and social impact of emerging genetic health technologies described above, staying the course does not appear to be a wise option. Formal ethics assessment, when it does occur, happens too late; this chapter is aimed to serve as proof of this. The fact that minimal HTA reports have been initiated around emerging genetic health technologies indicates that assessment is already behind. In the coming years the use of protocells and gene-transfer technologies will be starting human trials. Worldwide there are currently more than 500 clinical trials involving gene transfer in various stages of completion.\textsuperscript{71}
5.2.3.4 Oversight and regulation

In the book *Building Genetic Medicine*, Shobita Parthasarathy, provides a comparative analysis of how politics played a critical role in shaping the treatments for breast cancer in the United States and the United Kingdom. In this global era, national contexts and politics play an important role in the adoption of certain genetic technologies. In the UK, genetic testing for the BRCA is generally seen as a form of preventative medicine; whereas in the United States this genetic testing is more or less offered on demand. This difference in the offering of services, Parthasarathy notes, is likely due to differences in approaches to health care and commercialization of research.\footnote{72}

Many other scholars have called for regulation and oversight in the field of emerging genetic technologies. However, the only oversight that seems to be occurring is the oversight in determining which technologies are adopted and approved for use in the healthcare setting. Outside of this regulation conducted by the FDA in the US, the NIH have guidelines pertaining to what research is eligible for funding, which provides some level of oversight as the researchers seeking funding are obliged to follow the ethical guidelines set by the NIH.\footnote{73} Privately funded research, however, does not fall under the same regulatory guidelines.

5.3 Applying a nonlinear model to emerging genetic health technologies:

**Conceptualizing nonlinear thinking in this context**

In the first sub-section the context and justification will be given for the selection of emerging genetic health technologies as a case study. This area of research was
selected because of the aim in application to human health, the immense moral
controversies that are elicited, as well as the current stages of research of these
technologies (protocell cultivation and gene therapy). As previously stated, the primary
aim of this dissertation is to describe and justify the methodological foundations for the
nonlinear approach. The application articulated in this chapter is purely hypothetical. It
is outside the scope of this dissertation to engage a research project and fully carry out the
nonlinear approach in practice.

5.3.1 Phase one: identification and inquiry

There are two overarching activities that need to be completed in this phase.
First, the approach must be utilized by an emerging technology. Practically, it would be
helpful to have a designated facilitator and organizer for this process. The size of the
team necessary to carry out the approach is dependent upon the number of participants.
The more participants the larger the team needs to be to accommodate the steady and
efficient flow of the nonlinear approach.

It is noted throughout the literature that there is a lack of oversight and
regulations; this may or may not be beneficial. Oversight can be understood in two ways:
regulating research in this area, or initiating TA or HTA reports. This section will not
focus on regulation, but rather on lack of investigation into the ethical and social
ramifications, both positive and negative, of emerging genetic health technologies. There
are a number of oversight challenges; for example, how does one properly do risk
assessment; how does one deal with uncertainties and protections; and, in light of
increased ease of access to genetic materials, how does one address biosecurity and
biosafety, working together to help creative safety nets surrounding synthetic biology and emerging genetic technologies.

Regulatory programs from the US Department of Agriculture, FDA, Environmental Protection Agency, the Occupational Safety and Health Administration, Department of Transportation, and the Department of Commerce all play key roles in supporting the safety net to protect both the general public and those working in this field.\textsuperscript{74} For example, the FDA assesses particular foods, drugs and other goods that could be released in the general public. \textsuperscript{75} The EPA addresses safety measures with new chemicals and manages emergency programs for the cleanup of environmental contamination and hazards.\textsuperscript{76} Most applicable, however, is the role of the National Institutes of Health and the Center for Disease Control and Prevention. There are a number of oversight strategies employed by the US government, many of which address and oversee research dealing with recombinant DNA and synthetic biology. They strive to ensure ethical conduct of researchers and promote the safety of the researchers and the general public and biological research; this is done through risk assessments strategies, safety and containment standards for laboratories.\textsuperscript{77}

The biggest challenge to oversight is the fact that it only occurs for those labs and projects owned or funded by the federal government. This means that if a project is privately funded and is not taking place in any government related facilities they are not subject to the same NIH and CDC oversight standards.\textsuperscript{78} They do however have to comply with state and federal statutes and laws surrounding transportation, commerce, and distribution of the products and synthetic biology. To demonstrate this point, consider the Dickey-Wicker amendment which banned stem cell research in the United
States; all laboratories had to comply with this law. However, before the law was passed only labs that received federal funding had to follow the rules set by the NIH and the CDC surrounding the use of stem cells in research.  

The reason for addressing oversight so specifically at the start of this phase, is to identify the hardships that can exist in identifying those emerging technologies that need to be assessed. As stated in Chapter Four, the ideal way to execute this approach is to be on board at the start of a new research project, or to come on board shortly after one has been started.

For this hypothetical analysis, the technology that will be assessed falls under the category of synthetic biology. In the spring of 2014, scientists announced the first functioning semi-synthetic genome. That, in and of itself, is not a breakthrough, as Venter had created a fully synthetic genome successfully in 2010. The special aspect of this research was the addition of two nucleotides to the organism’s genetic code. The following excerpt from the abstract summarizes the work, published in Nature.

Organisms are defined by the information encoded in their genomes, and since the origin of life this information has been encoded using a two-base-pair genetic alphabet (A–T and G–C). In vitro, the alphabet has been expanded to include several unnatural base pairs (UBPs). We have developed a class of UBPs formed between nucleotides bearing hydrophobic nucleobases, exemplified by the pair formed between d5SICS and dNaM (d5SICS–dNaM), which is efficiently PCR-amplified and transcribed in vitro, and whose unique mechanism of replication has been characterized.  

What this scientific abstract reports is that two new “letters” (nucleotides or base-pairs) have been artificially added to the code of life—deoxyribonucleic acid (DNA). These are artificial and have been given the designation X and Y.
Every life form on earth, every single species from the fruit fly to humans, uses the same genetic code. It is comprised of nucleotides or bases represented by the letters A, C, G, and T. The sequence of nucleotides forms proteins, and proteins determine what types of cells to make. In a way, the addition of X and Y nucleotides has created an alien life form. This living organism is wholly different right down to the most basic, fundamental structure. This builds on Venter’s work and takes it to the next level. Adding more letters to DNA allows for more creativity and variability in modifying existing genomes or creating new ones.

The researchers were able to insert an X-Y pair—man-made, chemically created nucleotides. They were inserted into the common bacterium E. coli. The bacteria responded to the modified genetic code. The cell reproduced as bacteria do, and replicated the X-Y nucleotides along with the other naturally occurring nucleotides. This E. coli bacterium now has six letters in its genetic code. The researchers allowed the cell to reproduce 24 times (24 doublings) over the span of fifteen hours. The implications of this are astounding. In a New York Times article, one of the lead researchers stated: “If you have a language that has a certain number of letters, you want to add letters so you can write more words and tell more stories.” With the addition of stable nucleotides comes the possibility for new types of proteins and new types of organisms of a wider variety. This increases biological diversity, or at least has the potential to do so.

