Making the Breast Cancer Gene:
An Archaeology of the Translational Clinic

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Candace Massey

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Name:	**Candace Massey**
Degree:	**Master of Arts**
Title:	***Making the Breast Cancer Gene: An Archaeology of the Translational Clinic***
Examining Committee:	**Chair:** Dara Culhane Professor

Cindy Patton
Senior Supervisor
Professor

Michael Hathaway
Supervisor
Associate Professor

Coleman Nye
External Examiner
Associate Professor
Department of Gender, Sexuality,
and Women's Studies

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Abstract

Between 1994 and 1995, the discovery of two gene mutations—BRCA1 and BRCA2, combined with a genetic test, led to the creation of a clinical practice centered on diagnosing and managing genetic risk for breast cancer. The discovery of the BRCA genes is framed as a model of how genetic knowledge and technologies can be swiftly "translated" into improved health outcomes for patients, despite the fact that the role of genes in common diseases has come under scrutiny following the completion of the Human Genome Project in 2003. Examining what Michel Foucault terms as the "conditions of emergence" for a genetic theory of breast cancer, this project employs close textual analysis of newspapers, press releases, and scientific research articles to critically examine the link between the discovery of the BRCA genes and translational research. Tracing the shifting relationship between genes and cancer, this project explores the impact of public criticisms on post-genomic research, describing emergent research norms, values, and epistemic commitments for translational actors, including scientists and patient advocacy groups.

Keywords: BRCA; Post-Genomics; Translational Research; History of Science, Technology, and Medicine; Thought Style; Molecularization

Dedication

For my mother—

In the eclipse of your life, I continue to learn from you.

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Table of Contents

Chapter 1. Introduction

1.1. Assembling Hereditary Breast and Ovarian Cancer

In 1994, US researchers linked the discovery of an inherited susceptibility gene, BRCA1, with a documented pattern of familial breast cancer.[1] Four months before a research team headed by geneticists Dr. Yoshi Miki and Dr. Mark Skolnick cloned and patented BRCA1, competing scientists in the field remarked that the discovery was long overdue, and that the gene would be sure to surface "any day, any week, any month now."[2] Building on seventeen years of research in her laboratory at UC Berkeley, geneticist Dr. Mary-Claire King led an earlier study that provided researchers with a map of the chromosomal "neighborhood" where the gene might live, inspiring a two-year long international competition to pinpoint the "block," and eventually, "the precise street address" of the gene.[3] In 1995, the territory of the BRCA gene expanded to include the

[1] Yoshio Miki, Jeff Swensen, Donna Shattuck-Eidens, P. Andrew Futreal, Keith Harshman, Sean Tavtigian, Qingyun Liu, Charles Cochran, L. Michelle Bennett, Wei Ding, Russell Bell, Judith Rosenthal, Charles Hussey, Thanh Tran, Melody McClure, Cheryl Frye, Tom Hattier, Robert Phelps, Astrid Haugen-Strano, Harold Katcher, Kazuko Yakumo, Zahra Gholami, Daniel Shaffer, Steven Stone, Steven Bayer, Christian Wray, Robert Bogden, Priya Dayananth, John Ward, Patricia Tonin, Steven Narod, Pam K. Bristow, Frank H. Norris, Leah Helvering, Paul Morrison, Paul Rosteck, Mei Lai, J. Carl Barrett, Cathryn Lewis, Susan Neuhausen, Lisa Cannon-Albright, David Goldgar, Roger Wiseman, Alexander Kamb and Mark H. Skolnick. "A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1." *Science* 266, 5182 (1994): 66-71.

[2] Natalie Angier. "Vexing Pursuit of Breast Cancer Gene" *New York Times*, July 12th, 1994.

[3] "Vexing Pursuit of Breast Cancer Gene," New York Times, 1994; J. Hall, M. Lee, B. Newman, J. Morrow, L. Anderson, B. Huey, and M. King. "Linkage of Early-onset Familial Breast Cancer to Chromosome 17q21." *Science* 250, 4988 (1990): 1684-689.

discovery of a second gene mutation, BRCA2, associated with increased risk of ovarian cancer in families also affected by breast cancer.[4]

The discovery of the BRCA genes significantly altered the diagnosis, management, and treatment of breast and ovarian cancer in North America and the UK, and from which they continue to expand their global reach.[5] The identification of BRCA1 and 2, and Myriad Genetics' development of a genetic test for the genes, resulted in a new medical classification termed "hereditary breast and ovarian cancer syndrome." Hereditary breast and ovarian cancer syndrome is diagnosed based on the presence of one or both BRCA gene mutations. The BRCA genes confer a 45 to 65 percent lifetime risk of breast cancer, and between a 10 and 39 percent lifetime risk for ovarian cancer depending on if a person has BRCA1 or 2.[6]

Forging a new relationship between genetics and clinical medicine, research into hereditary conditions during the 1990s invited new collaborations between medical geneticists and oncologists working on the collective problem of identifying, managing,

[4] R. Wooster, Bignell G., Lancaster J., Swift S., Seal S., Mangion J., Collins N, Gregory S, Gumbs C., Micklem G. "Identification of the breast cancer susceptibility gene BRCA2." *Nature* 378, 6559 (1995): 789-92.

[5] On the development of the clinical infrastructure of BRCA testing, see: Sahra Gibbon. *Breast Cancer Genes and the Gendering of Knowledge: Science and Citizenship in the Cultural Context of the 'New Genetics.'* (London: Palgrave Macmillan, 1997).

[6] Lifetime risk refers to the statistical likelihood of an individual being affected by cancer in an average lifespan; the average is modified based on risk factors such as pre-existing health conditions, diet, stress levels, family history, and many other epidemiological, environmental, and genome-specific factors. Virginia Moyer, on behalf of the U.S. Preventive Services Task Force. "Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement." *Annals of Internal Medicine* 160 (2014): 271-281.

and treating patients harboring "inherited susceptibility genes."[7] Employing genetic testing to diagnose the condition based on the presence of gene mutations, this style of clinical practice also included preventative screening, risk management protocols, and genetic counselling services used to communicate genetic knowledge about conditions such as hereditary breast and ovarian cancer to an emergent class of at-risk patients.[8] Genetic counselling was developed to help BRCA carriers manage the psycho-social effects of genetic risk, supporting a new mode of patienthood in which preventing and managing the risk of cancer becomes the defining characteristic of the condition. The new diagnostic category inspired the development of patient activist groups such as Facing Our Risk of Cancer (FORCE), founded in 1999 with the purpose of advocating for improved access to counselling services and other resources for women genetically at risk for breast and ovarian cancer, and their families.

Since their highly-sensationalized discovery, the BRCA genes continue to attract the attention of scientists, policy-makers, and public actors. Popularized as the "breast cancer gene," public reception of BRCA1 and 2 has varied from cautionary optimism to a state of hyper-interest, met with increasing demands made on clinicians for access to genetic testing services.[9] Fueled by a surge in direct-to-consumer genetic testing offered through private biotechnology companies such as 23 and ME, and with a high-status celebrity such as Angelina Jolie publicly "coming out" as a BRCA carrier in 2013, stories about genetic testing continue to draw in patients who do not have a hereditary

[7] Vololona Rabeharisoa and Pascale Bourret. "Staging and Weighting Evidence in Biomedicine: Comparing Clinical Practices in Cancer Genetics and Psychiatric Genetics." *Social Studies of Science* 39, 5 (2009): 701.

[8] Rayna Rapp. "Chromosomes and Communication: The Discourse of Genetic Counseling." *Medical Anthropology Quarterly* 2, 2 (1988): 143-157.

[9] D. Wonderling, P. Hopwood, A. Cull, F. Douglas, M. Watson, J. Burn, & K. McPherson. "A Descriptive Study of UK Cancer Genetics Services: An Emerging Clinical Response to the New Genetics." *British Journal of Cancer* 85, 2 (2001):166.

predisposition to breast and ovarian cancer, and do not immediately benefit from testing. However, these stories about the impact of genetic testing on public understandings of disease are only one "translation" about the value of the BRCA genes. Beyond the domain of hereditary cancer research, social science researchers Pascale Bourret, Peter Keating, and Alberto Cambrosio examined how the BRCA genes are now being used to investigate the molecular properties of sporadic breast cancers.[10] While the BRCA assemblage continues to expand, the genes themselves are taking on different epistemic shapes as they enter into new scientific networks on a transnational scale.[11]

The discovery of the BRCA genes is often cited as a model example of how genetic knowledge and technologies can be "translated" into improved diagnostic procedures and tools in the clinic, acting as an origin story that clinicians, scientists, and patients return to when reasoning for the potential of genetic medicine.[12] But the theory of a gene for breast cancer is more than a hypothesis that was proven correct, a natural, determined outcome of scientific knowledge progressing towards greater "truth" about the biological nature of cancer; scientific understandings of genes have changed since the discovery of the "breast

[10] Pascale Bourret; Peter Keating, and Alberto Cambrosio. "From BRCA to BRCAness: Tales of Translational Research," in *Breast Cancer Gene Research and Medical Practices: Transnational Perspectives in the Time of BRCA.* Eds. Gibbon, Sahra; Joseph, Galen; Mozersky, Jessica; zur Nieden, Andrea; Palfner, Sonja. (New York: Routledge, 2014). 175-193.

[11] For a recent collection of work on the trajectory of BRCA research in a transnational perspective, see *Breast Cancer Gene Research and Medical Practices: Transnational Perspectives in the Time of BRCA*, Eds. Gibbon, S., Joseph, G., Mozersky, J., Zur Nieden, A., and Palfner, S. (New York: Routledge, 2014).

[12] M. J. Khoury, M. Gwinn, P. W. Yoon, N. Dowling, C. A. Moore, and L. Bradley, L. "The Continuum of Translation Research in Genomic Medicine: How Can We Accelerate the Appropriate Integration of Human Genome Discoveries into Health Care and Disease Prevention?" *Genetics in Medicine* 9, 10 (2007): 665-674; S. D. Schully, C. B. Benedicto, E. M. Gillanders, S. S. Wang, M. J. Khoury. "Translational Research in Cancer Genetics: The Road Less Traveled." *Public Health Genomics* 14 (2011): 1-8; Center for Disease Control and Prevention. "Genomics Translation." Accessed online at http://www.cdc.gov/genomics/translation.

cancer gene" and the many other "gene for" entities that populated the Human Genome Project, and from which research in genomics has been impacted by public reception of these early gene discoveries that included BRCA1 and 2. Drawing on theories and concepts in medical sociology and anthropology, history and philosophy of science, and science and technology studies, the first half of this project examines what Michel Foucault terms as the "conditions of emergence" for the theory of the gene for breast cancer, digging into two archaeological strata: The New Genetics and Post-Genomics.[13] The remainder of the project investigates how public reception of gene discoveries has co-aligned with changing epistemic priorities in genetic cancer research at the close of the Human Genome Project in 2003.

1.1.1. Strata X: The New Genetics

1.1.1.2. Sequencing the Genome

The international competition to discover the breast cancer gene was an early initiative undertaken in the so-called "New Genetics," a style of genetic research focused on the identification and mapping of genes that emerged in the 1970s amongst researchers

[13] In the *Archaeology of Knowledge* (2010[1969]), the historian Michel Foucault examines the discursive conditions that enable certain knowledge claims to be made, arguing that "...one cannot speak of anything at any time; it is not easy to say something new; it is not enough for us to open our eyes, to pay attention, or to be aware, for new objects suddenly to light up and emerge out of the ground" (45). Further, Foucault reminds us that is not a 'negative' or restrictive act of power that prevents discovery, as "…the object does not await in limbo the order that will free it and enable it to become embodied in a visible and prolix objectivity; it does not pre-exist itself, held back by some obstacle at the first edges of light. It exists under the positive conditions of a complex group of relations" (2010[1969]): 45. Examining the "conditions of emergence" for a scientific discovery is the act of uncovering the multiple layers—both conceptual, material, political, and historical—that bound and shape the object in a given sociotechnical practice. Michel Foucault. *The Archaeology of Knowledge*. (New York: Vintage Books, 2010[1969]).

in North America and the UK.[14] The theory of a cancer-causing gene was crystallized with the publication of the "oncogene hypothesis" by Robert Huebner and George Todoro in 1969.[15] Scientific interest in genes co-existed with the movement of mass amounts of state funding, resources, and experts into cancer research following US President Richard Nixon's declaration of a "War on Cancer" and the signing of the National Cancer Act in 1971.[16] Research in the New Genetics was driven by the assumption that there is a gene for every human trait, leading to the famous discovery of cancer-causing genes known as "oncogenes" by microbiologists Michael Bishop, Harold Varmus, Dominique Stehelin, and Peter Vogt in 1976; single genes associated with rare medical conditions such as Huntington's disease and retinoblastoma, and the more contentious finding of a "gay gene."[17] By emphasizing the causal role of the gene, the "one gene, one trait" logic of the New Genetics placed epistemic primacy on genetic explanations in medicine and society.

In the New Genetics, the quest to discover genes included large-scale research initiatives such as the US-based Human Genome Project (1990-2003), an international collaboration between researchers that lead to the enthusiastic discovery of over 22,200 protein-coding genes that make up the human genome. In the mid-1980s, the development

[14] Peter Keating and Alberto Cambrosio. "The New Genetics and Cancer: The Contributions of Clinical Medicine in the Era of Biomedicine." *Journal of the History of Medicine and Allied Sciences* 56, 4 (2001): 321-352.

[15] Robert J. Huebner and George J. Todaro. "Oncogenes of RNA tumor viruses as determinants of cancer." *Proceedings of the National Academy of Sciences* 64, 3 (1969): 1087-1094.

[16] National Cancer Institute. "National Cancer Act of 1971". Accessed April 12th, 2016. https://www.cancer.gov/about- nci/legislative/history/national-cancer-act-1971.

[17] Dominique Stehelin; Harold E. Varmus; J. Michael Bishop, and Peter K. Vogt. "DNA related to the transforming gene (s) of avian sarcoma viruses is present in normal avian DNA." *Nature* 260 (1976): 170-173.; Marcy E Macdonald; Christine M. Ambrose; Mabel P. Duyao; Richard H. Myers; Carol Lin; Lakshmi Srinidhi, and Glenn Barnes. "A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes." *Cell* 72, 6 (1993): 971-983; Dean H. Hamer; Stella Hu; Victoria L. Magnuson; Nan Hu, and Angela ML Pattatucci. "A Linkage between DNA markers on the X Chromosome and Male Sexual Orientation." *Science* 261, 5119 (1993): 321-327.

of early sequencing technologies in a small number of academic research centers brought forth the imagined possibility of mapping out the molecular infrastructure of the entire human genome. In 1988, this possibility was actualized when the US Congress offered funding to the National Institute of Heath to put together a large-scale genetic sequencing project that would be headed by James Watson, the "father of modern molecular biology," accredited with discovering the structure of DNA in the 1950s. Endorsed by the National Institute of Health and a newly formed Human Genome Research Institute, the "race" to sequence the genome was met with great excitement within the scientific community and in US popular media. The significance of the project was put on par with scientific breakthroughs such as the landing on the moon, and with the project working towards revealing the "secrets of life" that were lodged in the base pairs of DNA.[18]

Sensationalized in the US media as a major revolution in scientific thinking, the release of the First Draft from the Human Genome Project received a significant amount of attention from researchers and the public alike. Examining the media hype surrounding findings reported by the Human Genome Project, the sociologist Andrew Smart examined popular newspapers circulating in the US and the UK during the year 2000.[19] In the UK, many of these newspaper articles related the sequencing of the genome to surmountable advancements in medicine that included improved cures and treatments for disease, an increased life expectancy, and with some even arguing that the project represented a step towards immortality.[20] It was not only the media raving about what was termed as the completion of the "book of life," but also notable political leaders that included then US

[18] National Institute of Health. Understanding our Genetic Inheritance. The U.S. Human Genome Project: The First Five Years FY (1991-1995). NIH Publication No. 90-1590 (1990): 1-85.

[19] Andrew Smart. "Reporting the Dawn of the Post-Genomic Era: Who Wants to Live Forever?" *Sociology of Health & Illness* 25 1 (2003): 24-49.

[20] Ibid., 25, 30-33.

president Bill Clinton who released a public statement claiming that the First Draft was "…the most important, most wondrous map ever produced by humankind," comparing it to the mapping of the Americas by Lewis and Clark nearly two centuries before.[21] Using a Highlighting the therapeutic potential of the genomic feat, President Bill Clinton went on to explain:

> Today we are learning the language in which God created life. We are gaining ever more awe for the complexity, the beauty, the wonder of God's most divine and sacred gift. With this profound new knowledge, humankind is on the verge of gaining immense new power to heal.[22]

In the US President's speech, the sequencing of the human genome is painted in the language of the miraculous, taking on a transcendental quality as "…God's most divine and sacred gift." The value of genetic knowledge exceeds biomedical definitions of treating disease, representing an "immense new power to heal." This sentiment of mystical healing, fused with biomedical understandings of disease treatment, underwrites genetic discoveries in the New Genetics, and imbues in the gene an epistemic and aesthetic status.

1.1.2.3. Criticisms of Gene-Centered Research

While the completion of the Human Genome Project was widely celebrated, it was also met with sharp criticisms by news media outlets. What initially appeared to be a vast genomic territory turned out to be a much smaller than anticipated number of protein-coding genes, fueling critiques that sequencing efforts would need to be followed by research into the organization and the function of the genome before any real advances in

[21] Nicholas Wade. "Scientists Complete Rough Draft of Human Genome." *New York Times*, June 26th, 2000.