The aim is to use the artificially constructed proteins and genomes to create antibiotics, vaccines, and other health related and non-health related products. However, much more work needs to be done before these products can come to fruition. Ambrx, a biotechnology company based in San Francisco, is already incorporating novel
amino acids into the development of new site-specific treatments. In similar research, a team in Florida, lead by Dr. Benner, is attempting to build base pairs that do not exist in nature. Thus, it can be concluded that the world is not too far from witnessing usable replicating unnatural genetic structures.

Now that the technology has been identified, the next activity is to develop the research question. The research question proposed here is “How will expanding the genetic code, through chemically created nucleotides, impact our values and norms?”

In this hypothetical application of the nonlinear approach, the participants include eight scientists, two policy experts, six medical doctors, and four ethicists. Due to the fact that this is the first cycle addressing an emerging technology the participant pool is kept intentionally small. In subsequent cycles the participant pool will be expanded dramatically in order to provide a wider representation of diverse perspectives. In this model it is helpful to begin with a baseline; and experts in the field are in a prime position to provide this.

5.3.2 Phase two: research and data analysis

The second phase includes research and initial data analysis. That is, to determine what publications exist pertaining to any aspect of this technology and how does the aggregate of this information inform the current undertaking.

Of the three recommended ways to conduct the literature review, the third option was selected for this application. Given the author’s experience in bioethics research methods, this was used to conduct the literature review. This research was not outsourced, nor did it follow the guidelines suggested by Droste et al. Again, this
example reinforces the flexibility of the model in that it can adapt to different research styles and strengths.

A literature review was conducted. The search engines used were Google scholar, Ebsco host, PubMed and investigation of specific bioethics and scientific journals (e.g. *The Hastings Center Report, American Journal of Bioethics, Medicine, Healthcare and Philosophy, Journal of Medical Ethics, Nature, Science, Nature Review Microbiology, Nature Reviews Genetics*, etc.). The search terms included “expanded genome,” “synthetic nucleotides,” “ethics and expanded genome,” and “ethical issues in synthetic nucleotides.”

The research showed that others scientists were engaged in similar research simultaneously with Romesberg et al. Two of these included Yang et al who published *Amplification, mutation, and sequencing of a six-letter synthetic genetic system,* in 2011, and Yamashign et al published *Highly Specific Unnatural Base Pair Systems as a Third Base Pair for PCR Amplification* in 2012. Several other scientific research articles included Romesberg et al’s work as a reference. This work has been gaining some traction, which is evident from its recent article metric reports. The article has had over 70,000 views online, and it is referenced in eighty-nine news articles, forty scientific blogs, and forty-nine Google+ posts. The original article has been cited by thirteen other publications. Other relevant publications on this work include Thyer and Ellefson’s article *Synthetic Biology: New Letters for life’s alphabet* and two publications by Roy Sleator, *The genetic code,* and *Genetics just got SEXY: Sequences encoding XY.* Only one tangentially touched on ethical or social topics. These included Woyke and Rubin’s
Searching for the branches on the tree of life, which dealt with search for new forms of life.\textsuperscript{90}

Ethics publications on this specific topic were not found. However, there are a wealth of publications on synthetic biology, as a technology and as a discipline, and ethical considerations contained therein. These will be used to inform the questions surrounding the emerging technology of expanded genomes. Specifically, the ethics articles already mentioned in this chapter will be used as the foundation. The general lack of social and ethical considerations surrounding this recent breakthrough indicates that it is an appropriate place to start. The intended outcome for this research is threefold. First, to gain expert feedback, arguments, and opinions regarding the identified research question: “How will expanding the genetic code, through chemically created nucleotides, impact our values and norms?” The second outcome of this research is to identify gaps in understanding of social and ethical considerations pertaining to expanding DNA. The final outcome, for this cycle, is to identify additional stakeholders for future involvement in the concept mapping phase.

5.3.3 Phase three: concept mapping

Following the methodology articulated by Kane and Trochim, a concept map will be produced. The steps include (1) preparing for concept mapping; (2) generating ideas; (3) structuring statements; (4) concept mapping analysis; (5) interpreting the maps; and, (6) utilization.\textsuperscript{91} The application will follow all of these steps; however, this is purely hypothetical. No experts were actually consulted, and no participants were contacted.
This is strictly a thought experiment to demonstrate the basic processes and key considerations.

5.3.3.1 Preparing for concept mapping

Based on the literature review, a number of knowledge sources were identified in relation to the research question. These include molecular biology, genetics and genomics, synthetic biology, bioethics, public policy, law, social issues, and healthcare. This identification of knowledge sources indicates what groups or individuals should participate in the first round of concept mapping. These groups or individuals would include scientists with expertise in molecular biology, genetics/genomics, and synthetic biology, medical professions who utilized genetic/genomic tools and/or engage in research relating to genetics, professional ethicists (e.g. ideally individuals who have published on the topic), and the research team.

5.3.3.2 Generating ideas

There are two actions that must be completed in this step. First is the generation of statements. The second action is to distribute content and collect responses. Generating statements should be based upon the connection to the research question. The statement should also be informed by a literature review conducted in the previous step.

Based on the hypothetical research search question established in step one, as well as the literature review provided in step two, and for the purposes of this dissertation considering all points already discussed in this chapter, a number of hypothetical statements were developed. In this case, the statements created are intentionally broad.
This was done to allow experts as much flexibility and open-endedness in their responses as possible. Adjustments may have to be made depending upon the participant pool and the context of the project and research question. There is no magic number for the appropriate number of statements to give participants; for data management purposes, it appears that between six and ten statements are reasonable. Each participant will be asked to answer all of the following as fully as possible. Possible statements for this hypothetical application include:

1. Opinion: What does altering the ‘alphabet of life’, expanding the genetic code, mean for the future of medicine?
2. Opinion: What does this work indicate about life on this planet and possibly elsewhere in the universe?
3. Fill in the blank: Governments and regulatory agencies should,… ,in response to these developments.
4. What ethical considerations apply to this technology?
5. Open-ended question: This technology will impact…
6. Open-ended question: This technology will be considered successful, if, as a result, it produces…
7. Open-ended question: This technology will be considered a risk or unsuccessful, if…

After careful consideration and attention to wording and structure, the statements will be distributed to the fictitious participants. Given the technical nature of the content and low number of participants in this first cycle, it is recommended to send an e-document that can be completed by the participant in his or her own time.