[22] Ibid., para. 7.

treating common diseases could be made.[23] For example, a *New York Times* article released on the ten-year anniversary of the sequencing of the human genome in 2010, entitled "A Decade Later, Genetic Maps Yields Few New Cures," declared that the project had not revolutionized medical therapeutics as promised:

> The last decade has brought a flood of discoveries of disease-causing mutations in the human genome. But with most diseases, the findings have explained only a small part of the risk of getting the disease [cancer]. And many of the genetic variants linked to diseases, some scientists have begun to fear, could be statistical illusions.[24]

The value of genetic mutations, and their association with common diseases, is brought into question, with the article painting probabilistic knowledge about genetic risk as "statistical illusions." The Human Genome Project had left behind a legacy of genetic tests that can predict, but not treat disease, a flock of cloned sheep, and large bioinformation databases containing not only the sensitive medical information of patients, but also human tissues eagerly volunteered by patients who had given up body parts for what they believed was the good of the cause. The promise of genetic medicine seemed, for a moment, to have fallen quite flat. Returning to the original research plan for the Human Genome Project provides historical insight into the relationship between scientific research and public expectations.

In 1990, the National Institute of Health released a formal proposal entitled "Understanding Our Genetic Inheritance: The Human Genome Project, The First Five Years, FY 1991-1995." While the proposal was revised three times over the course of the

[23] Sequencing the genome, scientists had originally anticipated to discover upwards of 100,000 genes. Finding 20 percent of this humbled genome researchers, and formed one of many building realizations of the limitations of genes and gene-centered research.

[24] Nicholas Wade. "A Decade Later, Genetic Map Yields Few New Cures," *New York Times*, June 12, 2010.

1990s, the stated objective, or, *premise* of the original research plan is to generate scientific knowledge about genes, and to improve existing sequencing technologies: "the information generated by the human genome project is expected to be the source book for biomedical science in the 21st century."[25] The primary expectation of the Project is to produce knowledge in the form of a "sourcebook," or, a fundamental guide, that the will be valuable to present and future generations of basic science researchers.

However, throughout the research proposal, there are several statements that allude to potential, future applications of this knowledge in medicine and society. The futuristic, *forward-looking statements*[26] of the research proposal signal toward the development of increasingly cost-effective sequencing technologies that may be translated to institutions that include, but extend beyond medicine, such as in the agricultural sector and the environmental sciences.[27] The translation of scientific findings from the Project into clinical practice is given the estimated time frame of within 10-15 years, a point where this knowledge may not only "…produce information that will lead to the detection and diagnosis of genetic disease, [but] the long-range goal will go beyond this to providing improved treatment, prevention, and ultimately cure."[28] The proposal describes what social consequences may arise in the "interim phase" where knowledge about genetics is not yet met with improved treatments:

> The interim phase, before adequate treatment is available, is the one in which the most deleterious consequences can occur, such as discrimination against gene

[25] National Institute of Health, "Understanding Our Genetic Inheritance," vii.

[26] Anthropologist Mike Fortun coins the term "forward-looking statements" to describe how genomics research is fueled by hype, hope, and promises, a promissory vision that sometimes comes before any real results or findings, and is used to pre-emptively ascribe value to the work. Mike Fortun. "EverythingXNothing," in *Promising Genomics: Iceland and DeCODE Genetics in a World of Speculation*. (Berkeley: University of California Press, 2008).

[27] National Institute of Health, "Understanding Our Genetic Inheritance," 34.

[28] Ibid., 65.

> carriers, loss of employment or insurance, stigmatization, untoward psychological reactions and attention. Once effective treatment is available for an illness, most of these problems disappear. As the fruits of the Human Genome Initiative are realized, there will be an increased need for improved professional and public education to take advantage of the information gained.[29]

The social effects of producing knowledge about genetics that is not met with adjacent re-organizations of existing industries—in particular, that of the health sector, are described as "deleterious consequences." The most serious of these issues includes discrimination against gene carriers whose status, when disclosed, could warrant "untoward psychological reactions and attention" in their private and public lives. While the project proposal takes account of the messiness of disseminating knowledge and technologies that have yet to be regulated and routinized, and foresees the disruptive "lag" that will occur between their initial introduction and later acceptance and naturalization in public awareness, it nevertheless fails to anticipate how impactful this situation will be on future genomic research. The authors of the First Draft assume that once the public begins cashing in on new, genetic treatments brought about by the Project, "these problems disappear," and it will then only be a matter of teaching professional and public actors "…to take advantage of the information gained."

There are few statements made in the First Draft that link the goals of the Human Genome Project—generating genetic information and technologies—to the *immediate* therapeutic potential of its developments. How did this perceived gap between "what was actually done" in the Project and "what should have been done" come about? It is important to recognize how two different sets of expectations emerged for the two different types of statements made in the research project proposal: the *premise* and the *forward-looking statements*. The major premise of the Project is that research undertaken will provide

[29] Ibid., 65-66.

scientists with a foundation of knowledge that will lead to future innovations in the field; however, the forward-looking statements signal to the translation of this knowledge to improved treatments for patients at a later stage of development.

The premise of the research proposal appears in statements made by scientific researchers involved in the Human Genome Project. Dr. Harold Varmus, director of the National Institute of Health, and discoverer of the first cancer-causing "oncogene," defends the Project because "…genomics is a way to do science, not medicine,"[30] and in this regard, the Human Genome Project has been a successful basic science research endeavour. Another researcher defends the Human Genome Project, arguing that it has successfully carved out a paradigm for future work: "Having a common scaffold on which one can put all the information has dramatically accelerated progress."[31] In the opinion of scientists involved in the Project, the authors of the First Draft were faithful to their major research goal: producing basic science knowledge about the human genome. However, the document of the First Draft must be taken less as an objective record of scientific work and more as a polysemic text, which, disseminated amongst heterogeneous audiences across the US and abroad, is open to multiple, and at times, conflicting readings.

The announcement of the Project, and subsequent new reporting of its major findings, have been evaluated according to a set of expectations held by the US public. The sequencing of the genome, painted in the language of the miraculous in the speeches of politicians and in news media reports, has created a situation where the expectations of scientific work held by researchers and those held by public actors intersect, but do not always closely align. Critiques of the progress in gene-centered initiatives are more than just a common misunderstanding on the part of non-expert, lay actors regarding the goals

[30] "A Decade Later, Genetic Map Yields Few New Cures," *New York Times*, 2010, para. 9.
[31] Ibid., para. 24.

of the Human Genome Project. Examining the complex interactions between science and society, Ludwik Fleck explains how even the most qualified members of the scientific community are still dependent on public opinion, itself a form of "exoteric" knowledge that imprints on the "esoteric" work of scientists, that is, on the very facts, theories, and empirical findings that are generated in the laboratory.[32] Rather than dismissing these concerns over the perceived gap between basic scientific research in genetics and its clinical application, it is more productive to examine how these criticisms have impacted genomic research following the completion of the Project.

1.1.2. Strata Y: Re-Imagining the Genome

1.1.2.1. Post-Genomics

The race to sequence the genome, and adjacent scientific efforts to link genes with a spectrum of human traits, transpired under a particular set of understandings of what genes are, and what they could be used for. With the turn to post-genomics at the end of the twentieth century, scientists have begun researching the complexities of gene-to-gene and gene-environment interactions, and the molecular and cellular systems that genes operate within. Social scientists have debated what exactly the "post" in post-genomics refers to, describing a conceptual shift from research into 'genes' to an understanding of the whole 'genome,' met with a renewed interest in the complexity and multiplicity of biological systems.[33]

[32] Fleck, *Genesis*, 105.

[33] For recent work on post-genomics, see: John Dupre. "The Polygenomic Organism" in *Post-Genomics: Perspectives on Biology after the Genome*. Eds. Richardson, Sarah S., and Stevens, Hallam. (Durham: Duke University Press, 2015). 56-72.

While the discovery of genes formed the backbone of the Human Genome Project, post-genomic research efforts emphasize that the discovery of genes needs to be wedded to research into their biological functions. This includes research into the role of non-coding RNA, which had been referred to in popular news reports as "junk DNA" throughout the early 2000s. Epi-genetics, reasserting an interactionist model of how an organism shapes, and is shaped by specific developmental and environmental contexts, has challenged the epistemic primacy of the gene.[34] Decentering the gene as a deterministic agent of disease, this line of work images new objects of scientific interest within current biomedical practices. Reflecting on the aftermath of the Human Genome Project, former director Francis Collins (1993-2003) explains: "…whereas the tools of the Human Genome Project initially advanced research on single genes, they are now forming the basis for genomic-scale analysis of the human organism."[35] In projects undertaken by the National Institute of Health since 2003, the gene is contextualized as a node in a larger system: at the level of the organism, and the internal cellular systems and biological pathways in which genes "act" to encode proteins and carry out other functions.[36]

1.1.2.2. Translational Research

Established as a research imperative by the US National Institute of Health in 2003, translational research aims to quickly move basic science discoveries into new drugs, genetic tests, and treatments for patients.[37] Playing on the "bench to bedside" metaphor,

[34] Margaret Lock. "Eclipse of the Gene and the Return of Divination." *Current Anthropology* 46, S5 (2005): S47-S70.

[35] Francis Collins. "Medical and Societal Consequences of the Human Genome Project" *New England Journal of Medicine* 341 (1999): 33.

[36] Elias Zerhouni. "The NIH Roadmap." *Science*, New Series 302, 5642 (2003): 63-64, 72.

[37] Zerhouni, NIH Roadmap, 2003.

translational research seeks to "bridge the gap" between basic science knowledge produced at the laboratory "bench" and their transformation into treatments at the "bedside" of the patient.[38] Basic science research, interpreted as generating knowledge without an immediate end goal, sometimes is criticized as costly, lengthy, and an "unnecessary luxury"[39] that primarily only benefits scientists. This is contrasted with translational, applied research that generates knowledge with practical, tangible outcomes, and is also associated with being quicker, more cost effective, and more efficient. The director for the Office of Public Health Genomics, Dr. Muin J. Khoury, explains how the pressure placed on scientists to produce clinically-meaningful knowledge comes from increasing expectations about the ability of genomics to improve health outcomes and prevent disease, and from which translational research is a response aimed at the level of policy-making to reduce the time it takes for genomic discoveries to gain approval for clinical use.[40] Broken down into four phases, translational research is carried out with the aim of: 1) developing genetic tests for discovered genes; 2) implementing regulatory standards to determine what discoveries are clinically useful; 3) improving the even diffusion of knowledge about genomic knowledge to members of the public, academic researchers, patients, physicians, and funding agencies, and 4) to improve health outcomes on the population level.[41]

[38] Examining the values that guide translational research, Kaushik Sunder Rajan and Sabina Leonelli describe how "…the bench-to-bedside formulation assumes that too much research in the life sciences has failed to advance human health, either because it is esoteric in nature or, more commonly, because the institutional structures in which research is conducted do not facilitate its transformation into health outcomes" (2013:463). Kaushik Sunder Rajan and Sabina Leonelli. "Introduction: Biomedical Trans-actions, Postgenomics, and Knowledge/Value." *Public Culture* 25(3), 71 (2013): 463-475.

[39] International Council for Science. Accessed at https://www.icsu.org/most-recent

[40] Khoury, "The Continuum of Translation Research in Genomic Medicine," 665.

[41] D. M. Rubio, E. E. Schoenbaum, L. S. Lee, D. E. Schteingart, P. R. Marantz, K. E. Anderson, and K. Esposito. "Defining Translational Research: Implications for Training." *Academic Medicine: Journal of the Association of American Medical Colleges* 85, 3 (2010):470.

While the first phase of translational research poses a separation between the discovery of genes in the laboratory and their clinical applications, the second phase of translational research proposes the introduction of new standards for evaluating the utility of genomic discoveries before they reach the clinic. Genomic research focused on the discovery of single, heritable genes linked to diseases based on probabilities of genetic risk has led to improved diagnostic and preventative procedures for defined populations genetically "at risk" for a disease, but it has equated to few improved therapeutic outcomes for patients in the clinic. The social scientists Nicole Nelson, Peter Keating, and Alberto Cambrosio use the term "actionable" to describe an emergent sociotechnical regime in clinical cancer research from which gene mutations are discovered based on their association with FDA-approved drugs and therapies.[42] In the practices of translational medicine, the demonstrated clinical use-value of genomic discoveries acts as a precedent in the innovation process, influencing the type of research questions posed, the validation of results, and the objects produced from these research practices.

1.1.3. Social Studies of the New Genetics

1.1.3.1. Geneticization Thesis

Spanning across research in the humanities and the social sciences, and in US and international news media reports, there is an extensive archive covering the social impact of genomic discoveries in the 1990s. First predicted in the First Draft of the Human Genome Project, the crisis anticipated to arise during the "in-between" phase of the Project resembles the fear and uncertainty echoing through early public receptions of new genetic technologies, observable in news media reports released during the 1990s. During this

[42] Nicole Nelson; Peter Keating, and Alberto Cambrosio. "On Being "Actionable": Clinical Sequencing and the Emerging Contours of a Regime of Genomic Medicine in Oncology." *New Genetics and Society* 32, 4 (2013): 406.

period, popular discourse about genetics included discussions surrounding the ethical implications of pre-natal testing, and public morality debates about the possibilities of "designer babies," a development often analogized in news media reports to the practice of eugenics in Nazi Germany.[43]

This uncertainty of the new genetics, and its role in society, also appeared in the writings of sociologists of medicine in the 1990s writing under the banner of "geneticization." First coined by the sociologist Abby Lippman, the concept of geneticization describes how conceptions of health and disease are constructed through the language of genetics with the effect of reducing individual differences, medical conditions, and behaviours to a genetic origin.[44] Feminist scholars have employed the concept of geneticization to examine the further medicalization of the female body, pointing to the social impact of new genetic technologies on women's health decision-making; these include new personal and collective responsibilities towards health and family-planning observed for women who undergo genetic testing for breast cancer, and issues regarding female's reproductive rights with the slow routinization of pre-natal testing for conditions such as Down syndrome.[45]

[43] Michael D. Lemonick. "Designer Babies." *Time*, January 11th, 1999.

[44] Abby Lippman. "Prenatal Genetic Testing and Screening: Constructing Needs and Reinforcing Inequities." *American Journal of Law and Medicine* 17, 1-2 (1991): 19.

[45] For feminist critiques of geneticization, see: Nina Hallowell. "Doing the Right Thing: Genetic Risk and Responsibility." *Sociology of Health and Illness* 21, 5 (1999): 597-621; Rayna Rapp. *Testing the Fetus: The Social Impact of Amniocentesis in America*. (New York: Routledge, 1999); Nancy Press, Jennifer R. Fishman, and Barbara A. Koenig. "Collective Fear, Individualized Risk: The Social and Cultural Context of Genetic Testing for Breast Cancer," *Nursing Ethics* 7, 3 (2000): 237-249; Kaja Finkler, Cecile Skrzynia, and James P. Evans. "The New Genetics and its Consequences for Family, Kinship, Medicine and Medical Genetics." *Social Science and Medicine*, 57 (2003): 403-412.

The concept of geneticization emerges from an established line of thinking in medical sociology referred to as "medicalization." Medicalization is a term that has been used to explain how social identities, experiences, and issues are brought under the control of the medical profession, transforming social phenomenon related to gender, class issues, and sexuality into medical problems.[46] The medicalization thesis examines how the lifeworld comes to be colonized by hegemonic discourses in medicine and psychiatry, observable in the clashes between the "explanatory models" of clinicians and those of the patients they seek to treat, and ultimately, subjugate.[47] Re-vamped in the geneticization thesis, the critique of medicine as an institutional center of power and control over social life manifests in a separation between expert knowledge and the social experiences of the sick, promoting a lay/expert divide that anthropological works have attempted to bridge by drawing a dialectic between the medical expertise of clinicians, and the subjective knowledge of patients and families who form the other side of the interaction.[48] For many sociologists and anthropologists writing in the 1990s, developments in genomics are reduced to the negative effects of power, taking the form of controlling discourses and restrictive technologies, especially when directed towards the female body. In these analyses, science and society are approached as separate, but occasionally intersecting worlds, and with the "science" side represented as capable of penetrating the social, but never the reverse.

[46] Peter Conrad. "Medicalization and Social Control." *Annual Review of Sociology*, 18 (1992): 209-232.

[47] Arthur Kleinman, Leon Eisenberg, and Byron Good. "Culture, Illness, and Care: Clinical Lessons from Anthropologic and Cross-Cultural Research." *Annals of Internal Medicine* 88, 2 (1978): 251-258.

[48] Rapp, *Testing Women,* 1999.

1.1.3.2. Molecularization Thesis

Leading into the 2000s, social scientists began seriously examining how genomic developments relate to the positive effects of power. This includes viewing genomic knowledge not solely as a restrictive force, instead emphasizing its capacity to produce new objects and subject positions in society. Influenced by Michel Foucault's writings on biopolitics and works in science and technology studies, the sociologist Nikolas Rose's *The Politics of Life Itself* describes the transformative potential of developments in molecular biology leading up to the close of the Human Genome Project. In a process that Rose terms as "molecularization," clinical medicine is undertaken with a new power to visualize "life itself" at the level of DNA."[49] The sociological application of molecularization carries forward the Foucauldian genealogical interest in biopower and governmentality, describing the process to control and administer life through a new axis of knowledge/power in the twenty-first century.