In this hypothetical example, a month will be given for completion of the initial responses. Three open forums will be held via Adobe Connect, which is an excellent audio and web conferencing tool. The first is an optional information session describing the project, timeline, expectations, goals, and a question and answer period. This information will also be provided in the packet sent to participants. The two subsequent
meetings are discussion-based meetings, designed to focus on specific statements and participant answers. This will give experts the opportunity to cross-pollinate and exchange or inform ideas, facts, and opinions. This will also assist the participants in formulating their responses, as the discourse generated by the discussion group will encourage critical and in-depth thinking, as well as opinions and multiple perspectives.

Meetings may or may not be required depending upon the preference and flexibility of the facilitator and the context of the project. In this hypothetical case, the meetings are not required, but strongly encouraged. Of these two opportunities participants will be asked to participate in one. Ideally, each meeting will have a diversity of participants to the extent practicable. If the participants cannot attend one of these web-based meetings, their written responses should be included in the following steps.

After responses are collected the information must be synthesized. For the sake of this hypothetical application, the assumption is made that all twenty participants fully responded to all statements. This leaves the facilitator(s) with approximately 140 unique answers to the statements that must be reviewed and synthesized. The synthesis of these answers should result in the elimination of any redundancies and answers, determining what answers fall outside the scope of the current research question, and determining which answers are simply not relevant to this research at all.

To further this hypothetical application, statement 4 will be analyzed. Statement 4 asked participants to consider what relevant ethical considerations should be included. To begin the analysis, a list of all answers should be created. Individual participants might provide multiple answers to a single question; this is encouraged and all answers
should be recorded. One of the best ways to collect and sort information is through Microsoft excel. As demonstrated in the table below, all hypothetical participants, their demographic information, and responses to the statements, in this case statement four, can all be compiled in the same spreadsheet. The benefit of this approach is that it makes initial sorting and categorizing of respondents and relevant topics more simple. The table below has sorted all respondents based on their professional discipline.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Demographic (Profession)</th>
<th>Comment 1</th>
<th>Comment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>P4</td>
<td>MD</td>
<td>Implications for clinical trials - informed consent</td>
<td></td>
</tr>
<tr>
<td>P15</td>
<td>MD</td>
<td>Risks to patient health - drug interaction</td>
<td>Risk to patient health - implication for other gene's expression</td>
</tr>
<tr>
<td>P7</td>
<td>MD</td>
<td>Do more social good by providing more options for treatment</td>
<td></td>
</tr>
<tr>
<td>P5</td>
<td>MD</td>
<td>Biological diversity could improve the ecosystems and environment, thus improving human health</td>
<td></td>
</tr>
<tr>
<td>P11</td>
<td>Scientist</td>
<td>There are none, technology is value-free</td>
<td></td>
</tr>
<tr>
<td>P20</td>
<td>Scientist</td>
<td>Do not stymie scientific progress, as it is a social good</td>
<td></td>
</tr>
<tr>
<td>P16</td>
<td>Scientist</td>
<td>Science is a social good because it can improve human life</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>Scientist</td>
<td>Natural, non-natural, post-natural: does it matter?</td>
<td></td>
</tr>
<tr>
<td>P14</td>
<td>Scientist</td>
<td>Ethical consideration include uncertainties in risk assessment</td>
<td></td>
</tr>
<tr>
<td>P6</td>
<td>Scientist</td>
<td>Someone using the technology for nefarious purposes</td>
<td></td>
</tr>
<tr>
<td>P19</td>
<td>Scientist</td>
<td>The technologies will have a positive impact on the world, it is a moral obligation to pursue it</td>
<td></td>
</tr>
<tr>
<td>P13</td>
<td>Scientist</td>
<td>Ethics cannot be considered until the technology is developed</td>
<td></td>
</tr>
<tr>
<td>P18</td>
<td>Ethicist</td>
<td>How do we define natural vs. non-natural or postnatural if the organism is living?</td>
<td>What does it mean for something to be alive?</td>
</tr>
<tr>
<td></td>
<td>Ethicist</td>
<td>Implications for the transhumanist agenda</td>
<td>Considerations for the bioconservative agenda</td>
</tr>
<tr>
<td>---</td>
<td>---------</td>
<td>------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>P1</td>
<td>Ethicist</td>
<td>Ethically justifiable risks</td>
<td>Unanticipated and unknown risks may be unacceptable</td>
</tr>
<tr>
<td>P10</td>
<td>Ethicist</td>
<td>If applied to humans, what does it mean to be human?</td>
<td>What are individuals with expanded DNA?</td>
</tr>
<tr>
<td>P8</td>
<td>Social Scientist</td>
<td>Public attitudes: Yuck factor</td>
<td>Impact on religion, cultural influences</td>
</tr>
<tr>
<td>P3</td>
<td>Political Scientist</td>
<td>Policy makers should be educated about this surge in research</td>
<td></td>
</tr>
<tr>
<td>P12</td>
<td>Policy Expert</td>
<td>Oversight and regulation should be implemented</td>
<td>Biosecurity measure should be taken by laboratories</td>
</tr>
<tr>
<td>P9</td>
<td>Policy Expert</td>
<td>All novel organisms, whether modified or complete synthetic, ought to be registered for safety</td>
<td>Public safety should be above scientific progress</td>
</tr>
</tbody>
</table>

It should be noted that everything contained in this table is strictly hypothetical.

Obviously, the comments are not nearly as detailed here as they would be in reality. The table is meant to demonstrate organizational techniques as well as broad strokes of potential ethical and social issues that might arise, based on the research presented in this dissertation. The ethical and social considerations, as well as the risks and scientific considerations, do stem specifically from the literature. Yet, there is no way to know what is and what is not important for the participants listed above. An additional limitation in creativity represented in the perspectives provided above is due to the author’s lack of a scientific and medical background.

### 5.3.3.3 Structuring statements

Based on the responses for step two, the participants will be asked to perform three relatively simple tasks. Participants will be provided with the unique responses to all the questions; however the questions will no longer be important, only the resulting topics informed by the question. First, participants will sort each item and place them in
groups with those most related to it in meaning. Essentially, participants will be categorizing the items based on relationship. Participants should be informed of any specific guidelines. The basic guidelines include that there cannot be the same number of ideas as groups, this means that participants actually have to engage in the sorting process. They cannot establish every idea as separate from another, thereby having the same number of groups as ideas. All the statements cannot be put in the same group, because this provides no distinction. There should be no miscellaneous group. If the statement is wholly unique it should be separated out.

After the participants have sorted all the items into groups, they must rank the statements based on a set of criteria provided by the facilitator(s). In this hypothetical case, the participants are asked to rank the statements by perceived levels of importance. That means, does the issue or idea need to be addressed immediately or not. A simple Likert scale will be used to rank the statements. Participants will rank each item on a scale of 1 to 5, one being not important and five being very important. Items should be ranked on their own merits; they should not be ranked in relation to one another. For example, to items in the same group might have the same level of importance based on the criteria.

The final task participants will complete is to provide some very basic demographic information. This should include gender identification, age range, geographic region of residence, professional or employment status, type of employer (e.g. for profit, non-profit, government, university, etc.) level of education, ethnicity, religious affiliation, household composition (e.g. single, married, divorced, children, etc.), and household income. This basic demographic information will allow for the easy sorting of
participants into subgroups for more detailed analysis. For example, it would be very useful to know if a certain demographic, such as African-American females, widely accepted the potential use of emerging technology; whereas Caucasian males widely rejected the potential adoption of the same emerging technology. This sort of information can further inform and justify the appropriateness of the agreed upon action steps developed in phase four of the nonlinear approach.

Here is how this might hypothetically play out in this defined scenario. A snapshot of the process will be presented as it is necessary to provide a full assessment of fictitious data. After removing all redundancies and synthesizing responses into distinct opinions and ideas or conceptual domains, statements will be redistributed to the group of participants and they will sort them, and rank each statement. In an example provided by Kane and Trochim involving the Delaware Department of Health and Social Services, participants submitted more than 500 responses. This was synthesized into approximately 118 distinct conceptual domains. This number will vary from case to case. Regardless of the participant sample size Kane and Trochim recommend having no more than 100-120, as numbers beyond that can become unmanageable to both participants and facilitators.

In this hypothetical application, of the 140 responses to statements the assumption is that there are twenty-two unique conceptual domains or ideas. It should be noted that this is a completely arbitrary number. In this hypothetical example, the twenty-two distinct domains include: lives not saved if research is halted; bio security; dual use; unanticipated risks; unknown risks; unintended use; medical benefits; improve treatments; environmental applications; public attitudes; socioeconomic concerns; policy
issues (e.g. oversight and regulation); religion; cultural norms; health as a social good; reframes our understanding of microbiology; reframes our understanding of life and nature; playing God; impacted norms; autonomy; justice; and the obligation to minimize risks.

The twenty-two unique conceptual domains are then returned to the participants for sorting and ranking of importance. Several weeks should be allowed for the completion of this task. The hypothetical results of this are that the topics are sorted into four major categories: ethical considerations, risks, social issues, and scientific advantages. Connections identified by the participants are revealed, as not all participants placed each statement in the same grouping. Rankings were averaged across the domains to determine which were considered more or less relevant based on level of importance to immediately address.

5.3.3.4 Concept mapping analysis

Based on the information collected, a very simple pictorial concept map can be constructed. The pictorial concept map reflects the categorization and rankings of the statements by the participants. Sample rankings of importance are indicated on the concept map in numeric form for the category of “risks.” The sample rankings reflect the participant average in the Likert scores for each of the statements. For example, if three participants ranked a certain statement as a five on the Likert scale, while the other seventeen marked it as a one, this can be represented as an average, which would be 1.6. In this example, the Likert average appears in parentheses behind the topic name. Depending upon the context of the project, most importantly what the facilitators are
trying to express through the numbers—whether it reflects the popularity, importance, or feasibility surrounding the statements—it may be appropriate to represent this figure in different ways.

The crosscutting arrows represent potential crosscutting issues categorized by the different participants. For example, in the “ethical considerations” category a participant might put the obligation to minimize risk as well as the risk of not having the capacity to save lives. The green line in the concept map below linking those two ideas indicates this connection. In the concept map below, it is evident how unknown or unconstrained problems can be represented. They simply receive their own concept box. There are a number of stand-alone boxes in the concept map below that indicate unknown or unanticipated items.
The concept map above was created using MindMaple, a free iOS application. The information represented in this concept map is purely hypothetical. This is still useful in demonstrating the visual strength of this method. As participant numbers increase, utilizing the pictorial concept map becomes more and more challenging. This is when the transition to scatter charts or plot charts becomes critical. The software, suggested in Chapter Four, can handle robust statistical analyses and provide visual representation of their statistics. The process would be conducted in the exact same way; and the data would be collected and organized in the exact same way. However, the difference is the visualization of the data. When using a scatter chart or plot chart, the
data gathered from participant responses to statements, as well as their rankings, is actually entered into a matrix that can be statistically analyzed. That pure statistical analysis is represented; but there is room for human error in the pictorial concept map. The facilitators are responsible for providing an accurate representation of stakeholder perspectives in pictorial concept mapping. The justification for using the pictorial map in the first cycle is to explicitly and visually call out those cross-cutting themes. While scatter charts and plot maps are more reliant on statistics there are times when crosscutting connections are not always as obvious; this is simply due to the nature of the visual.

4.3.3.5 Interpreting the maps

It is strongly recommended that the concept map, pictorial or otherwise, be shared with the participants for additional reflection and feedback. This adds to the validity of the findings. It also promotes a culture of transparency and inclusion, which is helpful for emerging technology because it can alleviate some of the natural fears and speculation that can accompany new technologies.

Drawing conclusions from nonexistent data and hypothetical thinking is rather pointless. Yet, in this hypothetical exercise it is important to provide examples of how conclusions can be drawn based on the information presented. In the concept map above, there seem to be a lot of scientific considerations linked to risks, yet there are not as many ethical considerations linked to risk. This could indicate that among the hypothetical participants there is recognition of risks, but there is not the recognition of the underlying ethical implications that accompany risk. Given the fact that the hypothetical participants
were largely comprised of scientists and medical doctors this conclusion might make sense. Another conclusion that can be drawn from this basic hypothetical concept map is that there is a close relation between social issues and ethical considerations. Although, this should not come as a major surprise as ethical and social considerations are often taken together in the same context.

5.3.3.6 Utilization

The final step of the concept mapping exercise is to use the observations, connections, and data to discern actions steps. Based on this new information a series of steps can be taken to improve the scientific research process as well as the communicative aspects of emerging technologies. From this completely hypothetical set of data, one might conclude that it would be beneficial to educate scientists about the link between ethics and risk. Another possible action step would be to identify additional participants based on the results of this research. For example, comments surrounding oversight and policy hypothetically arose; thus it might be appropriate to engage more policy experts as well as those who work and regulatory fields that might apply to this emerging technology.

The most important aspect of this final step of the concept mapping process is to approach the data with honesty and transparency. Share the findings. Avoid any temptation to manipulate, skew or, positively or negatively, spin data. This final concept mapping step overlaps with and transitions directly into phase four of the nonlinear approach.
5.3.4 Phase four: evaluation

This phase calls for honest assessment of whether the intended outcomes, set in phase two, were met. To review, there were three outcomes identified. The first is to gain expert feedback, arguments, and opinions regarding the identified research question: “How will expanding the genetic code, through chemically created nucleotides, impact our values and norms?” The second outcome of this research is to identify gaps in understanding of social and ethical considerations pertaining to expanding DNA. The final outcome, for this cycle, is to identify additional stakeholders for future involvement. If the intended outcomes were not met, reflection on possible explanations for this should be completed. Also, the action steps identified should include some recognition of this and suggest ways to address it.