Comparable to the theory of geneticization, the molecularization thesis acknowledges, but does not completely lift the veil between science and society, positioning a unilinear flow of genetic knowledge and technologies from the laboratory to the public, and describing the creation of new subject positions under the biopolitical regime of genetics.[50] The revitalization of biopolitics in social studies of genetics has set the stage for subsequent works drawing out the connection between Big Science and the logic of the capitalist market-place with the creation and flow of human material as

[49] Nikolas Rose. *The Politics of Life Itself*. (Princeton: Princeton University Press, 2007). 14–15.

[50] Paul Rabinow. "Artificiality and Enlightenment: From Sociobiology to Biosociality," in *Essays on the Anthropology of Reason*. Eds. Ortner, Sherry; Dirks, Nicholas B., and Eley, Geoff. (Princeton: Princeton University Press, 1994). 91-111; Nikolas Rose and Carlos Novas. "Genetic Risk and the Birth of the Somatic Individual." *Economy and Society* 29, 4 (2000): 485-513.

"biovalue,"[51] examining how the biomedical sciences produce new forms of risk governance and management in society.[52]

While the molecularization thesis takes account of how sub-cellular entities—molecules, proteins, genes, cells, etc.—can move between scientific networks, and ultimately, reconfigure the sociotechnical worlds they come into contact with, it maintains an epistemic barrier between science and the society its ideas and tools claim to penetrate and transform. In the molecularization thesis, we encounter a social world that is transformed, at times, beyond recognition, where bodies, identities, and subjectivities are worked on with increasingly more sophisticated bio-technologies and tactics of power, subjection, and governance. However, following in the power/knowledge approach, the anthropologist Kaushik Sunder Rajan and the historian Sabina Leonelli caution that scientific-medical knowledge is immediately translated to the effects of power, and descriptions of the construction and materialization of this knowledge—in technologies, the artefacts of scientific papers, bio-entities themselves—is limited to their one-way translations to a pre-defined public.[53] Strictly adhering to the power/knowledge theory

[51] Kaushik Sunder Rajan. "Genomic Capital: Public Cultures and Market Logics of Corporate Biotechnology," *Science as Culture* 12, 1 (2010): 87-121.

[52] Adele Clarke; Janet K. Shim; Laura Mamo; Jennifer Ruth Fosket. "Biomedicalization: Technoscientific Transformations of Health, Illness, and US Biomedicine." *American Sociological Review* 68, 2 (2003): 161-194; Vincanne Adams, Michelle Murphy, and Adele Clarke. "Anticipation: Technoscience, Life, Affect, Temporality." *Subjectivity* 28 (2009): 246-265.

[53] This project draws on conversations about the relationship between knowledge/value in post-genomics first initiated in a series of lectures and workshops led by STS scholars at the University of Chicago in 2011. Emerging from this work, the anthropologist Kaushik Sunder Rajan, writing with historian Sabina Leonelli, proposes a shift from the Foucauldian interest in the power/knowledge nexus in social studies of post-genomics to an examination of knowledge/value, citing a major limitation of the former approach: when knowledge production is tied to regimes of power, it limits the ability to explore how this knowledge is co-produced by society, and is articulated under different value systems by the diverse communities that take it up in their practices; the focus on knowledge/value allows room to speculate on the situated, and ever-shifting conditions of scientific knowledge production. Sunder Rajan and Leonelli, "Introduction: Biomedical Trans-actions…", 464-467.

provides limited room to speculate on how scientific, "expert" knowledge is also contingent on the social and historical contexts it claims to have transformed; critically examining scientific knowledge not solely as an effect of power invites an analysis of the dynamic, ever-shifting relationship between social practice and epistemology, and between scientific fact and socially-prescribed value.

This range of "-ization" studies have prompted social, ethical, and moral questions about genetic knowledge and technologies, promoting critical discussion of the political and economic register of emergent biotechnologies. However, these studies have also limited discussion of the multiplicity of scientific knowledge, that is, in its capacity for movement and transformation as it is taken up at multiple sites in society. Rather than studying the dissemination and consumption of genomic knowledge by pre-described, or otherwise docile subjects, a primary aim of this project is to examine how scientific knowledge about breast cancer is "co-produced" and legitimated by so-called "non-experts": patients and patient advocacy groups.[54] In their seminal work, *Laboratory Life*, Bruno Latour and Steven Woolgar critique the distinction between social and technical aspects of scientific work, describing how social analyses are not limited to the personal conversations scientists have in the lunchroom, but can be extended to the experimental procedures of the laboratory.[55] Drawing from Latour and Woolgar, alongside Sunder Rajan and Leonelli's critique of the power/knowledge approach, this project will explore the "molecularization" of breast cancer, and the power of genomic explanations in society, but will do so while acknowledging the complex relationship between social values and scientific knowledge, expressed in the movement of scientific knowledge between diverse communities—both scientific and popular. Examining the dynamic interplay between

[54] Jasanoff, Sheila. "The Idiom of Co-Production" in *States of knowledge: The Co-Production of Science and the Social Order*. (London: Routledge, 2006). 1-12.

[55] Bruno Latour and Steven, Woolgar. *Laboratory Life: The Construction of Scientific Facts*. (Princeton: Princeton University Press, 1979). 23-30.

science and society, a second aim of this project is to examine how translational science moves to the public, and how expectations, promises, and visions inform genetic cancer research leading up to the close of the "interim phase" of the Human Genome Project.

1.1.3.3. Case Study: The Breast Cancer Gene

The discovery of the breast cancer gene is a cornerstone of genetic cancer research, emerging at the forefront of the New Genetics, and inspiring further investigations of the genetic basis of a range of common diseases. This project examines what philosopher Nelson Goodman terms as the "world-making" potentials of genetic knowledge practices, that is, the multiple ways that reality is described, perceived, and constructed by different social groups.[56] Drawing from the concept of "world-making," this project signals to a *constructivist* understanding of scientific knowledge production, a theoretical move that is closely aligned with *constructionism*, but differs in a few significant ways. Both constructionism and constructivism share similarities in 1) challenging the positivist's view that there is an external reality that can be apprehended by a single, knowing subject; 2) proposing, instead, that reality is constructed through cognitive constructs and linguistic categories, and 3) taking a relativist stance regarding what "reality" is, arguing that there are multiple "realities" that are meaningful to those who participate in their construction.

Constructivism is often tied to the learning theory of Jean-Piaget in educational psychology, and examines how individuals, through interaction with one another, perceive and construct the world around them. Constructionism, while also interested in the role of individual learning and perception, departs from constructivism by attending to the

[56] Nelson Goodman. "Words, Works, Worlds." *Erkenntnis* 9, 1 (1975): 57-73.

"categories" or "constructs" themselves, as opposed to the actual process of learning and structures of knowledge. Media scholar Edith Ackermann (2001), contrasting the constructivism of Piaget with the constructionism of Seymour Papert, explains that constructionism focuses on the contexts of learning and knowledge transmission, and the "media" forms by which knowledge is transmitted, rather than the "cognitive potentials" of learning.[57] For Ackermann (2001), the "cognitive potentials" of Piaget can be taken as an attempt to define the structural operations of a cognitive-perceptual apparatus in the act of knowing/learning, and that suggests a stronger degree of realism in Piaget's theory of how "reality" is constructed compared to constructionist theories that focus instead on the content or meaning of linguistic categories. This project acknowledges the nebulous line between constructivism and constructionism, but moves in a constructivist impulse to describe how a genetic theory of breast cancer was formulated within the discursive constraints of the New Genetics, then examining how a new set of conditions has altered how knowledge claims (observations, inferences, and conclusions) in translational science are made. Following this approach, knowledge is not only transmitted between individuals, but is actively created through interaction—both with other social actors, and, taking a term from Ludwik Fleck, also with an existing sum of "collective knowledge" that transcends the individual.[58]

My analysis is based on a close textual analysis of a range of documents: newspaper articles, scientific journal articles, and press releases that are approached as "textual artefacts" of scientific-medical work. Referring to these documents as "artefacts" signals to a constructivist view of the text as a material extension of a knowledge practice. Referring to a theoretical understanding of the performative function of material "things"

[57] Edith Ackermann. "Piaget's Constructivism, Papert's Constructionism: What's the Difference." Future of Learning Group Publication 5, 3 (2001): 4.

[58] Ludwik Fleck. *Genesis and Development of a Scientific Fact*. (Chicago: University of Chicago Press, 1979[1935). 38.

in scientific practice also has methodological implications. Rather than treating these documents as communicative devices that can be read solely for content, these documents are approached as objects (and occasional "actors") that can move between scientific networks with the potential of reconfiguring them. A secondary focus of this thesis is to examine the dynamic between scientific "facts" and "objects," that is, to trace out the process by which a tentative fact, a speculation, or a hypothesis comes to stabilize as an object-in-the-world. Critically engaging with the process of fact-making in scientific research articles, this project examines the formation and transformation of the breast cancer genes, and genes at large. Following from these observations are critical speculations on how these articles fit into larger discursive shifts in fact-making for the communities where this knowledge is produced and practiced—at the intersecting networks of scientists, clinicians, and patients.

Methodologically, this project employs Michel Foucault's archaeological method, in particular, his conception of the "discursive formation", to refer to the process by which scientific statements and their objects are bounded by rules that govern the limitations and possibilities of knowledge at a given historical moment. While the archaeological method is especially useful for tracing the formation (and disruption) of "positivities," or, fields of positive knowledge in the disciplines of the human and life sciences, it is limited in its capacity to describe the circulation of this knowledge into "non-scientific" arenas.[59] The method of archaeology is supplemented with theoretical tools from Science and Technology Studies (STS) to explore the dynamic feedback loop between science and

[59] Foucauldian archaeology locates analysis to the level of the discursive "statement," taking an internalist view of how knowledge claims are created, modified, and obliterated *within* emergent and/or defined fields of positive, "expert" knowledge. In Foucault's archaeologies (IE: not the genealogies), it is unclear how the "statement," once disseminated through media or other institutions, is taken up at different social sites. By moving the analytic gaze from the discursive groupings of scientific disciplines to other groups in society, it is possible to examine how this structure and content of this knowledge is affirmed and modified through movement and interaction at different social sites.

society. Interactions between scientific and public actors are negotiations of value, and from which genetic knowledge about cancer is produced in line with the interests of varying actors in situated networks. How are genes re-imagined in research assemblages classified under the banner of post-genomic science? Drawing on assemblage theories in anthropology and history of science, the distinction between the New Genetics/Post-Genomics designates how certain elements—conceptual and material—are related to one another, rather than stable, fixed historical markers subject to a linear notion of scientific progress. Ultimately, this project seeks to trace the translations between assemblages towards describing how the multiple "worlds" of genetic cancer are made and re-made with changing knowledge practices.

Chapter 2. Analytical Framework

2.1. Constructivist Works Approaching Scientific Practice and Innovation

2.1.1. Capital 'D' Discovery: the Kuhnian Paradigm-Shifts of Normal Science

There is an Indian story -- at least I heard it as an Indian story -- about an Englishman who, having been told that the world rested on a platform which rested on the back of an elephant which rested in turn on the back of a turtle, asked (perhaps he was an ethnographer; it is the way they behave), what did the turtle rest on? Another turtle. And that turtle? 'Ah, Sahib, after that it is turtles all the way down.

— Clifford Geertz, *the Interpretation of Cultures*[60]

Open your local newspaper on an typical day of the week, and you are to encounter at least one headline proclaiming that a "scientific breakthrough" or "discovery" has occurred, one that has completely changed the way that we think about an aspect of existence, ranging from the expansiveness of deep space to the "true cause" of obesity. If we are to take these headlines at face value, it appears that we are living in a time of endlessly repeating scientific miracles, a horizon of intellectual possibility that stretches with further technological expansion. The "technological imperative" that guides biomedical work is expressed in the belief that with better tools, the limits of the world break open, and out falls the *knowable unknown*, which was always there, but until now

[60] Clifford Geertz. *The Interpretation of Cultures*. (New York: Basic Books Inc., 1973). 28-29.

escaped detection due to the limits of human perception.[61] The *knowable unknown* is not a nod to the pre-existing objects that populate the reasoning of positivism, nor is it referring to the process of invention as an act of inevitable discovery, or the unique fruit born of an individual genius. The *knowable unknown* refers to an object much like the gene described in Mary-Claire King's UC Berkeley laboratory back in 1993: a shape-shifter, an idea-not-yet-object, a hypothesis caught up in the process of materialization.[62]

Engaging with positivist understandings of scientific objectivity, science and technology studies (STS) is an interdisciplinary field that proposes a critical examination of the contextual nature of technical innovations and scientific progress. While positivist approaches are founded on the conviction that there is an external reality that may be apprehended apart from the 'subjective' experience of the observer through the method of empirical observation, science and technology studies challenges the epistemological and ontological status of scientific knowledge as *a priori* 'facts.' Asserting that knowledge cannot be separated from its producers or the conditions of its production, critical engagements with science bring into question the detached, "God's eye view" of scientific

[61] The "technological imperative" refers to the increasing routinization of technology in medicine and society (Koenig 1988). In the health-care setting, the "technological imperative" is a persuasive, moral position that constraints action for physicians and patients alike, resulting in a situation where social and medical problems can be solved by recourse to technology (Hofman 2002). For works on the technological imperative in medicine, see: Barbara Koenig. "The Technological Imperative in Medical Practice: The Social Creation of a "Routine" Treatment," in *Biomedicine Examined*. Eds. Lock, M., and Gordon, D. (Netherlands: Kluwer Academic Publishers, 1988). 465-496; Bjorn Hofmann. "Is There a Technological Imperative in Health-Care?" *International Journal of Technology Assessment in Health Care* 18, 3 (2002): 675-689.

[62] In interview, Mary-Claire King compares the breast cancer gene to the fictional character Odo from *Star Trek: Deep Space Nine.* Odo, an intergalactic orphan known for his shape-shifting abilities, resembles the epistemic malleability of the breast cancer gene, a point of frustration and fascination for researchers working to identify and clone BRCA1 in the 1990s. "Vexing Pursuit of Breast Cancer Gene." *New York Times*, 1994.

work,[63] emphasizing the role of learning and transmitting collective knowledge in the everyday practices of science.

Writing the cultural history of a scientific innovation challenges its authors to decide what events to foreground, and to determine the specific contingencies between these events. Where does the innovation begin—in the laboratory, with the first few half-formed notions scrawled on a notepad, or in the patenting office? Summarizing a parable, the anthropologist Clifford Geertz compares the search for a transcendental origin to the world's beginning to an infinite stacking of animals: the world rests on a platform, this platform on an elephant, the elephant on a turtle, the turtle upon a turtle, and on that turtle, another turtle. For Geertz, any attempt to define a singular, "true" meaning, cause, or interpretation of culture is to start with one turtle, and to end up with "turtles all the way down." Similarly, a cultural analysis of scientific discovery can only expect to encounter complexly interlaced dependencies and "situated knowledges"[64] that cannot be divorced from the practices, tools, and actors that make up a given scientific moment. Engaging in a "thick description"[65] of the events, technologies, and actors of two pivotal moments in genetic cancer research—between the New Genetics and Post-Genomics—this project seeks to reign the breast cancer genes in from the forefront of translational science,

[63] Donna Haraway. "Situated Knowledges: The Science Question in Feminism and the Privilege of Partial Perspective. *Feminist studies* 14, 3 (1988): 575-599.

[64] Donna Haraway critiques "unlocatable" objectivity, arguing for feminist objectivity as a method that aims for researcher accountability, and an awareness of the social, historical, and political contexts in which knowledge is produced. As knowledge is always situated, all "vision" is delineated on the lines of race, class, sex, and gender (1988:583-84).

[65] For Geertz', the method of thick description seeks to understand culture through "context"—that is, through the symbols and signs that grant cultural significance to an event, object, or persons. As Geertz argues: "…culture is not a power, something to which social events, behaviors, institutions, or processes can be causally attributed; it is a context, something within which they can be intelligibly-that is, thickly-described" (1978:14).

examining how a hypothesis worked out over seventeen laborious years in a UC Berkeley laboratory became a bonified fact about the genetic basis of breast cancer.

Examining the larger historical arc of genetic cancer research, it is first necessary to articulate the relationship between everyday tinkering in the laboratory and large-scale "paradigmatic" changes that are often associated with a "discovery" or "breakthrough." The historian Thomas Kuhn's *The Structure of Scientific Revolutions* has been particularly influential in understanding how scientific progress is bounded by a 'paradigm' that includes the skills, technologies, and intellectual conventions that condition what questions and results may be formulated in the everyday workings of 'normal science.'[66] For Kuhn, normal science is then organized around the activity of 'puzzle-solving' from which scientists employ the conceptual and material tools provided by the paradigm. As 'anomalies' emerge from which the puzzles can no longer be solved using the same tools, resistance to the paradigm signals a 'crisis' in the scientific community leading to what Kuhn terms as a 'paradigm shift,' or in other words, a scientific revolution.[67] For Kuhn, scientific experimentation is rendered in the form of a capital 'D' Discovery that occurs at the macro-level, and follows a dialectical model which sees to the erasure of existing paradigms as they are replaced with a new theory following the revolution. The distinction between 'normal science' and society remains in-tact in Kuhn's analysis, and from which paradigm-shifts are initiated from within scientific disciplines. Arguably, Kuhn's paradigm theory offers up a view of scientific progress as a less-than-linear, less-than-cumulative model of scientific innovation, but is limited in its capacity to explain micro-shifts in scientific thinking, and their relationship to non-expert domains and "social" influences.