In this hypothetical application, the first and second outcomes were met. However, in this example the sample size was small. The second cycle may wish to remain within disciplinary expertise, as this first cycle did, but broaden and increase the number of participants. Arguably, the third outcome has been addressed as well, yet not completely answered. There was an identification of the need for additional experts from the fields of policy and regulatory bodies. As the cycles continue over time, this outcome will likely need be continually assessed as new stakeholders and other relevant parties are identified. This outcome will provide a good starting point when the approach is reengaged for a second cycle.
5.3.5 Phase five: closing the loop

Reflection should occur on two levels. First, reflections surrounding the methodological aspects in the process should be conducted. Take time to identify problem spots and pitfalls. It is helpful to identify what did not run smoothly, or what was particularly difficult to address, and this information can shape future cycles. It is also helpful to articulate what did work and what was helpful in the process. As different organizations find certain aspects, techniques, or software that work well for them, documenting this and sharing it with other organizations will assist in furthering the discourse surrounding this approach, as well as overall development and improvement of this approach.

The second level of reflection that needs to occur is when the approach needs to be reengaged. This approach is not meant to run through a single cycle. It is meant to have as many cycles as needed to shed light on the relevant issues, frame the question properly, and provide insights for decision-makers and policymakers. It is unlikely this will be attainable in one cycle. Since this approach is engaging emerging technologies very early in the research and development phases, they are likely to be substantial breakthroughs and benchmarks that are met throughout the research process. As these benchmarks are met and major breakthroughs occur, the approach should be reengaged and the process should start over building on the work of prior cycles.

As John Cupato, Professor of Chemistry and Biochemistry at Arizona State University suggests, there are some foreseeable next steps in which to apply this technology, including, “developing systems that carry more than one unnatural base pair and encode functional information; finding new ways to reduce the dependency of an organism on
nucleoside triphosphates supplied to the medium; and increasing the scale of the bacterial cultures so that large quantities of modified protein can be produced by recombinant protein expression. These might serve as sound benchmark points that spark the re-engagement of this cycle. Another determining factor will be the scope and goals of the current research team whom are applying this approach.

In this hypothetical assessment some recommended actions would include the following: (1) additional research into any number of the hypothetical crosscutting themes surrounding ethics and risk; (2) broadening to participant pool to more experts and relevant stakeholders; and, (3) monitoring the literature for relevant publications and monitor the technology for advances, benchmarks or breakthroughs.

5.4 Discussion and analysis

This section will address the results of the previous section by providing a summary overview and analyzing the benefits of limitations of a nonlinear approach in this hypothetical application.

5.4.1 Benefits of the nonlinear approach

The benefits of the nonlinear approach include increased time, sound methodologies, increased inter- and multi-disciplinary collaboration, the inclusions of wider ethical and social issues including socioeconomic issues, allowing for improved transferability of information, and finally it is a step closer toward creating consistency in ethics assessment while not stymieing scientific progress.
The benefit of increased time was evident in the fact that this technology is still at least five to ten years from human health or cosmetic application. This allows ample time to conduct several cycles of the nonlinear approach, as well as engage in meaningful reflection and discourse. This also allows for the integration of new literature as it is published, the inclusion of additional relevant parties as they become apparent, as well as the comparison of data between cycles.

Through continued collaboration over cycles, the efficiency of the approach will be enhanced. Each phase is grounded in a sound methodology, lending validity to the whole process. The validity of the whole approach is demonstrated in the ability to effect positive action and if necessary positive change. This can be accomplished through social programming as technologies near market readiness or ensuring that certain populations will have access to beneficial treatments. An overarching benefit of the nonlinear approach is that ethics assessment occurs as the technology develops. This is immensely important because it can reduce the risk of slowing the progression of scientific research. It also addresses one of the largest obstacles in HTA, which is time. For example, the roots of stem cell research date back to the 1950’s and 1960’s with the discovery of stem cells; by 2001 stem cell research was well underway, but brought to an abrupt halt through a reduction in federal funding, under the Bush administration, when ethical, social, and legal considerations came to light. It is possible that some of the ethical, social, and legal concerns could have been anticipated and addressed if ethics assessment had occurred earlier in the process.96 This approach embraces these opportunities. This also ties directly to the benefit of enhancing consistency and validity of ethical assessments, while not stymieing the progress of science and development of
new technologies. This is because this approach is not meant to be a watchdog or oversight tool. It is intended to provide accurate data surrounding important ethical and social considerations related to an emerging technology and support actions to either better understand these issues (e.g. through additional research) or provide recommendations and actions to begin addressing these issues.

A plethora of perspectives on multiple issues can be taken into consideration collectively in an effort to develop a map of the moral and social landscape through the nonlinear approach. Elements such as: ethical concerns surrounding risks, benefits, human health and enhancement; social concerns such as socio-economic implications and public perception; economic considerations such the impact of bioeconomy; political considerations surrounding policymaking; and, global impact will be considered collectively, rather, than singularly as recent scholarship has done. The example provided in the hypothetical application surrounding the significant variance in perspective of African American females and Caucasian males shows a small snapshot of the types of connections and data that can be gathered.

It has been suggested by scholars, and has been asserted in this approach, that ethics can play an informative role in priority setting. This includes priority setting not only for the assessment of emerging technologies but also priority setting for philosophical ethics as well as bioethics. For example, through continued cycles of this approach it may become evident that issues surrounding the definition of life are not as important as understanding how informed consents might be impacted by this new technology. Characterizing or defining “life” it is very important for our ontological understanding of humanity and nature, and this topic should not be dismissed. However,
it should be recognized that there may be more pressing issues than concluding this
debate. If policymakers, scientists, the public need ethical guidance pertaining to the
issues of surrounding autonomy and informed consent the bioethics community should
contribute to that discourse. As the overarching aims continue to guide development, the
nonlinear approach should continue to yield valid results in the form of action steps taken
and completed.

An additional benefit of this methodology is that it can inform the HTA and ethics
community as to what type of publications would be most beneficial. This could be viewed as a type of priority setting for academics. This adds to the relevancy of bioethics publications. This can be linked to the benefit of providing transferable data. The dissemination of data will vary from team to team, and from organization to organization. Regardless of how the information is shared, it should be understandable since it can be represented in multiple ways, including pictorial concept maps, scatterplots, statistics and so on. In the hypothetical example, the concept map clearly expresses crosscutting themes and ideas; it also represents the level of importance of each topic. This visual representation is very intellectually accessible.

5.4.2 Limitations of the nonlinear approach

There are limitations in and of the nonlinear approach. It is susceptible to some of
the same obstacles as other ethics assessment in HTA. The largest obstacle centers on
fiscal challenges, specifically budget projections and resource allocation. Since this
approach runs in multiple cycles, and it cannot be completely predicted how many cycles
this will involve, it is very difficult to anticipate the cost of implementation. After the
approach has been in place for a few fiscal cycles, these issues will likely work
themselves out. However, this approach will still require annual funds. From a purely
speculative position, this approach will likely cost more than other ethics methodologies
and tools.

Another limitation is that this approach may fall victim to the same treatment as
other ethics methodologies and tools; that is they are acknowledged, accepted, but not
acted upon. There is the risk that the study will produce valid data, but that data will not
be acted upon. If the nonlinear approach is to be effective the final phase, closing the
loop, must occur. The data collected, conclusions drawn, and action steps drafted must
be enacted. Anything less than this renders the entire process rather pointless.

Possibly the greatest limitation of this approach is the fact that it was produced
largely in a vacuum, albeit a very well-informed vacuum. This was not produced in
conjunction with an HTA process or with a research team. Therefore, anticipating any
pitfalls or challenges is very challenging when conducting a hypothetical application.
That does not discredit the observations made here, and merely points the fact that there
are going to be some challenges not addressed in this dissertation. Yet, it is important to
note that the primary aim of this dissertation was to demonstrate the methodological
soundness and validity of this approach. Dabbling in the practical application was
necessary to demonstrate some of these points. Concrete conclusions cannot be drawn at
this point about certain practical implementation elements of the nonlinear approach.
Even the hypothetical application did not shed much light on practical pitfalls and trouble
spots. These can only be identified as they come up in the course of implementation.
It may seem that the results can still be manipulated by some individual with a specific biases or agenda or interpret with a particular spin. No research is tamper-proof; however, the built in checks and balance system for sharing the concept mapping results with the participants can alleviate some of this concern, and lends additional validity to the process. The real advantage is the ability to take into consideration those problems for which scholars and society lack answers. For example, in the concept map there was a box for unknown and unanticipated risks. The fact that the existence of unknown and unanticipated risks can be taken into account is critical, especially as additional information and layers are added to the concept map. By keeping them on the radar, these issues will not be neglected or avoided. In addition, they will also not dominate the discourse, as the data will show what issues should be prioritized. Despite some of these practical limitations, the benefits assessed in the previous section outweigh them. The only potential non-starter for this approach is the budgetary allocation issue.

5.5 Conclusion

Chapter Five has provided an overview of existing and emerging issues in genetic health technologies. Specifically, ethical issues surrounding the use of whole genome sequencing as a diagnostic tool in medicine as well as biobanking were explored. There are many ways that genetic technology impacts daily life; these two were selected as case studies because even though they are in use there are still many ethical questions that need to be addressed. With regard to emerging technologies the emphasis was placed on the contributions of synthetic biology. A review of some emerging products of synthetic biology was described including genetically modified organisms, genetically modified
foods, applications in medicine, specifically protocells and gene therapy. An overview of some of the ethical questions and considerations that these technologies elicit was provided, specifically those surrounding protocells and gene therapy. This was done to set the stage for the hypothetical assessments of a very specific emerging technology that could utilize both protocells and within the next decade or two could have dramatic implications for gene therapy.

The emerging technology assessed by the nonlinear approach was the expansion of the “alphabet of life,” the expansion of the genomic code, moving from nucleotides from four base pairs to six. All phases of the nonlinear approach were demonstrated through the hypothetical application. Suggestions on practical implantation strategies were addressed and discussed.

The final portion of this chapter examined the projected benefits and limitations of the nonlinear approach within the context of the hypothetical example. The example yielded a number of hypothetical next actions, including additional research and inclusion of wider and more diverse perspectives.

The final chapter will provide concluding remarks and further reflection on the nonlinear approach and its application to emerging genetic health technologies.

ENDNOTES


6 Jegalian, Genetics: The Future of Medicine, 11.


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Chapter Six: Conclusion

6.1 Summary

This dissertation has presented the nonlinear approach as a way to conduct ethics assessments in HTA. The overarching aims of the approach are: (1) begin ethics assessments earlier, (2) provide a flexible framework whereby ethics experts and non-experts can coherently work together; (3) support, not stymie, scientific progress; (4) provide meaningful discourse and recommendations; and, (5) continually improve by assessing the ethics assessment mechanism itself.

The nonlinear approach includes five overarching phases: identification and inquiry, research and data analysis, concept mapping, evaluation, and closing the loop. These five phases are grounded in established methodologies from various disciplines including bioethics, sociology, and mathematics. The summary provided in this chapter reviews the foundational arguments and the model itself, and provides closing remarks on the future of genetic health technologies.

6.2 Foundations

Chapters One, Two and Three laid the foundation for this approach. The argument is that technology has normative value; it is value-laden. Technology is not value-neutral or value-free. This is proven to the extent that it can be, through inductive logic, by the following argument. Humans create and invent for a purpose; and our human activities have purpose and normative value and normative force.
Heidegger was correct in cautioning against humanity’s quick embrace of technology and of the technological mindset centering on efficiency. This potential, if gone undetected, could have profound effects on human ontology and dramatic implications for our ethical paradigms. Society and technology are not sole drivers of one or the other. Society is not completely determined by technology; and, similarly, technology is not wholly determined by society. They are two sides of the same coin; they shape each other.

The understanding of the relationship between society and technology is directly impacted by one's perspective on the value-laden nature or value-neutrality of technology. This dissertation argues that not only is technology value-laden, but also those technologies that impact human health carry special status.

Given the current state of health care in the United States and globally, cost-effectiveness has become a huge issue. Every reimbursement agency must pick and choose pharmaceuticals, medical devices, and other health technologies that they will support.

HTA is conducted differently by every agency and organization. There are evidence-based practices available in economic evaluations and comparative effectiveness. This is because safety and cost effectiveness are considered the most important aspects of a new technology that is going to be integrated into the health system. Yet, there is a general consensus on the importance of ethical and social considerations of new technologies. However, standards for assessing organizational impact—which includes social and ethical considerations—are few and far between.

HTA procedures and methodologies are more developed in Western Europe and North
America than other parts of the world. Multinational organizations, such as EUnetHTA, HTAi, and INAHTA, are making positive strides, and seek to assist those nations with underdeveloped HTA programs.