[66] Thomas Kuhn. *The Structure of Scientific Revolutions*. (Chicago: Chicago University Press, 1970[1962]).

[67] Ibid., 65.

2.1.2. Situated Logics: Fleck's Thought Style and Polanyi's Tacit Knowledge

In his monograph, *Genesis and Development of a Scientific Fact*, the physician Ludwik Fleck investigates the shape-shifting of the concept of syphilis from the fifteenth century into the nineteenth century, and its accreditation as a "fact" with the development of the Wasserman reaction in the early 1900s. In his case study of syphilis, Fleck argues that scientific concepts are historically-bounded, and as such, are never simply discovered, but continually emerge and re-emerge from what he describes as earlier "proto-ideas."[68] The various developments that take place in science, both conceptual and material, are bounded by a "thought style" that conditions what is perceived and accepted as a scientific fact or prevailing 'truth' within what he terms as a given "thought collective," or, community of thinkers. The "thought collective" extends into any stabilized group of "thinkers" in the realms of art, fashion, religion, and science, and from which Fleck identifies an 'esoteric' circle of experts who have been initiated into the thought style, and an 'exoteric' circle that consists of non-experts pertaining to the public sphere.[69] Initiation, in this context, is the training and experience that individuals accrue within the 'thought style' of the collective.

"Experience," here, is neither a hermeneutic quality or achieved status of interiority, but is a kind-of exteriorized subjectivity that denotes a learned position taken to a larger body of knowledge. For Fleck, cognition is a distinctly social ("collective") activity, and from which he defines the 'thought style' as "a readiness for stylized (that is, directed and restricted) perception and action."[70] The thought style, learned and transmitted between members of the collective, determines what relations can be made between

[68] Fleck, *Genesis*, 26.
[69] Ibid., 105.
[70] Ibid., 95.

concepts in the processes of scientific observation, experiment, and the verification of results. Fleck describes how scientific facts come to appear to resemble a reality that pre-exists the subjectivity of the individual scientist as they are constructed and verified according the 'stylistic' constraints of the collective. Fleck's approach to "comparative epistemology" proposes that as thought styles mutate over time, so, too, do the facts, objects, and possible realities that are produced in line with these stylistic constraints.

Returning to Fleck's thought style, it is possible to elucidate differences in a constructivist approach to scientific innovation versus Kuhn's distinction between normal science/paradigm shifts.[71] While Kuhn poses a separation between the workings of "normal science" (scientific disciplines) and society, Fleck's "thought style" invites an understanding of how scientific concepts, theories, and objects emerge within and in relation to particular socio-historical conditions. Science is not only a social enterprise contained within a single laboratory, or a series of laboratories, it is also cultural and political. Further, while Kuhn claims that innovation occurs through paradigmatic shifts where an old structure for research is replaced by a new one, the concept of the "thought style" allows for an understanding of how innovation occurs as more of a patchwork of theories, concepts, and objects, and from which the "proto-ideas" from one historical moment are able to twist and bend into new configurations as they enter into new thought styles.

[71] Debates persist amongst historians and sociologists of science about how much Thomas Kuhn borrowed from Ludwik Fleck in his formulation of the paradigm theory, and general writings on scientific innovation. In the preface to his seminal work, the *Structure of Scientific Revolutions* (1970[1962]), Thomas Kuhn acknowledges the impact of Fleck's "unknown monograph," *Entstehung und Entwicklung einer wissenschaftlichen Tatsache* (1935), originally written in German, and translated into English as *Genesis and Development of a Scientific Fact* in 1979 (1970[1962]:vi-vii). In the foreword to Fleck's *Genesis*, Kuhn states that he is "…almost totally uncertain" of how much he borrowed from Fleck, and with some then arguing that Kuhn capitalized on the obscurity of Fleck's findings leading up to the translation of his monograph into English nearly forty-five years later (1979[1935]:viii).

The polymath Michael Polanyi's path-breaking work, *Personal Knowledge: Towards a Post-Critical Philosophy*, takes a Fleckian view of stylized knowledge with an explicit focus on the relationship between perception, knowledge, and scientific practice. Constructing his theory of "personal knowledge," Polanyi draws on Heidegger's concept of "indwelling" to refer to the act of the knower embedding themselves in an epistemological framework to strive towards a collective goal or purpose. Polanyi positions the systems of science and religion as "mental dwelling places" from which the scientist or the believer accumulates experience and a learned appreciation for beauty, or, in other words, an estimation of what is good, virtuous, and valuable within a particular community.[72] Just as a member of a religious or artistic community is socialized to accept certain norms, values, and codes of practice (What is a "virtuous" way to conduct one's self? What is "good" art?), the system of science is compared to the cultural life of these communities in that it seeks to elicit and reinforce "correct modes of feeling."[73] In contrast to formal logic, this kind of feeling-knowing cannot be replicated on a standardized test, or even fully explained to another, but can only be demonstrated in practice as it is embodied in the skills and "know-how" of the individual scientist. As a form of "tacit knowledge," these values, skills, and know-how form the "subsidiary awareness" of the scientist, which are enacted in the performance of everyday tasks, and that directs attention towards the "focal object," or, central research objective or task at hand. For instance, Polanyi uses the example of playing an instrument such as a piano in which one must temporarily decentralize the individual notes (subsidiary awareness) towards the goal of performing the composition (focal object).[74] It is not the individual machinations of the fingers hitting

[72] Michael Polanyi. *Personal Knowledge: Towards a Post-Critical Knowledge.* (Chicago: University of Chicago Press, 1974[1958]).

[73] Ibid., 133.

[74] Ibid., 55-56.

particular keys, but their arrangement into meaningful "wholes" that constitutes a successful performance.

The act of discovering a scientific object begins with a question, and all good questions in science are ones that are believed to have answers and can be solved. Both Fleck and Polanyi were interested in the role of perception and cognition in their respective theories of scientific discovery, coming up with similar models of how innovation occurs through a process of "making connections" within the space of formal logic. For Fleck, formal logic includes a collective corpus of knowledge that determines what "stylized" relations can be made between concepts. Comparable to Fleck, Polanyi argues that as the 'explicit,' or formal rules of scientific procedure are grasped through the 'tacit,' or implicit domain of knowledge, innovation occurs when formal logic is not sufficient to answer a particular question. The 'logical gap' that lies between formalized procedures is crossed as the scientist 'anticipates,' or, tacitly apprehends the solution to the problem that is hidden in the 'particulars' of formalized logic.[75] Michael Polanyi compares the practice of scientific experimentation to the experience by which one comes to "grope for a forgotten name," from which scientific discovery is the unexplainable leap from formal logic to a conceptual relation previously hidden from view.[76] To formulate a new conceptual relation is to move from working within the patterns or rules of formal logic (A = B) that the scientist has been trained to recognize, inviting previously hidden connections (Does A always = B? Under what conditions may it actually = C?) to be seen. Under what conditions do these rules determine the kind of relations can be made, or in other words, by what mechanism are the limitations and possibilities of making certain knowledge claims enacted?

[75] Ibid., 130.
[76] Ibid., 137.

2.1.3. The Foucauldian Statement and Theories of Object Formation

The sociologists Bruno Latour and Steven Woolgar's *Laboratory Life: The Construction of Scientific Facts* is an early work that addresses the 'in situ' production of scientific knowledge in the everyday practices of scientists in the laboratory. Taking a constructivist approach, Latour and Woolgar argue that laboratory activity is organized through 'literary inscription,' or, the processes by which the observations gathered through the 'technical' benchwork of the laboratory are transformed into 'persuasive' scientific statements, or, documents.[77] Latour and Woolgar' describe how thyroptropic releasing factor (TRF) is established as a 'fact' in the scientific papers through the juxtaposition of statements and external documents within the articles themselves. Once the 'fact' begins to travel in the form of a scientific paper that is divorced from the context of its production in the laboratory, Latour and Woolgar describe how a scientific statement undergoes the process of "splitting" and "inversion" to become both an object and a set of statements about that object as it begins to circulate into other networks.[78] For Latour and Woolgar, scientific knowledge is both constructed and materialized in facts, documents, and machines, and comes to take on the appearance of an external 'reality' through its expansion into new networks of scientific activity.

The Latourian "statement" bears a strong resemblance to the archaeological "statement" in the works of the historian Michel Foucault. In his early work *the Archaeology of Knowledge*, Foucault puts forward a method for investigating the emergence of new forms of positive knowledge in the life sciences during the nineteenth century. From a methodological standpoint, archaeology is not so much interested in the genealogical concept of power/knowledge, but rather it seeks to confront the rules or laws

[77] Latour and Woolgar, *Laboratory Life*, 45.
[78] Ibid., 177.

that condition the emergence of kinds of knowledge practices and their objects. Central to this investigation is then a question of how knowledge is constructed and performed in what Foucault terms as "discursive practices." For Foucault, discourse, a group of signs, does not just signify or represent objects, but is also the practices that shape the object.[79] Foucault's conception of a discursive practice then attempts to do away with the structuralist relationship between signifier (word) and the signified (thing) by examining the performative function of language. To do so, Foucault describes how signs, as the "atoms" of meaning, are ordered into "statements," which, in turn, are the atoms of the discursive formation. An archaeology of the "statement" does not seek to examine the internal components of a text, as a proposition, a sentence, or to analyze its construction in terms of the rules of formal logic; the "statement" is not the residual, linguistic product of the knowing subject that speaks it, and does not possess a symbolic shadow that a hermeneutic analysis may read for its "hidden" or "underlying" meaning. Rather, it is characterized by its "rarity" and "exteriority"—it appears under certain conditions of existence, and is performed in practices and linked up with objects, and with other statements. The statement is "not a unit, but a function," performing in the interface between language and its material traces, such as the written word on the paper.[80] These bundles of material-semiotic relations are ordered and dispersed by a discursive formation, or, a set of rules and conditions for making knowledge claims. As Foucault explains: "the rules of formation are conditions of existence (but also of coexistence, maintenance, modification, and disappearance) in a given discursive division."[81] A discursive formation is a set of relations between statements and objects as much as it is the process of their formation and transformation.

[79] Foucault, *Archaeology*, 49.
[80] Ibid., 93.
[81] Ibid., 38.

2.1.4. Epistemic Things

Drawing on the works of Michel Foucault and Jacques Derrida, the historian of science Hans-Jörg Rheinberger's employs the concept of the "experimental system," as well as that of the "epistemic" and "technical" object, in his theory of scientific innovation and object formation.[82] Experimental systems, for Rheinberger, are assemblages of concepts, technologies, and objects that form the base from which new scientific knowledge is produced.[83] The differences that exist between an "epistemic" and "technical" object denote the relational elements that structure experimental research in consistently changing and unstable laboratory practices. In contrast to the instrumentality of technical objects, the epistemic object encapsulates the sublime fascination and challenge that a particular knowledge question poses to researchers. As Rheinberger notes:

> the first entity, the scientific object, is that hardly definable something for the sake of which the whole experimental enterprise exists and around which it revolves. Paradoxically speaking, it embodies, in an experimentally manipulable fashion, exactly that which one does not yet know exactly.[84]

The quest to know what is currently "unknown" is undertaken with the use of technical instruments in the laboratory. In contrast to epistemic objects, "technical" objects are laboratory apparatus such as beakers, tubes, PCR machines—objects whose action is limited to measuring, quantifying, controlling, and calculating what "is there," and in what capacity, in the search for what "could be" (the epistemic object). The many technical objects that make up the assemblage "require a certain measure of rigidity and precision to keep the vagueness of the scientific objects at a sub-critical level,"[85] and in this sense, bound and "make" the epistemic object. Further, technical objects may also consist of

[82] Hans-Jörg Rheinberger. "Consistency From the Perspective of an Experimental Systems Approach to the Sciences and Their Epistemic Objects." *Manuscrito* 34, 1: 307-321.

[83] Ibid., 310.

[84] Ibid., 311-312.

[85] Ibid.,:312.

formally “epistemic objects” that have stabilized into technical parts of the system. The status of these epistemic and technical elements in the system are continually changing, as Rheinberger notes:

> Within a particular research process, former epistemic things can gain sharp contours and become transformed into technical objects, thus becoming part of the technical conditions of the system. But parts of the technical system also can gain or regain an epistemic status and so be re-transformed into research objects. In this view, the dialectic between the epistemic and the technical is the core of an experimental system; it is its driving force.[86]

Complicating Rheinberger’s dialectical approach, historians of science Cyrus Mody and Michael Lynch coin the term “test objects” in their argument that technical and epistemic objects can continually shift back and forth between these statuses depending on the practices they are being performed in.[87] With this in mind, the shifting status of laboratory artefacts offers insight into how assemblages of rare genes, their techniques, and practices, become “experimental systems” that can be translated to new arenas of research to produce biotechnological innovation.

[86] Ibid., 312.

[87] Cyrus Mody and Michael Lynch. "Test objects and other epistemic things: a history of a nanoscale object." *The British Journal for the History of Science* 43, 3 (2010): 426, 429.

Chapter 3. Discovering the Breast Cancer Gene

3.1. Dr. Mary-Claire King and the Genetic Thought Style

The discovery of BRCA1 ("the breast cancer gene") is often credited to geneticist Dr. Mary-Claire King, a leading member of the UC Berkeley laboratory that used DNA linkage analysis to pin-point the gene to a region of chromosome 17 in 1990.[88] The chromosomal map produced by King and colleagues initiated an international competition amongst researchers to clone the gene between 1990 and 1994. While it was a competing laboratory that would successfully clone BRCA1 in 1994[89], the highly-cited paper produced by King's laboratory was the first to investigate the hypothesis that familial patterns of breast cancer could be causally linked to a gene. Emerging in competition with viral and environmental theories of cancer causation, King's genetic theory of familial breast cancer was novel in that it relocated disease to the level of the gene, introducing a new practice of classifying breast cancer patients based on evidence of genetic risk, and inspiring later scientific pursuits to discover the genetic basis of a range of common diseases.

Reviewing her broad portfolio, Mary-Claire King is a good example of an experimental researcher who has actively sought to apply her genetic thesis in multiple scientific, medical, and social contexts. King's career is distinctly interdisciplinary and complex, initially studying mathematics before she was convinced by her mentor Allan

[88] Hall et al., "Linkage," 1990.
[89] Miki et al., "A Strong Candidate," 1994.

Wilson at UC Berkeley to switch to evolutionary genetics in the 1970s.[90] From this switch, King's first major success came with a publication in *Science* in 1975 that made the bold claim that humans and chimpanzees share 99 percent of the same DNA.[91] Her later life-long project has been her work to uncover the genetic basis of breast and ovarian cancer. In interview with the *New York Times* in 2015, King describes how a gyre of personal, professional, and epistemic forces contributed to her decision to study breast cancer:

> I needed a job and was very lucky to be offered one at the University of California, San Francisco, studying breast cancer. Of course, breast cancer wasn't my field. But I thought genetics, evolutionary biology and statistics might add something to the newly launched War on Cancer. And my closest childhood friend had died of cancer. I wanted to try.[92]

King's interview with the *New York Times* suggests that her move from evolutionary biology to breast cancer research was motivated by opportunism, curiosity, and personal loss. Combining her past professional experience working with mathematical models in evolutionary genetics, King entered the field of breast cancer research with an interest in translating the evolutionary laws of population genetics to the

[90] 'Mary-Claire King,' *DNA Learning Center*, accessed April 12th 2015, https://www.dnalc.org/view/16055-mary-claire- king-.html.

[91] Mary-Claire King and Allan Wilson. "Evolution at Two Levels in Humans and Chimpanzees." *Science* 188, 4184 (1975): 107-116.

[92] Claudia Dreifus. "A Never-Ending Genetic Quest: Mary-Claire King's Pioneering Gene Work, From Breast Cancer to Human Rights," *New York Times*, February 9th, 2015.

study of the epidemiology of disease.[93] Contrary to the idealized image of the astronaut with a lifelong passion for outer space, or the engineer who has been tinkering with household electronics since young adolescence, King's genius lies in her ability to work with her genetic tool-set (theoretical, methodological, conceptual, technological) to answer a range of epistemic problems within and across different "thought collectives," that is, communities of thinkers formed through mutual interaction and the exchanging of ideas.[94] Describing the field of medical genetics as a "thought collective" as opposed to a "scientific discipline" has both methodological and philosophical implications.

First, what is a scientific discipline? Defining what social aggregations *are*, and where they begin and end, is to engage in the task of boundary-making for both the analyst and the communities under study. The term "discipline" sets out boundaries between various epistemic communities by subject of study ("physics, history, chemistry, anthropology, and sociology"), and these subjects correspond with field-specific methodologies, concepts, theories, and objects of study. The Fleckian concept of the "thought collective" attempts to destabilize the notion of a monolithic scientific discipline that endures throughout time without much change or contestation, instead emphasizing the dynamic interactions between, and within thought collectives as the

[93] It is important to note that King did not just "land" in the field, but whose work on genetic breast cancer was shaped by the social and political landscape of U. S. society in the 1970s. In interview with *NPR*, King describes the various institutional barriers she faced as a woman employed in the sciences during this time. Jokingly referring to herself as a "child of affirmative action," King explains how she had to be "three times as effective" as her male colleagues to be recognized as an equal contributor in the field. Titling the article in which this interview is embedded as "How Being Ignored Helped a Woman Discover the Breast Cancer Gene," interestingly, the journalist also suggests that King's "outsider status" as a woman, and constant dismissals of her work, may have positively contributed to her success as a researcher. Facing constant dismissals, King explains how she had no choice but to acquire strong evidence for her theory over a 17-year period in relative obscurity: "But if you've had 17 years to develop your evidence then you're in a much better position to defend it well." Nancy Shute, "How Being Ignored Helped a Woman Discover the Breast Cancer Gene," *NPR*, March 27th, 2014.

[94] Fleck, "Genesis," 9.

basis for group organization and innovation. Further, each thought collective works within a "thought style," that is, a set of norms, theories, and practices that conditions how reality is perceived and constructed.[95] As Fleck claims that individuals can belong to a variety of "thought collectives," he argues that this "creative expert" is then capable of generating new ideas through the synthesis and translation of concepts from the "thought style" of one collective to another.[96]

The task of the scientist is often this kind of bricolage[97]—that is, the practice of working with the available materials at-hand, shuffling and combining various elements to arrive at an inventive solution for a common problem. It is perhaps this ability to shuffle concepts between "thought styles" that has enabled King to make some of the most significant discoveries in genetics in the last forty years. The first section of this chapter will situate Mary-Claire King's work on hereditary breast cancer in the larger socio-political landscape of cancer research in the 1970s, describing the historical relationship between virology, a genetic theory of disease, and germ theory. The second section of this chapter will examine how genetics acts as a "thought collective," that is, a social enterprise that trains members of the scientific community to ask and respond to intellectual questions. Drawing on Fleck and Polanyi, the third section of this chapter will describe how the object and study of breast cancer was "stylized" with genetic knowledge, concluding with a discussion of how King's hypothesis set the stage for further investigations of breast cancer at the genetic and molecular level.

[95] Ibid., 105.

[96] Ibid., 118.

[97] The concept of bricolage has been used in the philosophy of science and cultural studies to refer to the improvisational use of the tools at one's disposal (both conceptual and material) to produce a new structure. See: Claude Levi Strauss. *The Savage Mind* (London: Weidenfeld and Nicholson, 1966[1962]). 16-36.

3.2. The Molecular Turn in Oncology

In 1976, Mary-Claire King was appointed as a professor to the department of genetics and epidemiology at the University of California, Berkeley. In her seventeen years researching the genetic basis of hereditary breast cancer, King's work has been undertaken during two pivotal moments in the life sciences: 1) the emergence of a genetic theory of cancer in 1969 and the discovery of the first cancer-causing "oncogene" two years later, and 2) the reallocation of funding and resources into the "War on Cancer" with the signing of the National Cancer Act in 1971. The following section will situate the discovery of the gene for breast cancer within the larger socio-political landscape of cancer research leading up to, and following the publication of the oncogene hypothesis.

In competition with viral theories of cancer, oncogene research reinstated that cancer, much like its viral competitor, was the product of a singular cause: a cancer-causing gene. However, oncogene research differed from virology in that it displaced a biomedical view of disease as an external agent, substantiating a view of disease as a jointly biological *and* pathological state, that is, as a dysfunction of the normal human body.[98] The genetic etiology of cancer narrativizes the seat of the disease to the level of genes and molecules, and from which environmental and epidemiological factors are placed in parentheses. With the publication of the oncogene hypothesis in 1969, Richard Huebner and George Todoro's theory of a cancer-causing genes represented not only a shifting understanding of the cause of disease, but also reflected a new spatialization of disease within the body, equipped with new ways of classifying cancer and cancer patients.

[98] See: Alberto Cambrosio and Peter Keating. *Biomedical Platforms: Realigning the Normal and the Pathological in Late Twentieth-Century Medicine.* (London: MIT Press, 2003).

In a recent interview with *New York Times*, King explains how the viral theory of cancer that dominated scientific thought during the 1970s could not account for a pattern of breast cancer in some affected families: "The dominant theory was that cancer was viral. I thought that inheritance had to be involved in at least some families."[99] In the 1970s, the most cutting-edge research on cancer was taking place in the field of virology. With the development of tissue cell culture techniques in the 1950s, it became possible to extract and cultivate viruses in glass tubes that could be used to inoculate test animals: predominantly, mice and chickens, making them popular research objects.[100]

Virology, the view that disease is caused by invading viruses, is an extension of germ theory. In the twentieth century, germ theory emerged as the dominant view that microorganisms (viruses, bacteria, fungus, etc.) are the underlying cause of disease. Germ theory rests on three central premises: that disease can be investigated for its specific aetiology (there is one cause or source); a focus on the internal rather than the external environment (how disease affects cells, organs, tissues), and the metaphor of the body as a machine (the body is composed of parts that may become broken but can be fixed).[101] The sociologist Peter Conrad argues that germ theory, emerging in competition with environmental and lifestyle theories of disease, has dominated scientific investigations in virology, and shares many of the same characteristics with the new genetics of the 1990s. These characteristics include identifying single genes as the cause of the disease, expressed in the "gene for" metaphor of disease (the "gene for"

[99] "A Never-Ending Genetic Quest." *New York Times*, 2015.

[100] Joan Fujimura. *Crafting Science: A Sociohistory of the Quest for the Genetics of Cancer*. (Cambridge: Harvard University Press, 1996). 51.

[101] Drawing on microbiologist Rene Dubos' work on the structure of germ theory, *Mirage of Health*, sociologist Peter Conrad Peter provides a thorough examination of the parallels between germy theory and the New Genetics. See: Peter Conrad. "A Mirage of Genes." *Sociology of Health & Illness* 21, 2 (1999): 228-241.

breast cancer); deterministic views of genes that exist apart from their environmental context, and assuming the gene as a part and/or blueprint underlying the machinery of the human body.[102] For Conrad, the alignment of germ theory and the new genetics has fueled the acceptance of genetic theories of disease in science and society. Drawing on Conrad, it is significant to examine how these three components of germ theory outlined have shaped genetic cancer research.

In 1969, Robert Huebner and George Todoro proposed that the RNA of ancient viruses ("oncogenes") were implanted in human cells at an unknown phase of evolutionary history.[103] The theory proposed by Huebner and Todoro represents a cleft in the viral understanding of disease (disease is caused by an invading agent) and an emergent theory of disease as genetic (disease is a consequence of DNA changes in the normal human gene). Huebner and Todoro made the radical claim that unlike the view of viruses as invading pathogens, "these agents [oncogenes] behave more like cellular genes than like infectious virus,"[104] supporting an emergent view of cancer as both a biological and pathological entity. The normal cell, infected with the ancient virus (pathological agent), was responsible for causing tumours in humans and other vertebrates.

Termed the Oncogene Hypothesis, the claim that all human cells were infiltrated by ancient cancer-causing viruses put forth by Huebner and Todoro was met with sharp criticisms from the scientific community that included that it was both "untestable" and "all-encompassing," and a "pessimistic" way to go about researching cancer.[105] The

[102] Ibid., 231.

[103] Huebner, Robert J. and George J. Todaro. "Oncogenes of RNA tumor viruses as determinants of cancer." *Proceedings of the National Academy of Sciences* 64, 3 (1969): 1087-1094.

[104] Huebner and Todoro, "Oncogenes," 1087.

[105] Graham Chedd. "The Molecular Roots of Cancer." *New Scientist*, June 29th, 1972.

hypothesis put forward a deterministic, internalist view of disease as it is enmeshed in the normal functionings of the human body, however, the influence of external, environmental factors such as radiation in triggering tumour growth were accounted for in Todor and Huebner's paper.[106] Unlike a virus or a germ that could be "othered," conceptually separated, and eventually expelled from the normal, healthy human body, the oncogene theory represented an emergent view of disease as "the enemy within." It is not within the scope of this project to determine how and in what contexts researcher attitudes changed towards cancer genes, but it is significant to point out that the first real attempt to define cancer as a genetic condition was not readily-accepted as an obvious or even desirable theory. However, the prominence of germ theory in the formation of the oncogene hypothesis is illustrated, suggesting that the internalist view of disease was strengthened and pushed to an extreme in a scientific community that still valued the view of an external, "other" disease such as that of invading pathogens like viruses and other microorganisms.

In 1976, a team of microbiologists Michael Bishop, Harold Varmus, Dominique Stehelin, and Peter Vogt were accredited as proving the oncogene hypothesis, scuttling it from its position as a speculative claim to a full-fledged theory of how cancer develops.[107] While Todoro and Huebner maintained that viruses caused cancer, Bishop's team's re-working of the oncogene hypothesis re- located cancer to the seat of the cell, to its everyday machinery. Rather than viruses implanted in a normal cell, Bishop's team argued for the long-term existence of proto-oncogenes in normal cells, that, when triggered by a mutation, were converted to "oncogenes" active in the process of carcinogenesis. In the oncogene theory, cancer is not an external agent that can be

[106] Huebner and Todoro, "Oncogenes," 1087.

[107] Stehelin; Varmus; Bishop, and Vogt, "DNA related to the transforming gene (s) of avian sarcoma viruses is present in normal avian DNA," 1976.

eliminated, but is a pathogenic state taking place within the normal workings of the human body**.** In his acceptance speech for the Nobel Prize in Medicine, Bishop described the proto-oncogene as a "a keyboard on which various carcinogens can play."[108] The machine metaphor is prominent in Bishop's vision of the oncogene as a biological structure that exterior influences (carcinogens) can act on.

In 1971, the US Congress passed legislation to increase funding to cancer research and to raise public awareness about the disease.[109] Declared by US President Richard Nixon as a "war on cancer," the war metaphor was instrumental in mobilizing a diverse set of public actors—pharmaceutical companies, academic researchers, and investors—to attack cancer as one would an enemy in a state of war.[110] The hyper-masculine, offensive tactics of the war logic were applied to a variety of social issues including the war on [poverty], [crime], and [drugs]. In line with the specific aetiology of germ theory, the war metaphor has a rhetorical function,[111] substantiating a biomedical view of cancer as an single invading enemy that must be destroyed. With the signing of the National Cancer Act in 1971, later investigations, supported by NIH funding for research into the biological workings of cancer, combined methods from the field of tumour virology, immunology, biochemistry, and molecular biology to answer the collective problem of cancer's biologically precise etiology.[112] This interdisciplinary commitment to a common research goal saw what anthropologist Joan Fujimura terms as the rise of a "molecular biological bandwagon" in cancer research during the 1980s,

[108] Sharon Kingman and Ian Anderson. "Nobel Prizewinners Celebrate with a Baseball Match." *New Scientist*, October 14 1989.

[109] National Cancer Institute, "National Cancer Act of 1971," 2016.

[110] Douglas Hanahan. "Rethinking the War on Cancer." *The Lancet* 383, 9916 (2014): 558-563.

[111] Judy Segal. *Health and the Rhetoric of Medicine*. (Carbondale: Southern Illinois University Press, 2005). 115.

[112] For an extensive historical investigation of the development of genetic cancer, see: Joan Fujimura, *Crafting Science*, 1996.

an "package" that included the theory of the oncogene and techniques such as recombinant DNA technologies.[113] By 1982, research in genetic cancer, and in particular, oncogenes, included benefits to researchers such as "…clearly articulated experiments, research funds, high credibility, short-term projects, increased job opportunities, and the promised generation of downstream doable problems."[114] Between 1982 and 1984, increased funding from the National Cancer Institute and the National Institute of Health increased the legitimacy and credibility of scientific findings in the fields of genetic cancer research and molecular biology.[115]

3.3. Making a Problem: Genetic Thought Style and Tacit Knowledge

In the 1970s, King was one of many freshly-graduated researchers called to the frontlines of genetic cancer research. Notable researchers also include geneticist Alfred Knudson, accredited with formulating the "two hit" hypothesis to explain the pathogenesis of retinoblastoma. In the two-hit hypothesis, a class of genes known as tumour suppressor genes are "switched off" following a mutation of the both alleles of the gene, leading to the uncontrolled growth of cancer cells.[116] Like King, Knudson also entered the field from a background in statistics with an interest in mathematical modeling. In interview, Knudson explains how he was "snagged by genetics" which allowed for more "elegant," statistical

[113] Joan Fujimura. "The Molecular Biological Bandwagon." *Social Problems* 35, 3 (1988): 261-283.

[114] Ibid., 274.

[115] Ibid., 275.

[116] Alfred Knudson. "Mutation and Cancer: Statistical Study of Retinoblastoma." *Proceedings of the National Academy of Sciences* 68, 4 (1971): 820-823.

explanations than other competing fields in biology at the time.[117] The recruitment of researchers trained in statistics and mathematics informed early research into cancer genetics, a theoretical framework that was compatible with the method of documenting the statistical frequency of dominant and recessive traits in Mendelian genetics.[118]

King's research into breast cancer began by attaching a set of additional questions about family history to a pre-existing study of oral contraceptive use amongst women sponsored through the National Cancer Institute. For King, the problem of high breast cancer rates in some families was a "statistical question": "Does breast cancer cluster in families more than we'd expect by chance?"[119] For King, the first question, if a statistical frequency of breast cancer could be observed in the family history of women with the disease, was tied with "statistically likely" explanation that it was due to a gene mutation.[120] In 1974 when King began her project, the Human Genome Project had not been conceptualized, genetic and molecular technologies were limited, and there was little information available about genes or their functional roles. As King notes, the race to discover the breast cancer gene "…began with no genome sequence, no integrated physical maps, no awareness of genomic architecture, and certainly no genome browser."[121] How

[117] Ezzie Hutchinson. "Alfred Knudson and His Two-Hit Hypothesis." *The Lancet Oncology* 2, 10 (2001): 642-645.

[118] In 1866, Gregor Mendel first observed that certain traits of garden peas, including height, colour, and shape, could be selected for using cross-breeding techniques. The theory of Mendelian inheritance was expanded by Thomas Hunt and his students working on the genetics of the fruit-fly Drosophilia. In the theory of classical genetics, the expression of a trait (phenotype) is dependent on the combination of the two copies of a gene that an individual organism receives from both parents. The copies can be dominant or recessive, and with dominant traits being expressed when paired with recessive traits.

[119] "A Never Ending Genetic Quest," *New York Times*, 2015.

[120] Ibid., 2015.

[121] Mary-Claire King. "'The Race' to Clone BRCA1." *Science* 342 (2014): 1462-1465.

then did King make this correlation between a familial pattern of breast cancer and a gene mutation?

The training that a geneticist undergoes during their initiation into a "thought collective" includes learning to formulate hypotheses, that is, to ask questions about the nature of some aspect of reality, from a defined theoretical position. While the individual scientist may ask the question, the question is formulated within, and in response to the collective knowledge of the scientific community.[122] The possession of a set of specialized knowledge and skills influences how one behaves and thinks about the world around them. For example, an engineer looking at a toaster might make a connection with the basic theory of electrical conduction, whereas an environmental scientist could look at the same object and make a connection with the issue of energy conservation.

These connections between concepts, performed like an intellectual reflex, are pre-conditioned by the training, experience, and knowledge that comes with being initiated into a "thought collective." For Fleck, scientific thought is structured by a set of rules that govern the combination of conceptual relations in a historical moment, allowing for their construction and arrangement into new "ideas." Terming this structure as a "thought style," Fleck asserts that initiation into a thought collective requires the scientist to take on "…a readiness for stylized (that is, directed and restricted) perception and action,"[123] that is, to be able to discern conceptual relations with an automatic reflex. A good example of reflexive knowledge is demonstrated when writing a timed essay on an exam for a university course. In this situation, the student is not being tested for their memorization of the total content covered throughout the semester, but is being evaluated in their ability to retrieve, select, and arrange concepts from the course into meaningful "wholes"—that is,

[122] Fleck, Genesis, 38.
[123] Fleck, *Genesis*, 95.

the object of the essay itself, further broken down into subject and theme. The immediate, lightning-bolt identification of selected patterns amongst disparate phenomenon is a learned skill that is honed through practical experience. Fleck notes that stylized thought is one in which "an answer becomes largely pre-formed in the question,"[124] and with thought then being directed not only in act of making observations, but in the formulation of questions, and in the practice of verifying results. The "thought style" of medical genetics can be taken as a set of specialized skills and knowledge that informs how reality is being perceived and constructed.

Even though her genetic theory of breast cancer was a minority view when she began her work in the early 1970s, King explains how she was compelled to find a common factor for breast cancer in families where the disease was observed to cluster, explaining that "there was no evidence of a smoking gun. That opened the possibility that there was something else."[125] For King, her unwavering commitment to genetic explanations of biological life acts in her "tacit" knowledge of what cancer is—that is, "the logical way of thinking about cancer, that all cancer is genetic in the sense that it's a consequence of changes in DNA."[126] In contrast to formal knowledge, the philosopher Michael Polanyi coins the term 'tacit knowledge' to account for the ineffable, "mute" dimension of knowledge that informs perception.[127] Drawing from Gestalt psychology, Polanyi situates tacit knowledge as the inextricable link between 'subsidiary' and 'focal' awareness: while subsidiary awareness forms the 'particulars' (details) that compose a pattern, focal awareness is the attention directed towards a form or figure that emerges from the

[124] Fleck, *Genesis*, 95.