Some very foundational questions arise. What is the role and scope of HTA? What is the role and scope of ethics in HTA, if any? Most countries understand HTA is important; but there are significant questions concerning the scope and how to most effectively integrate HTA. Each country and organization performs HTA a little bit different, or very different in some cases; this makes the sharing or transferability of information incredibly difficult. In a sense, each agency is on its own at this point in time. Outside of the multinational organizations, which emphasize collaborative work, many HTA bodies are developing their own standards and processes. The HTA landscape is constantly in flux, which makes contributing to the field all the more difficult. Is HTA to simply be informative, or should the assessment cross into the appraisal category, with recommendations expected as a result. If recommendations are expected to be provided, as they are with appraisals, then the inclusion of ethics is inescapable. Yet if HTA processes remain completely neutral, taking a value-free or value-neutral position on technology, it can be difficult to make a case for ethics.

Despite HTA's origins dating back to the 1970s, little progress has been made with regard to standardization. Perhaps the lack of standards, agreed upon methodologies, and dissemination of information are reflective of the social and political contexts in which healthcare systems rest.

Several arguments were provided in order to present a philosophical justification for the integration of ethics in HTA. However, this is not just a philosophical argument.
When reviewing the evidence and analysis provided in Chapters One and Two, it is clear that all technologies have some special status as they must go through extensive testing, licensing procedures, and in many cases some form of HTA. It is clear that federal governments and global organizations have elevated emerging technologies to a special status because they have the ability to do great good or great harm. One of the overarching goals in medicine, the primary goal in fact, is to help people. Health technologies produce a social good, because they increase the quality of human life. Therefore, these technologies must be regulated and checked for safety in order to stay true to this goal. Nor should major corporations profit from promising to heal people but rather selling ineffective drugs. The argument simply stated is that the promotion of health, the absence of pain, and improved health are considered a moral good. Technology is a means to that intended end. Therefore, when assessing risks and benefits, and engaging in comparatives effectiveness evaluations and economic analysis, the underlying presupposition is that this is being done to achieve a moral good. These normative implications provide justification for including ethics in HTA.

Evidence was also presented that there is a general consensus among the HTA community of ethics relevance and integral position in the process. Many concerns that arise under the categories of benefit, risk, and cost effectiveness are inextricably linked to moral concerns. Health is valued by all. Emerging health technologies directly impact health; so a variety of perspectives must be taken into account in technology assessment since health is relevant to almost everyone. Furthermore, especially in health care, when new technologies are introduced they create new care or therapeutic options that will impact those already in existence.
Emerging genetic health technologies pose an even greater challenge. This is due partially to the increased level of uncertainties and unanticipated outcomes of the adaptation of genetic technologies. In addition, the ethical questions posed by emerging and genetic health technologies call one to question and reevaluate their existing ethical paradigms—for example, the way one understands autonomy, and the way one understands the very nature of humanity.

6.3 The nonlinear approach

The nonlinear approach was developed specifically for emerging genetic health technologies. Emerging genetic technologies are of a unique variety, as the very nature of the technology calls into question some of society’s most foundational normative principles. As such, at this point in time, a practical methodology is needed to address these specifically. This is largely due to the level of uncertainty in risk prediction surrounding unanticipated and unknown risks. This is tempered with the knowledge that emerging genetic technologies, as well as the products of synthetic biology, can yield a great public good, such as increasing the quality of life for humans, improving the environment, providing alternate fuel sources, and so on.

The aim of the approach is to be flexible, accessible, and inclusive. It is flexible based on the context of technology. It can be adapted to meet the needs and scope of the project. It is an accessible methodology in that it is easily understood. However, experts are needed to undertake the data analysis and project design aspects. This approach can be used by scientists, developers, and any person(s) involved in the development of a given technology.
This assessment tool would be employed while the technology is still in the research and design phase. This means that it is employed long before formal HTA processes address the technology. It can be engaged from the very start of a new project. This is a recurring approach. As the project reaches certain benchmarks for major breakthroughs, the process will continually be re-engaged. The ethics assessment will continue to grow with the emerging technology.

In phase one, researchers identify a technology by engaging a specific research team, firm or study. The first cycle of the approach begins with a research question. Depending upon the development of the technology, this research question may be more or less developed. The aim is to select an emerging technology, not a technology that is ready to go to market or being evaluated for licensure. While the basic methodology would work, the cyclical nature of the nonlinear approach requires more time for maximum effectiveness.

Phase two consists of performing initial research, including a literature review and analysis of that research. This can be done in one of three ways. The research can be conducted internally, utilizing evidence-based practice research methods specifically for HTA. Those methods were published by Droste et al, and reviewed in both Chapters Three and Four. This initial research can be outsourced to a research firm, university, or other appropriate organization. The third option is to conduct research internally based on disciplinary research methods. This was the method utilized in the hypothetical application in this dissertation. In any case, the research team must familiarize themselves with the material and conduct an initial analysis of existing publications. This
will indicate whether or not they need to reassess the research question proposed in phase one.

Phase three is the most labor-intensive phase in this approach. A concept map should be developed by soliciting the perspectives and opinions of experts, stakeholders, and other relevant parties. This is labor-intensive because it requires organization of participants, the execution of a fairly robust methodological process, and concept mapping. Concept mapping also includes collecting, sorting, and mapping the data collected from the participants. The depth and breadth of information that can be collected, integrated, and visually displayed in the concept map is robust; furthermore, the validity and outcomes of this methodology warrants its use. Visual representation of statistics can lead to the identification of crosscutting themes and perspectives, social and ethical problems that may arise with adopting the new technology, and general attitudes of the public. The concept mapping methodology utilized in this dissertation was that forwarded by Kane and Trochim, both of whom have extensive publications and experience in this area. There are six general steps in concept mapping, they include (1) preparing for concept mapping; (2) generating ideas; (3) structuring statements; (4) concept mapping analysis; (5) interpreting the maps; and, (6) utilization. The hypothetical application, surrounding the expanded genome of E. coli bacterium, presented this approach. Throughout this process, commentary was provided about flexibility, potential pitfalls, as well as recommendations on evidence-based methods and best practices. A hypothetical concept map was developed.

Phase four evaluates all the information and data collected thus far in the process. This includes taking into account the initial research question, literature review,
participant responses and interactions, and concept map. The primary activity is to reflect upon the outcomes set in phase two, as well as the results of the concept map.

Phase five requires the researchers to close the loop. This closure happens in two ways. First, based on the evaluation in phase four, action should be taken. The action can simply be pursuing further research or it could be as extreme as engaging in some sort of public education initiative. The outcomes of the concept map will identify the gaps in understanding, as well as illuminate additional connections in social and ethical understanding and attitudes towards emerging technologies. The second aspect of closing the loop is a reflective exercise. This reflection occurs on two levels. The first reflection occurs on the process as a whole, identifying what worked, what did not work, and what can be improved. This reflection is noted so refinements can be made and the second cycle undertaken. The second level of reflection that occurs is when to reengage the approach. It is recommended that with any shift and technological development or major breakthrough that the approach be reengaged to adjust to these new findings.