[125] Alice Park. "Lessons from the Woman Who Discovered the BRCA Cancer Gene." *Time*, June 2nd, 2014

[126] "A New Ending Genetic Quest," *New York Times*, 2015.

[127] Michael Polanyi. *Personal Knowledge: Towards a Post-Critical Knowledge. (Chicago: University of Chicago Press*, 1974[1958]).

background of these particulars. Polanyi employs the example of using a hammer to drive in a nail to a board. As attention is directed towards the nail, the subsidiary awareness of feeling the hammer in the hand merges with the 'focal' awareness of driving in the nail.[128] As both focal and subsidiary awareness are jointly constituted, the meaning of the performance is then dependent on the recognition of a whole or pattern. To focus on an external purpose or goal then requires the integration of the particulars of subsidiary awareness into a whole/focal point that guides and directs action.

In the thought style of medical genetics, the central idiom through which disease is understood is that of DNA. Discussing the meeting ground between genetics, molecular biology, and clinical medicine, the pediatrician and geneticist Barton Childs describes how the clinical logic of disease has come to be framed in the language of DNA:

> DNA provides a language that prefigures possibilities and constraints for both the development and the present state of the homeostasis of cells, organs, and individuals, while also encoding their phylogenetic history. So the language of the DNA connects physiology with evolution. It is a language common to biology and medicine, a language useful for describing how and why things work and fail to work.[129]

The semiotic system of DNA acts as a hybrid language spoken between epistemic communities, acting as a "boundary object," that is, one of many "scientific objects which both inhabit several intersecting social worlds…and satisfy the informational requirements of each of them."[130] The epistemic boundaries of these objects are mutable, and to this degree, can serve the interests of different scientific communities. The concept of DNA, and the object of the gene, can be understood as boundary objects that

[128] Polanyi, *Personal Knowledge*, 55.

[129] Barton Childs. *Genetic Medicine: A Logic of Disease.* (Baltimore: JHUP Press, 2003). 5.

[130] Susan Leigh Star and James R. Griesemer. "Institutional Ecology Translations' and Boundary objects: Amateurs and Professionals in Berkeley's Museum of Vertebrate Zoology," *Social Studies of Science* 19, 3 (1989): 387-420. 393.

flow between the fields of molecular biology, genetics, and into clinical cancer research. The gene is composed of a sequence of nucleotides that forms a segment of DNA, and each gene functions to code for a protein that will perform one or multiple tasks towards maintaining the homeostasis of the body.[131] In both scientific and popular discourse in the 1990s, genes have been envisioned as "...master molecules, or as the basis of material life, or as the codes of codes."[132] that form the basis of biological life. The gene is spoken in the idiom of information coding, and with the genome often described with the metaphor of a "blueprint" for human life.[133] In the 1990s, the uptake of the gene in clinical medicine has been carried out in the logic of the "gene for," that is, with the assumption that a single gene is responsible for a medical condition. The metaphor of the gene as the "master molecule" aligns with the deterministic aetiology of germ theory, and from which the gene and genetic explanation emerge as powerful explanatory tools in medicine and society.

Firstly, King's interpretation of the familial pattern of breast cancer follows a deterministic etiology, encapsulated in her metaphor of the "smoking gun" behind familial patterns of breast cancer. In other words, the gene mutation is the cause of the disease. Secondly, King takes an internalist view of disease, that is, that disease must primarily be examined at the biological level of tissues, genes, organs, cells, and genes as opposed to environmental factors. King explains how the statistical observation, tied to a deterministic aetiology, was paired with her internalist understanding of cancer as "a consequence of changes in DNA." King's view of the "logical way of thinking about

[131] A. R. Venkitaraman. "Cancer Susceptibility and the Functions of BRCA1 and BRCA2." *Cell* 108 (2001): 171-182.

[132] Donna Haraway. "Gene" in *Modest_Witness@Second_Millennium. FemaleMan©_Meets_OncoMouse™: Feminism and Technoscience*. (New York: Psychology Press, 1997). 144.

[133] Celeste M. Condit and Deirdre M. Condit. "Blueprints and Recipes: Gendered Metaphors for Genetic Medicine." *Journal of Medical Humanities* 22, 1 (2001): 29-39.

cancer" is inseparable from genetic explanations of DNA and DNA changes. The stylization of thought eliminates the possibility of competing, and perhaps even contradictory perceptions of the information at hand as King could "not see any other way the relationship between a tumor and host could possibly persist." The metaphor of vision, of seeing and not seeing, provides an entry-way into questioning how even the most "objective" observations are made within a cognitive-perceptive framework that selectively chooses and cancels out certain conceptual relations.

3.4. Making the Gene: Stylized Knowledge and the Construction of Boundary Objects

For King, the "particulars" of the disease are assimilated to the focal point of the gene. While the oncogene theory became the dominant view of scientific researchers from a range of disciplines including genetics, molecular biology, and cancer research in the 1980s, scientists continued to research cancer as the result of interactions between multiple genes and environmental factors.[134] King's "stubborn"[135] belief in the deterministic gene behind familial breast cancer is implicated in her view of the gene as a pre-existing object that only needed to be discovered by scientists:

> Our strategy was to use the idea of mapping a gene as an epistemological tool. We felt that we could prove the existence of a gene by showing where it was. And that's what we did. It took 17 years, from 1974 to 1990, but by 1990 we really had incontrovertible proof that there was a gene that lived on chromosome 17 in a particular physical locale.[136]

[134] Laurie McHale. "Putting the Puzzle Together: in the jigsaw world of human genetics, UW professor Mary-Claire King found a crucial piece that helps solve the mystery of breast cancer." University of Washington Alumni Association Accessed April 10th 2016. http://www.washington.edu/alumni/columns/sept96/king1.html.

[135] "Lessons from the Woman Who Discovered the BRCA Cancer Gene." *Time*, June 2nd, 2014.

[136] Shute, "How Being Ignored Helped a Woman Discover the Breast Cancer Gene," 2014.

The problem of breast cancer could be solved by finding the gene, but this involved the difficult process of rendering the "epistemological" concept of a gene into the factual and the concrete object of a gene as a thing-in-the-world. Paraphrasing Plato, Michael Polanyi explains how scientific questions or problems are always framed in the light of existing knowledge, and from which the solution or object that emerges from experimentation is conditioned by the tacit knowledge used to discover it: "...to search for the solution of a problem is an absurdity; for either you know what you are looking for, and then there is no problem; or you do not know what you are looking for, and then you cannot expect to find anything."[137]

In 1990, King and colleagues sought to investigate whether a causal gene was responsible for familial breast cancer patterns in a study of 23 affected families, arguing that "among the common cancers, breast cancer is particularly suited for this approach, because family history of the disease is a significant risk factor in all populations," citing "epidemiological evidence [that] consistently indicates that a woman's risk of breast cancer is increased by the occurrence of the disease in her mother or sisters."[138] Citing the strong, well-documented correlation between breast cancer risk and heredity, the decision to study breast cancer is partially due to its heuristic value as a case study that can be used to explore how the rules of population genetics play out in the domain of heritable diseases. The "familial clustering" of breast cancer has been a long-standing "clue" to the disease, formalized as a pedigree of breast cancer patterns in a selected family by physician and anthropologist Paul Broca in 1866.[139] In King's paper, the theory of cancer as a "consequence of DNA changes," however, must struggle to find expression amongst competing forms of evidence-making in oncology: epidemiology.

[137] Polanyi, *Personal Knowledge*, 22.

[138] Hall et al., "Linkage of Early-onset Familial Breast", 1684.

[139] Anne Krush. "Contributions of Pierre Paul Broca to Cancer Genetics." *Transactions of the Nebraska Academy of Sciences and Affiliated Societies* paper 316 (1979).

The modern practice of epidemiology is the study of patterns of human disease in defined populations, employing mathematical models to identify the statistical occurrence of health risks stratified by heredity, age, sex, ethnicity, socioeconomic status, diet, height and weight, hormones, and environmental toxins, to name a few.[140] In King and colleagues paper, existing epidemiological data of breast cancer risk are re-organized to fit with Mendelian laws of inheritance. The risk datum (primarily, age and sex), pathology reports, and personal history statements of living patients themselves and their retroactive descriptions of 'affected' deceased relatives make up what is termed as the "unavoidable epidemiologic realities"[141] that are complicating genetic analysis. These epidemiologic "complications" are like currents that must be struggled against to reach the shore of truth: "cancer is a consequence of DNA changes."

In King and colleagues paper, the object under study is an "autosomal dominant allele," that is, a gene variant that is correlated with a high risk of breast cancer.[142] In the logic of Mendelian genetic inheritance, a child inherits two copies of a gene (alleles) from both parents, and these gene alleles can either be dominant or recessive. The combination of alleles determines the phenotypical expression of a trait such as eye colour. For example, brown is a dominant allele for eye colour relative to recessive alleles for blue or green eye colour. If the mother of a child has brown eyes and the father has blue eyes, the child would inherit the dominant allele of the mother (brown) and a recessive trait (blue) from the father, resulting in the child having brown eyes. The mathematical model of segregational analysis

[140] The epidemiological risks listed were documented in 1990. Genetic risk was still speculative with one study conducted 10 months prior to Hall et al.'s that documented breast cancer risk in relation to a discovered oncogene termed as "HER2." Natalia Pier G., Maria R. Nicotra, Aldo Bigotti, Irene Venturo, Dennis J. Slamon, Brian M. Fendly, and Axel Ullrich. "Expression of the p185 encoded by HER2 oncogene in normal and transformed human tissues." *International Journal of Cancer* 45, 3 (1990): 457-461.

[141] Hall et al., "Linkage of Early-onset Familial Breast", 1684.

[142] Ibid., 1684.

places a high p-value on the dominant gene variant whose frequency can be predicted in succeeding generations of individuals who inherit this copy of the dominant disease allele. However, it is not the allele that the researchers are after—but the allele as a clue to the gene that harbours the mutated allele. The genes, presumed to be the deterministic drivers of the disease, are the desired "epistemic things" of the experiment: "the ultimate goal of gene mapping of human traits is to move from a known chromosomal location to identification of the crucial gene and characterization of its critical alteration."[143]

The fruit of an individual life, expressed in these epidemiological complications, must be pared away to get at the truth of the disease—the gene, a hard, impenetrable core. The "penetrance" of the genes in question can be determined by bracketing "unaffected subjects" in the family lines.[144] Penetrance is a concept in genetics that refers to the ratio of individuals who possess both the genotype and a phenotypical expression of the disease.[145] To assure the penetrance, that is, the absolute value of the autosomal dominant gene, the pedigree is re-stratified by sufferers versus non-suffers, and genetic linkage analysis, a form of recombinant DNA technology, is performed only on the women with breast cancer. Employing the technique of linkage analysis, King and colleagues identify several "candidate genes" on chromosome 17 across the breast cancer cases— those that code for enzymes and proteins, an oncogene known as HER2, and a speculative relation to a gene shared with familial ovarian cancer.[146] King and colleagues relate the breast cancer incidences to the epidemiological data, determining that there is a higher rate of breast cancer for women over the age of forty with the autosomal dominant allele than the rate for sporadic breast cancer in women of the same age. The highly-cited paper introduces a

[143] Ibid., 1688.

[144] Ibid., 1684.

[145] AJF Griffiths, JH Miller, and DT Suzuki. "Penetrance and Expressivity." *An Introduction to Genetic Analysis. 7th edition*. (New York: W. H. Freeman; 2000).

[146] Hall et al., "Linkage of Early-onset Familial Breast", 1688.

new framework for organizing breast cancer cases based on the rule of Mendelian inheritance of a rare autosomal dominant allele, conceptually separating breast cancer into two species: hereditary and sporadic.

Combining epidemiological risk in cancer research with allele frequency ratios in Mendelian genetics, the breast cancer gene acts as "boundary object" that is traded between molecular biologists, geneticists, epidemiologists, and cancer researchers. For cancer researchers, the gene is a diagnostic marker that signifies a statistical risk for breast cancer for a defined population of patients. However, King and colleagues suggest the gene can be used to investigate the "tumor-promoting steps" that may be the same in both hereditary and sporadic breast cancers, evoking the tacit knowledge that both heritable and common, sporadic cancers can be investigated at the causal level of DNA changes.[147]

3.5. Finding the Skeleton Key

The theory of a gene for breast cancer emerged in a moment in cancer research when a genetic "thought style" was still being formalized. In the early 1980s, increased government funding and heightening scientific interest in oncogene research paved a path for biomedical investigations of life at the molecular and genetic level. Epistemologically, early oncogene research aligned with the dominant view of germ theory as it was stylized in the field of virology, but re-positioned the external agent of disease (viruses, bacteria, and other microorganisms) to an internal agent: the deviated state of the normal human gene. The oncogene theory pushed forward a determinist aetiology that sought to bracket external factors ("carcinogens") to understand and cure disease at an underlying biological-pathological level.

[147] Ibid., 1684.

In addition to increased funding to oncogene research in the 1980s, Peter Conrad points out how later developments in genetics during the 1990s aligned with germ theory to enhance the acceptance of genetic theories in medicine and society. In 1990, King's theory of a causal gene operating behind familial patterns of breast cancer followed up on these developments in genetic cancer research with an interest in applying the principles of evolutionary biology and population genetics to study the distribution of disease. From the perspective of evolutionary biology, human populations share most of the same DNA, and the cause of most common, complex diseases such as cancer can be linked to rare gene variants that arose from a recent point in human evolutionary history. Following this principle, King and colleagues' paper proposes that while breast cancer patients can be re-classified based on the possession of a rare autosomal dominant allele, the rare gene may also offer insights into the etiology and pathogenesis of common cancers. Fusing the method of populations statistics in epidemiology to identify individuals at risk for breast cancer with King's training in mathematical modeling, King and colleagues used gene segregation analysis to examine how Mendelian laws of inheritance (particularly the rule of autosomal dominant allele transmission) influence the distribution of genes in selected families. Observing that certain genes were inherited together through linkage analysis, King's team uniquely constructed a geneticized pedigree that remaps heredity vis-à-vis several rare gene mutations suspected to be responsible for breast cancer.

The breast cancer gene, as a "boundary object," is generative of new questions and findings in multiple thought collectives. The oncogene theory was poised as a "grandiose" theory that made broad connections with research in molecular biology and other lines of cancer research, and from which Fujimura describes how "…the unifying theory appealed to scientists because of its elegance, a term they use to describe a theory that can precisely and simply explain many disparate observations."[148] The fusion of the "elegant logic" of

[148] Fujimura, "The Molecular Biological Bandwagon," 270.

Mendelian genetics with statistical methods in clinical epidemiology appears to have held the same appeal for researchers investigating the patterned distribution of breast cancer cases in a defined set of affected families. However, as an "epistemic object," the elegant theory of the breast cancer gene acts as a window into the study of multiple questions in the life sciences beyond the narrowly defined problem of a familial patterning of breast cancer. While the rare autosomal dominant gene initially acts as the key to unraveling the mystery of why breast cancer 'clusters' in some families and not others, it is a skeleton key that can be used to open a variety of locks. The finding of a candidate gene for breast cancer invites additional epistemic possibilities for cancer researchers to examine the molecular basis of carcinogenesis, as well as for molecular biologists who may further investigate the critical operations of the normal gene in its pathological state.

Chapter 4. Genes, Genes Everywhere, and Not a Disease to Treat?

4.1. Genes, Genes, Everywhere, and Not a Disease to Treat?

Water, water, everywhere/ And all the boards did shrink;/ Water, water, everywhere,/ Nor any drop to drink.

-Samuel Taylor Coleridge, "The Rime of the Ancient Mariner," 1834

The discourse of genetics has undergone a "mutation" since the nineteenth century when the scientist and Austrian monk Gregor Mendel first demonstrated that certain physical characteristics of garden peas—including the colour of the seeds, the size of the stems, and the shape of the pods—were passed on from one generation to the next through the transmission of 'genes,' the basic units of heredity.[149] Mendel's law of inheritance displaced "blending theory," a dominant view of inheritance as a process whereby the traits of both parents are "blended" in the new generation. Leading up to the close of the twentieth century, Mendelian gene-thinking has captured the imagination of scientists working at the intersection between genetics and biology, inspiring international research initiatives such as the Human Genome Project, a ten-year long research endeavour that resulted in the discovery of between 19,000-20,000 genes forming the human genetic code. However, following the completion of the Human Genome Project, gene-centered research has been critiqued on the grounds that the discovery of genes has been met with limited

[149] Gregor Mendel. "Experiments in Plant Hybridization." 1856.

knowledge of their functions, and consequentially, with few improved treatments or cures for the patients who carry them.[150]

Publics criticisms of genetic discoveries co-exist with an entrenched view of disease and "life itself" as a mystery that can be decoded in the language of the gene. Consequentially, scientific and popular discourses surrounding developments from the Human Genome Project, and the pursuit of Mendelian genes, is marked by heterogeneity. In interview with the popular international magazine *SPIEGEL*, the entrepreneur Craig Venter reflects on the legacy of the Human Genome Project. Venter is best known for successfully competing with researchers in the Human Genome Project to sequence the human genome, continues to be a controversial figure working at the interface between genomic science and private industry. Never shying away from public debate, Venter takes a critical stance regarding the gene-centered approach of the New Genetics, and notably, the "false expectations" that fueled the discovery of genes in the Human Genome Project.[151] These include overestimations of the number of genes that make up the genome, as well as the assumption that a gene could be identified for each human trait, as Venter explains:

> We were simply always looking at single genes because they were the only genes we had…And if you want to cure greed, you change the greed gene, right? Or the envy gene, which is probably far more dangerous. But it turns out that we're pretty complex. If you want to find out why someone gets Alzheimer's or cancer, then it is not enough to look at one gene. To do so, we have to have the whole picture.[152]

Venter offers insight into the kind of epistemic constraints that researchers were working with in the years leading up to the commencement of the Human Genome Project, describing how research into "single genes," that is, genes tied to heritable conditions such as breast cancer, acted as a model to investigate the genetic basis of various social and

[150] Wade, "A Decade Later, Genetic Map Yields Few New Cures," 2010.