The prospective benefits include increased time, sound methodologies, increased inter- and multi-disciplinary collaboration, the inclusion of wider ethical and social issues including socioeconomic issues, improved transferability of information, and finally it is a step closer toward creating consistency in ethics assessment while not stymieing scientific progress. This approach allows for the involvement of more individuals; and inclusion increases transparency. This approach is cyclical in nature, meaning that it is not a one and done process. It is ongoing and happens concurrently with technological development. That allows for increased checks and balances, accuracy and validity. The approach is accessible as it is based on best practices from a range of disciplines that
offer structured and organized methods to conduct intellectual inquiry. This approach is accessible to scientists and non-ethics experts due to its interdisciplinary methodology. However, ethics expertise is still needed in the research and evaluation portions of the approach. These benefits were demonstrated in a hypothetical thought experiment. The limitations include the status quo of ethics assessment, the sum of the parts problem, the way in which this approach was generated, and the required need of ethics expertise. The final issue to address is that ethics assessment does not necessarily solve ethics issues, problems, or controversies. Overall, it was argued that the benefits outweigh the limitations.

6.4 Ethics

The nonlinear approach embodies ethics at two levels. The first is nonlinear approach’s consistency with philosophical foundations calling for the inclusion of ethics in HTA, and the second is the ethics assessment conducted within the nonlinear approach.

The consistency of the nonlinear approach with strong philosophical traditions is of great benefit. Based on the arguments from technology as value-laden, the relationship between society and technology, and the role health technologies there is a strong argument for a moral obligation to conduct ethics assessment in emerging technologies. The nonlinear approach builds on this philosophical foundation and is consistent with it, thereby giving it additional soundness.

The second level of ethics engagement is the ethical considerations within the nonlinear approach. Through concept mapping a wide range of diverse perspectives are
taken into account through participant involvement. This leads to enhanced issue identification and making the connections between various ideas and concerns, which has the potential to lead to heightened discourse surrounding these ethical issues. Ethical approaches that included stakeholder participation early in the research and design phases of research, like the nonlinear approach, can assist in building transparency, public education, and identifying key action steps necessary for either integrating or not integrating a particular emerging technology. This nonlinear approach allows ethics and emerging genetic health technologies to move from the theoretical arguments of philosophy and sociology into the practical world. It does not matter how strong a theoretical argument is—if it remains difficult to hear, people will ignore it. This is evident from the lack of ethics integration in HTA. However, if tangible and valid evidence is produced, it cannot be ignored. The nonlinear approach is grounded in valid methodological practices, and has a strong theoretical basis and justification as well.

The nonlinear approach will not solve ethical problems, although it has the potential to address some ethical problems. The final phase of the nonlinear approach calls for the drafting of actions that can be taken based on the data and information gathered. These action steps can include identifying areas for further research, social change initiatives (e.g. awareness campaigns, education, advocacy initiatives, and so on), or priority setting for research in bioethics (e.g. research and discourse needed to understand ethical dimensions of emerging trend in society or technology). The action steps identified in phase five can dramatically impact multiple areas, as suggested above.

A long-term goal for all ethics assessment should be to support objective assessment of science and technological development, and make informed ethical and
social decisions grounded evidence-based practice. In a perfect world the goal would be to move away from political agendas. It seems as though whichever party has controlled the White House determines what science is ethically acceptable and ethically unacceptable. In conclusion, one of the long-term goals of ethics assessment in emerging health technologies should be to elevate ethical assessment and discourse out of political agendas. Ethics assessment should follow sound methodologies to arrive at well-supported justifications and evidence based guidelines for both scientific and technological research and progress.

6.5 Emerging genetic health technologies

The specific technology assessed using the nonlinear approach was a semi-synthetic organism that had an expanded genome. All life on this planet as we know it consists of the genetic base pairs A (adenine), T (thymine), G (guanine) and C (cytosine). The research team led by Romesberg added two additional nucleotides to the E. coli bacterium. These nucleotides were man-made and chemically created; they were given the designation X and Y and are called unnatural base pairs for short (UBPs). Other researchers have pointed out that this is a significant breakthrough. However, there is still much work to be done. Looking ahead, this emerging technology has the potential to impact molecular, pharmaceuticals, medicine, biotechnology, and biochemistry. If these organisms can stabilize with these new man-made base pairs, this could also dramatically increase biodiversity.

There are a plethora of other emerging genetic technologies that will be applied to human health. These range from genetically modified organisms (GMOs) geared toward
improving the environment or specific ecosystems, to those applied to medicine as gene therapy treatments or new cancer interventions. One of the goals of ethics assessment is to address those social concerns and attitudes that typically arise from emerging technologies. The goal of ethics is to discern not only whether the emerging technology poses minimal physical risk, but also how it impacts social norms and values. The recent debacle in the Florida Keys is a prime example of how all of this went awry. In recent years in the Florida Keys there has been an uptick in two mosquito borne diseases, dengue and chikungunya, both of which are quite painful. Researchers at Oxitec have developed a mosquito with an altered genetic code. As a result, it causes the offspring of any aegypti mosquito that mates with the GM mosquito to die.\textsuperscript{1} Oxitec’s application to the FDA is still under review. However, attitudes in Key West City are hostile toward the release of genetically modified mosquitos.

The trial is set to run near Key Haven, a location with over 400 homes within close vicinity of the release. It should be noted that more than 70 million mosquitoes have been released as a result of trials in other counties. The results have been very positive; some reports note 60-70\% reduction in the aegypti mosquito population. Brazil is currently planning a commercial release of the modified mosquito.

The benefits include the use of fewer pesticides, cost-savings (as ten per cent of the pesticide budget is going specifically toward aegypti mosquitos, which comprises one per cent of the mosquito population in the Keys), and human health and safety benefits. Yet, these GMOs are met with hostility, fear and, more specifically, a petition signed by more than 150,000 individual opposing the release.\textsuperscript{2}
Emerging genetic health technologies, such as those similar to GM mosquito mentioned above or those applied directly in a hospital or care setting, are geared toward improving human life. The goal to help a people, this is the goal of medicine, and it has moral implications. Thus, close attention must be paid to these technologies, and they must be assessed.

6.6 Closing remarks

The HTA landscape is scattershot and constantly in flux. Ethics methodologies and integration into HTA processes are even more uneven. This is not the fault of any particular group or individual; there are a lot of excellent efforts underway to support this integration. However, the current HTA landscape is not conducive for this. It is immensely difficult to create a clear picture in one's mind of what is currently happening in HTA, even more so in ethics and HTA. This challenge is compounded when the aim is to make recommendations, as it is hard to make recommendations about a moving target. This dissertation has attempted to address this chaos by providing an approach that can be adapted both outside and inside of HTA processes. It also benefits any size organization that wishes to employ this approach; whether it be a small research team or multinational organization this methodology can be executed at any level due to its flexibility.

ENDNOTES


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