[151] SPIEGEL. "Interview with Craig Venter: 'We Have Learned Nothing from the Genome.'" July 29th, 2010: 4.

[152] Ibid., 4.

medical conditions. The "one gene, one trait" model of Mendelian genetics has been highly useful for research into rare genetic disorders, but Venter suggests that it has been erroneously applied to the study of "complex" conditions—for instance, Alzheimer's disease and cancer, and as an explanation for complex social traits such as greed and envy. Analogizing scientific interest in genes to the search for a pair of lost keys, Venter explains how "…when people lose their keys at night, they look under the lamp post. Why? Because that's where you can still see something,"[153] positing that single genes have provided a well-illuminated area of inquiry for researchers interested in the genetic basis of biological life. However, while the lamp-post may be the most obvious starting-point, Venter asserts that is in the "dark" where the "keys" to unlocking the mystery of the disease are actually located.

The turn to post-genomics signals to a new sociotechnical practice for investigating the biological basis of disease. Venter's comparison of the quest to discover genes with the search for a pair of lost keys illuminates the struggle of scientists to "make sense" of observations in the present, working with the theories and technologies available to come to a conclusion about a defined research problem, or, "puzzle."[154] For researchers of the Human Genome Project, genes were like puzzle pieces that needed to be discovered and fitted into what was assumed to be the whole, complete "picture" of the human genome. However, the situation may be that some of the pieces that make up the puzzle have been hidden from view—some are still in the box, stuck beneath a puzzle-fitter's arm, or have fallen under the table—and upon their discovery, the perception of the size and composition of the picture itself may begin to shift. With the completion of the Human

[153] Ibid., 4.

[154] For Thomas Kuhn (1970[1962]), the everyday "puzzle-solving" of scientific work is a normative practice in that is bounded by the rules of the discipline in which it is practiced. In this sense, it is possible to examine how the rules that dictated the "puzzle" of the human genome have changed, and are met with a new set of theoretical and aesthetic commitments for post-genomic researchers.

Genome Project, researchers discovered that the size of the "picture" of the genome was much smaller than anticipated, discovering a significantly lower number of protein-coding genes, that is, the genes involved in major biological operations. Further, the composition of the "picture" itself shifted as researchers began to formulate the new image of the genome as a complex system of gene-to-gene interactions. The following section will draw out the "picture" that enframes current research into the genomic basis of biological life, analyzing how genes such as BRCA are being re-fitted into a post-genomic "puzzle" of disease.

4.1.1. Locating Translational Research as a Discursive Formation

Scientific interest in single genes has shifted with the completion of the Human Genome Project, leading to the creation of new "post-genomic" research initiatives. Established in 2005, the Cancer Genome Atlas has been poised as a preceding platform to the Human Genome Project, focused on the continued sequencing and cataloguing of gene mutations for a range of common cancers. The etymology of the word "atlas" refers to a collection of maps, charts, and tables, referencing the cataloguing efforts of the research initiative. The word "Atlas" may also be a reference to the Greek God, Átlas, "Bearer of the Heavens," who, after losing a war with the Titans, was punished by Zeus to "to carry the weight of the world on his shoulders," to use a popular phrase. To take the word "Atlas" figuratively, The Cancer Genome Atlas is much like the mythological Atlas, poised by scientists to carry the speculative world of genetic medicine proposed by the Human Genome Project forward, producing genomic knowledge that has value in the realm of cancer therapeutics.

While the Human Genome Project has been criticized for failing to make significant advances in the clinical treatment of diseases such as cancer, the Cancer Genome Atlas responds to concerns of the gap between basic science research in genomics and its clinical

application. While several research platforms of the Cancer Genome Atlas have successfully added more genetic mutations to the list started by the Human Genome Project, there is debate amongst scientists about the future direction of the project with some scientists arguing that genomes should continue to be sequenced with the purpose of cataloguing more gene mutations,[155] and with others asserting that further investigations should examine the functions these genes have, and consequentially, how knowledge about the genetics of cancer may lead to improved treatments for patients.[156] Scientific interest in the function of genes, and the clinical significance of genomic discoveries, is informed by criticisms of the progress of genetic medicine.

While "gene discovery is the goal of most contemporary human genomic research," translational research at the first phase claims to intervene in the preceding stages of research by developing "applications" for genomic knowledge in the form of genetic tests to improve the diagnosis, prevention, and management of disease.[157] The discovery of BRCA1 and 2 is praised as a model of phase one translational research in-action, standing as one of the first cases where genomic knowledge and technologies were readily integrated into clinical practice in the form of genetic testing, screening, and counselling services for a new-subset of genetically "at-risk" cancer patients.[158] However, for the discoverer of BRCA1, Dr. Mary-Claire King, the clinical value of the breast cancer gene was still undetermined, and with King describing the shock that she felt to witness her "little idea"

[155] Gene mutations, and other genetic variants, with a high penetrance are often described as the "critical alterations" and "drivers" of cancer.

[156] Eric Green; James Watson, and Francis S. Collins. "Human Genome Project: Twenty-Five Years of Big Biology." *Nature* 526, 7571 (2015): 29-31.

[157] Khoury et al., "Continuum of Translational Research," 666.

[158] Under the heading of "Genomics Translation" on the website for the US Center for Disease Control, the discovery of BRCA1 and 2 is featured prominently as a model of translational research. Narrativized as "The Story of BRCA: An Example of Translation Research," the authors argue that "…only a few genomic applications are ready for use in health care practice. One of these applications is the genetic test for breast cancer genes called BRCA1 and BRCA2" (2012).

of a breast cancer gene develop into a full-fledged clinical apparatus for managing and treating the new condition of "hereditary breast cancer syndrome:"

> But I honestly didn't appreciate at all how important and directly useful the inherited component would be. The idea that oncologists and medical geneticists would take that information and systematically be able to put into place screening programs that enable women to learn that they had mutations, and do something about it to save their lives, wasn't the way I thought. If somebody had said that this was possible, I would have said, 'Golly, maybe it was.' But nobody said that to me.[159]

King offers a contrasting vision of the relationship between basic science research and clinical medicine at the point when BRCA1 was discovered in 1994, describing how the clinical translatability of gene mutations was not an explicit priority for researchers working to find the breast cancer gene. On the contrary, King explains how the clinical trajectory of BRCA1 did not feature in her personal realm of what "was possible" at the time, and while it seems reasonable to her now, "nobody said that to me [her]." Considering the context of the discovery of BRCA1, undertaken as a "race" and a "competition" by geneticists and entrepreneurs to secure patenting rights to gene mutations, King's comments suggest that the "translational" component of the research was, at best, a tacit apprehension of the clinical utility of the gene mutation. Meanwhile, capitalizing on the clinical potential of the BRCA genes was an explicit goal for some researchers, such as the team that worked with Myriad Genetics to clone BRCA1 in 1994.[160] Two years later, in 1996, BRCA1 and a recently discovered BRCA2 were linked with a genetic test through Myriad Genetics. However, Myriad's overprotective patenting rights inhibited the

[159] Alice Park. **"**Lessons From the Woman Who Discovered the BRCA Cancer Gene." *Time*, June 2nd, 2014.

[160] In their abstract, Miki et al. first emphasize how the discovery of the BRCA1 gene can be used to improve the diagnosis of breast and ovarian cancer, and from which the second sentence discusses its contribution to basic science research, appearing as an important, but not "leading" claim about the impact of the finding: "Identification of BRCA1 should facilitate early diagnosis of breast and ovarian cancer susceptibility in some individuals as well as a better understanding of breast cancer biology" (1994: 66). Miki, "A Strong Candidate," 66.

development of a clinical infrastructure centered on genetic testing for women genetically at-risk for breast cancer. While the BRCA gene mutations have been "translated" to the clinic, this principle of gene discovery did form the common worldview of researchers at the time. In translational research practices, the "translatability" of knowledge is a precedent for the discovery of gene mutations, working alongside developments in post-genomics that demand the discovery of gene mutations with proven biological functions, and informed by the demands of patient advocacy organizations who have, in simple terms, had enough with genomic research that does not lead to treatments. Arguably, it is an act of "retroactive description"[161] of past events from the position of the present that the discovery of BRCA1 and 2 meets the definitions of the NIH as a translational research effort. What can we then make of this present, the one that is laid over the past like a silk-screen, imprinting an image that comes to be naturalized as a historical fact of how these scientific developments proceeded?

The value ascribed to the function of genes, and the clinical utility of genomic discoveries, represents an emergent "epistemic virtue" held by scientists that is informing how genetic cancer research is being conducted. The historians Peter Galison and Lorraine Daston define "epistemic virtues" as a set of norms and ethical values that are internalized by the scientist, and which are then operationalized in the everyday practices of scientific work.[162] Epistemic virtues are tied to practiced ways of classifying and representing reality,

[161] The philosopher Ian Hacking employs the term "retroactive redescription" to describe the process by which past experiences are re-described using medical categories and pathologies from the present day. Importantly, Hacking reminds us of the political dimension of memory, arguing that the past is "indeterminate," and that it is not only re-described, but is also re-experienced in relation to the dominant sensibilities and agendas of the present. From Ian Hacking. "An Indeterminacy in the Past," in *Rewriting the Soul: Multiple Personality and the Sciences of Memory* (New Jersey: Princeton University Press, 1995). 234-257.

[162] Lorraine Daston and Peter Galison. "Epistemic Virtues," in *Objectivity*. (Cambridge" MIT Press, 2007). 39-41.

conditioned by ideals and values held about some aspect of existence being researched. For example, Daston and Galison note how, in the nineteenth century, the development of photography inspired an epistemic virtue of "mechanical objectivity," that is, a view of the scientist as an external agent working to capture an "objective" and individuated representation of the external world.[163] Objectivity is not a fixed and stable concept, but is shown to mutate with new technologies and shifting moral values.

While the Human Genome Project used physical mapping to locate the relative position of genes on segments of chromosomes, the integrative approach of the Cancer Genome Atlas employs multiple epistemic "platforms" to analyze tumour samples: these include emergent technologies that trace the functional expression of genes (mRNA expression) and older techniques such as immunohistochemistry, a tool that identifies tissues based on the bonding of antigens and antibodies. Beyond locating genes, the new wave of sequencing technologies are capable of producing integrative knowledge of the functional relationships between genes as they interact in a larger cellular network. These technological developments are met with emergent systems for classifying and representing disease, moving from physical maps of single-sited genes to multi-gene images that depict the functional expression of genes, equivalent to the artistic shift from the technique of pointillism to the documentation of movement in the style of expressionism in the twentieth century.

Translational research emerges as a new rationale for conducting genomics, producing scientific knowledge that is "…converging on a set of unifying principles that link apparently disparate diseases through common biological pathways and therapeutic approaches."[164] In the quest for new "unifying principles," translational research is

[163] Ibid., 20.
[164] Zerhouni, "The NIH Roadmap," 2003.

producing a new rulebook for "making sense" of the complexity of (post)-genomic science. Translation research, beyond being carried out merely as an economic or political agenda, is also an epistemological move that proceeds with new rules and conditions for knowledge-making. Translational policies determine the limits of biomedical knowledge production, acting as what Michel Foucault terms as a "discursive formation," that is, a system in which discursive statements are formed and transformed, setting the conditions of possibility for what can and cannot be said. Driven by these new "principles of unification," translational research possesses a set of rules that condition the appearance of disease objects, and from which the following sections will trace out the linguistic and perceptual codes that are applied to "read" the changing relationship between diseases, genes, molecules, and organisms.

4.1.2. The Epistemic Things of Translational Research: Forging a New Pathway

Gene mutations have been the much-sought after objects of biomedical practices unified under the banner of the New Genetics, and with laboratories and private biotechnology companies competing to patent these gene-things on a global scale. Gene mutations, while still being discovered and catalogued in large-scale projects such as the Cancer Genome Atlas, have taken on a new role in translational research endeavours. The David H. Koch Institute for Integrative Cancer Research at MIT (The Massachusetts Institute of Technology) is a collective that draws together clinicians, biologists, and engineers researching translational approaches to cancer treatment. Echoing the future direction of the Cancer Genome Atlas, the Koch Institute acts as a translational enterprise that prioritizes the discovery of genes with a demonstrated biological function.

The gene, and the theory of Mendelian genetics, is re-imagined in the practices of translational research. One oncologist who specializes in genomics at MIT analogizes the

process of cataloguing gene mutations to "…coming up with a parts list. You need to have a parts list of what's broken before you can think in engineering terms of how you fix this problem."[165] Employing an industrial analogy, the researcher envisions genes as "parts" that can be used to fix the problem that is disease. The case study presented by the MIT researcher is the development of a gene-targeted therapy for ovarian cancer that began with the collection of "200 or more genes" that were then sorted, and from which certain genes were selectively silenced to "...understand their function within a tumor's molecular machinery."[166] The machine metaphor, and the image of the scientific engineer, is continuous with the vision of biological life and disease in the gene-centered practices of the New Genetics.[167] Framing cancer as a "machine" that can be repaired with the "problem-solving expertise of engineers"[168] reinforces a view of the organism as a series of mechanical elements that can be unfixed and reassembled following feats of scientific ingenuity. However, while genes formed the pillars of research into Mendelian gene disorders, the director at the Koch Institute suggests that genes have a different role in the "machine" of disease, describing how MIT researchers are trained "…to think about complexity and network behavior, and [this] allow[s] them to do mathematical and computational modeling that's more sophisticated than what typically trained biologists do."[169] The emphasis placed on "complexity" and "networks" suggests that the discovery of single genes is not an end-goal, but is a sign-post leading to the generation of more knowledge about cancer from a systems biology approach. Dwelling on this point, how might genes take on different roles in new experimental procedures?

[165] Lauren Clark. "A New Era in Cancer Research." *Spectrum*, Winter 2011. Para. 11.
[166] Ibid., para. 12.
[167] Conrad, "A Mirage of Genes," 1999.
[168] Clark, "A New Era in Cancer Research," para. 4.
[169] Ibid., para. 4.

The preceding question is illustrated in the debates that followed the discovery of the structure of DNA by the geneticists James Watson and Francis Crick in 1953. The discovery of the structure of DNA, historicized as the "birth of molecular biology," has been eclipsed by more immediate questions of the mechanistic role of DNA damage and repair. One researcher argues that "…the aesthetic appeal of the DNA double helix initially hindered notions of DNA mutation and repair, which would necessarily interfere with its pristine state."[170] While the repair mechanism in plants was known long before the discovery of the structure of DNA, the researcher continues on to explain how "…even at the time the DNA double helix was unveiled, its 'pathology' and the biological consequences thereof were far less compelling problems than deciphering the genetic code or understanding the essential features of DNA replication."[171] Why did the mechanism of DNA repair, a question that has become so vitally important to researchers in the present, not act as a central question for Watson and Crick's research? Analyzing the anecdote, the "epistemic thing" of Watson and Crick's search was the structure of DNA itself, that which is presently "unknown" to scientists and what drives experimental research towards its discovery.[172] Scientific discovery is built on existing structures of experimentation, determining what type of research "problems" are worth funding and investigating at a given moment in the life sciences.

The genes that form the basis of molecular inventories or "parts lists" are not the central objects of scientific interest in post-genomic research efforts, but act as instruments that can be used to generate new knowledge about the cancer genome. Examining the shifting status of laboratory artefacts offers insight into how assemblages of biomedical entities, techniques, and practices act as what Hans-Jörg Rheinberger refers to as

[170] Errol C. Friedberg. "DNA Damage and Repair." *Nature* 421, 6921 (2003): 436-40.
[171] Ibid., 437.
[172] Rheinberger, "Consistency from the Perspective of an Experimental Systems Approach," 312.

"experimental systems" that can be translated to new arenas of research to produce novel forms of biotechnological innovation.[173] Employing the concept of the "experimental system," it is possible to imagine how single Mendelian genes like the BRCA pair, once an "epistemic thing" for researchers working on the problem of hereditary breast cancer, can become unfixed and mobilized as "parts," or, "technical objects"[174] in the molecular assembly line of translational research. If researchers are no longer searching for Mendelian genes, what exactly is it then that they are looking for?

4.1.3. The Mutation of a Scientific Fact-Object: Splitting the BRCA Pair

Decentering the "driver gene" as the central object of scientific investigation, the cancer genome is represented in the images of "clusters," "pathways," and "networks" that depict the functional expression of genes, and the interaction between genes as nodes within a larger cellular system. The National Cancer Institute defines a pathway as a "conceptual entity," or, an abstract set of qualities used by researchers to identify "…a set or series of interactions, often forming a network, which biologists have found useful to group together for organizational, historic, biophysical, or other reasons."[175] Burgeoning research interest in the pathways that genes operate within represents the adoption of a mechanistic approach in translational scientific practices. These include "…classic metabolic, regulatory, signaling, drug, and disease pathways"[176] that have a defined

[173] Ibid., 310.

[174] Ibid., 312.

[175] "NCI Thesaurus," National Cancer Institute, 2016. Accessed Online at https://ncit.nci.nih.gov/ncitbrowser/.

[176] " "Pathway Ontology," BioPortal, 2016. Accessed Online at https://bioportal.bioontology.org/ontologies/PW.

function in the normal human body. However, while drug pathway is listed as a distinct entity, research into the functional pathways operating in cancer tumours is driven by the "clinical fact" of these pathways responsiveness to treatment.[177]

Engaging in citational analysis of research articles published through the *Web of Science* database from 2000 to 2009, an interdisciplinary team of social science researchers headed by Pascale Bourret examined the emergence of "BRCAness," a concept that links the breast cancer genes—BRCA1 and 2, with cases of sporadic breast cancer.[178] Bourret et al. trace the concept of BRCAness to a highly-cited opinion piece that was published in Nature Reviews Cancer in 2004, "Hallmarks of 'BRCAness' in Sporadic Cancers." The article is written by a translational research team composed of oncologists Nicholas Turner and Andrew Tutt, and molecular biologist Alan Ashworth, researchers who have gone on to contribute to studies published in the Cancer Genome Atlas. BRCAness is based on a similar molecular phenotype exhibited by BRCA breast cancers and some forms of sporadic cancer, correlated with a shared DNA repair pathway found in hereditary and sporadic diseases. Treating the DNA pathway with a new class of drugs known as Parp INIHbitors, Bourret et al. argue that epistemic interest in druggable pathways "…signals a shift from a narrow focus on genes and mutations to the examination of the complex chains of cellular reactions in which genes and their products are dysfunctionally involved."[179] Signaling to a shift from clinical practices centered on the diagnosis of genetic risk, Bourret et al. highlight how research into the BRCA DNA repair pathway is undertaken with the goal of discovering individualized gene-drug targets for both sporadic and hereditary cancers.

[177] Nelson et al., "On Being Actionable," 2013.

[178] Bourret; Keating, Cambrosio, "From BRCA to BRCAness: Tales of Translational Research," 175-193.

[179] Ibid., 183.

Brought to light by Bourret et al., the concept of BRCAness demonstrates the epistemic elasticity of the BRCA genes, capable of forging a new relationship between hereditary and sporadic breast cancer. While BRCAness is a product of translational research, it is important to note that BRCA gene mutations are artefacts of Mendelian genetics, culminating in the combination of both gene mutations in the clinical classification of hereditary breast and ovarian cancer syndrome. In the practices of translational research, the relationship between gene mutations, including BRCA1 and 2, with common diseases, is debated based on the principle that gene mutations must have a proven biological function. In Turner et al's article from 2004, the relationship between BRCA1 and BRCA2 becomes an explicit point of discussion, if not a kind of semiotic dissection of the gene-twins from which the authors re-evaluate the relation between BRCA1, BRCA2, and the emergent concept of BRCAness.

Placing epistemic primacy on the functional properties of gene mutations and the pathways they act in, BRCA1, to the exception of BRCA2, is praised for its "broad cellular role" that includes, but is not limited to DNA-damage repair.[180] Describing the biological landscape of breast cancer, Turner et al. explain how "…in contrast to the distinctive phenotype of familial-BRCA1 tumours, using current techniques it has been hard to define histopathological characteristics that distinguish familial-BRCA2 tumours from sporadic cancers."[181] The authors highlight the phenotypical differences between BRCA1 and BRCA2 tumours on a histopathological level, arguing that BRCA1 tumours possess a unique signature compared to sporadic, or, non-hereditary cancer tumours. However, BRCA2, tumours are indistinguishable from sporadic cancer tumours. The phenotypical difference between BRCA1 and 2 is explained as the result of molecular differences

[180] Nicholas Turner; Andrew Tutt, and Alan Ashworth. "Hallmarks of 'BRCAness' in Sporadic Cancers." *Nature Reviews Cancer*, 4, 10 (2004):814-819 (1-6).

[181] Ibid., 2.

between the pair, and from which the "…BRCA1 mutation might impose a defined gene-expression pattern mandating basal characteristics; this seems likely to result from the loss of BRCA1 function(s) other than those involved in the maintenance of genomic instability."[182]

The ontological and epistemological status of the BRCA genes is subject to variation within and across experimental contexts—neither determinately epistemic or technical objects, they act as "test objects" that may aid in the generation of new knowledge about Mendelian genes (epistemic objects), while in other situations they are the medium of experimentation that leads to the discovery of new knowledge and epistemic objects (technical objects), such as molecular pathways. The molecular pathway, more than just an object-in-waiting, functions as an "epistemic object" and *sublime unknown*, that which cannot yet be completely understood or apprehended as it exists on the cusp of available knowledge. The molecular pathway holds true to its name, forging a "path" between hereditary and sporadic cancers, and acting as the frontier of genetic research into breast cancer. The BRCA genes were once this frontier, inspiring the curiosity and frustration of the countless researchers working to isolate them in labs across the US. However, as technical-leaning objects, the BRCA genes find new roles in the experimental procedures of translational research.

Further, scientific interest in the biological mechanisms of gene mutations invites a new understanding of the relationships between genes and existing medical classifications. While BRCA2 is still cited alongside BRCA1 in the definition of "BRCAness," the function of BRCA1 is described as "diverse" and that of BRCA2 as "restricted," and with Turner et al. citing further limitations of BRCA2 that includes

[182] Ibid., 2.

research gaps in DNA methylation studies.[183] The BRCA gene mutations, melded together in the clinical classification of hereditary breast and ovarian cancer syndrome, are like the androgynes of Plato's *Symposium,* split into two based on new rules for investigating the functional role of gene mutations in common diseases. While the druggable molecular pathway remains the primary object of epistemic interest for translational scientists, BRCA1, demonstrated to be more epistemically adaptable to translational studies of genetic cancer, at times takes on an epistemic role in studies of the relationship between hereditary and sporadic breast cancer; to the contrary, BRCA2 is described as a limited tool for investigations of the mechanistic operations of genetic breast cancer, and operates as a technical object in translational research practices.

4.2. The Epistemic Value of Rare Genes

The degree to which genetics contributes to complex diseases such as cancer, hypertension, diabetes, and osteoporosis has been subject to debate amongst scientists since the turn of the twentieth century.[184] Termed the "rare versus common allele hypothesis," the debate has been undertaken by two intellectual camps—the Mendelians and the Biometricians—with the former arguing that "…discrete units of heredity, such as Mendelian-segregating genes could not, it seemed to them, explain the continuous range of phenotypic variation seen in real populations."[185] In contemporary debates, the view of complex disease from a Mendelian perspective, focusing on single, heritable genes with a

[183] Ibid., 1.

[184] NJ Schork; SS Murray; KA Frazer, and EJ Topol. "Common vs. Rare Allele Hypothesis for Complex Diseases." *Current Opinion in Genetics and Development* 19, 3 (2009): 212-219.

[185] Ibid., 212.

high penetrance, co-exists with the non-deterministic, "…more polygenic or multifactorial forms of inheritance of the type envisioned by the Biometricians."[186]

Since the discovery of BRCA1 in 1994, Dr. Mary-Claire King continues to vocally support using genetic knowledge and technologies to confront medical and social issues, including advocating for genetic testing for all women over the age of 30, regardless of their carrier status. King's genetic activism extends to issues on a global political scale, including use of mitochondrial DNA tests to reunite the children who were "disappeared" from their parents in the Argentinian conflict of the 1980s. Most recently, King has used her genetic thesis to net findings in the study of complex diseases such as schizophrenia.[187] Forging a unique career path through the fields of mathematics, evolutionary genetics, and hereditary cancer research, King's recent work on complex diseases offers a platform to examine how King's own commitment to the theory of the Mendelian gene has developed in the post-genomic era.

Appearing in the journal *Cell* in 2010, "Genetic Heterogeneity in Human Disease" is a highly-cited article published by Dr. Mary-Claire King, in collaboration with neuro-psychologist John McClellan. Written as an essay, King and McClellan's article takes an opinionated stance on the ability of genome wide association studies (GWAS) to discover genes for complex illnesses. GWAS is a method that has been used since the completion of the Human Genome Project to discover common genetic variations by comparing sets of DNA between groups of people. However, while these studies have produced "…previously unreported variants in healthy individuals, including single base pair substitutions, small insertions and deletions, and larger copy number mutations,"[188] most

[186] Ibid., 212.

[187] Jon M. McClellan, Ezra Susser, and Mary-Claire King. "Schizophrenia: A Common Disease Caused by Multiple Rare Alleles." *The British Journal of Psychiatry* 190, 3 (2007): 194-199.

[188] Jon McClellan and Mary-Claire King. "Genetic Heterogeneity in Human Disease." *Cell* 141, 2 (2010): 210.

of these variations do not have a proven function. King and McClellan's argument is summarized in the abstract proceeding the article:

> Strong evidence suggests that rare mutations of severe effect are responsible for a substantial portion of complex human disease. Evolutionary forces generate vast genetic heterogeneity in human illness by introducing many new variants in each generation. Current sequencing technologies offer the possibility of finding rare disease-causing mutations and the genes that harbor them.[189]

The first sentence, "Strong evidence suggests that rare mutations of severe effect are responsible for a substantial portion of complex human disease," employs the verb "suggests" to introduce a speculative claim about the role of rare gene mutations in complex diseases. The "strong evidence" that backs the claim is drawn from the field of evolutionary genetics, and from which the second sentence acts as a denotative sentence about the concept of genetic heterogeneity and its role in producing new disease variants. The stage is set to introduce another tentative claim, that sequencing technologies (in contrast to GWAS) "offer the possibility" of discovering rare gene mutations associated with complex diseases. The speculative claims found in the first and last sentence are reinforced by the high-level "facticity" of the middle sentence, suggesting that the established "fact" of genetic heterogeneity will be experimentally translated to the uncertain question of what role rare genetic variants have in complex diseases.

The abstract is common to that found in a formal scientific review article: a knowledge claim is being made based on empirical findings from a collection of case studies, including the identification of rare gene variants for breast and ovarian cancer, inherited deafness, autism, and schizophrenia. However, alongside references to empirical research in the life sciences and clinical cancer research journals, the essay includes a literary quote from the Russian author Leo Tolstoy: "Every unhappy family is unhappy in

[189] Ibid., 210.

its own way," wrote Tolstoy in Anna Karenina. Tolstoy was reflecting on the individually unique nature of human tragedy."[190] In what follows, the pair go on to relate the individual nature of tragic experience to a similar principle underlying the etiology of complex human diseases from an evolutionary perspective. The inclusion of the literary reference can be contextualized by examining the stylistic constraints of the scientific essay as a genre. Writings under the grouping of "Essay" often include reviews of recent technical or theoretical innovations, personal reflections and opinions on a topic and/or on the progress of the field, and arguments for the purported significance of a proposed approach to a topical question.[191] While scientific review articles can be limited to a small sub-set of scientists working on a specialized topic, essays are often written for both scientists and a wider public audience, and "take an imaginative approach to a provocative question, with an engaging though rigorous investigation of the problem."[192] In this sense, the essay in *Cell* offers a vantage point to examine how King and McClellan "imagine" new possibilities for rare gene mutations, extending beyond their demonstrated role in hereditary breast and ovarian cancer.

4.2.1. Rewriting a Mendelian Disease Etiology: The Anna Karenina Hypothesis

Referencing a line from Leo Tolstoy's novel, *Anna Karenina*, King and McClellan's theory of disease etiology rests on the claim that "…this principle [individuality] also captures the misfortune of human disease. That is, from the perspective of genetics, we suggest that complex human disease is in fact a large collection of

[190] Ibid., 210.

[191] PlosBiology. "Other Article Types." Accessed Online, March 2016 at http://journals.plos.org/plosbiology /s/other-article-types

[192] Ibid., 2016.

individually rare, even private, conditions."[193] In interview, King has referred to this claim as her "Anna Karenina Hypothesis," analogizing the experience of tragedy and suffering, unique to each individual, to the study of complex diseases which are also unique in that they can be associated with individual-specific gene mutations. The Anna Karenina Hypothesis builds on the Mendelian view of complex disease, emphasizing the causal role of rare gene mutations, and underemphasizing the multiple factors that may contribute to the development of complex diseases.

Drawing on theoretical concepts from the fields of evolutionary biology and population genetics, King and McClellan describe how complex disease is characterized by "molecular heterogeneity," the view that disease types are not uniformly the same, biologically, but are individualized by genetic markers specific to the tumour. To support this claim, King and McClellan cite the "Out of Africa" hypothesis, that is, that most human differences first appeared before populations began migrating out of Africa 50,000-60,000 years ago, and from which most genetic variation is shared by the majority of the population. Rather paradoxically, King and McClellan claim that rare, disease-causing alleles are recent variations occurring at the micro-scale of populations and individual families, and while they are "rare," they are responsible for most common diseases.[194]

To support their argument, King and McClellan engage in a literature review that encompasses some of the major and a few secondary projects of their careers, including studies of inherited hearing loss and lipid metabolism, and McClellan and King's work on neuropsychiatric disorders such as autism and schizophrenia. Despite the diversity of these efforts, they cite King's research on hereditary breast and ovarian cancer as the "model" for studying complex diseases, explaining how the genetic heterogeneity of breast cancer

[193] McClellan and King, "Genetic Heterogeneity," 210.
[194] McClellan and King, "Genetic Heterogeneity," 210.

"…results from any one of thousands of different mutations in any one of multiple different genes, but all the implicated genes encode proteins in related pathways."[195] Listing several genes associated with an inherited susceptibility to breast cancer: BRCA1, BRCA2, p53, PTEN, CHEK2, PALB2, ATM, BRIP1, CDH1, and STK1, King and McClellan explain how each possesses "individually rare" genetic mutations that lead to errors in DNA replication and repair, causing cancer tumours to develop.[196] It is not the genes themselves that take centre stage, but their mechanistic role in repairing DNA damage, and the shared "pathways" that exists between these genes. In this sense, models are not only reference examples for scientific work, but also act as instruments that researchers use to move from what is known about a certain area of inquiry to questions of what is currently unknown. However, it is also important to remember that models, as argumentative structures, can be used to promote a certain view of how research should be conducted, masking the criticisms, debates, and contexts that made the "model" possible to begin with. The impact of the discovery of BRCA1/2 is felt beyond the domain of hereditary cancer research, providing researchers with a "blueprint" to think through how rare genetic mutations contribute to common human diseases, while also reinforcing a genomic hold on the diagnosis, management, and treatment of disease.

4.2.2. From Gene-as-Risk to Gene-as-Function: Making Mutations with "Biological Relevance"

For King and McClellan, discovering the role that rare alleles play in the development of disease represents a "paradigm shift" in the field of human genetics.[197] Referencing the debate between rare vs. common alleles, King and McClellan explain how

[195] Ibid., 211.
[196] Ibid., 211.
[197] Ibid., 213.

the latter perspective has endorsed a view of disease as the combinative effect of many common alleles, that, on their own, "…confer only a small degree of risk, with no one variant sufficient to cause the disorder."[198] From an evolutionary standpoint, King and McClellan argue that common variations have been subject to the process of natural selection, and so deleterious variations—that is, those that cause disease, are likely sourced from new genetic variations that have not been subject to the same evolutionary pressures. In critique of genome wide association studies (GWAS) that identify common variants, King and McClellan support a determinist view of the Mendelian rare gene:

> To date, genome-wide association studies (GWAS) have published hundreds of common variants whose allele frequencies are statistically correlated with various illnesses and traits. However, the vast majority of such variants have no established biological relevance to disease or clinical utility for prognosis or treatment…More generally, it is now clear that common risk variants fail to explain the vast majority of genetic heritability for any human disease, either individually or collectively.[199]

The authors critique genome-wide association studies for identifying common risk variants with no proven biological function, and/or clinical significance. Most human variation is "ancient," and so, recent deviations are located not in these "common" genes or genetic sites, but in rare genetic mutations that represent recent aberrations in human DNA.[200] The emphasis placed on the function of genes, and the clinical utility of gene mutations, reinforces the principle of translational research: to produce knowledge of genes and gene mutations that is "clinically-actionable."[201] Critiquing the common disease, common variant model, King and McClellan bring into question the ontology of the gene as it has been researched in genome-wide association studies, questioning the association

[198] Ibid., 213.
[199] Ibid., 213.
[200] Ibid., 210.
[201] Nelson et al., "On Being Actionable," 213.

between discovered risk variants and medical disorders in the absence of a "functional link" between them:

> It has become common practice to describe risk variants derived from GWAS as "in" a gene, suggesting that the gene harboring the variant influences the disorder. But "in" in this context has a purely physical meaning: that the risk variant lies somewhere in a genomic locus that also includes a gene. In the human genome, approximately 35% of base pairs lie in introns, and therefore approximately the same proportion of SNPs lie "in" genes. In this context, "in" is a tautology, not a proof of biological relevance.[202]

King and McClellan question the causality of risk variants that are assumed to be somewhere "in" a gene, suggesting that simply locating the physical location of a risk variant "in" a gene does not prove that it has a demonstrated function. In other words, to associate a research finding with, and "in" a gene does not grant it an *a priori* importance, and to do so is, as King and McClellan argue, a "tautology." The commentary offers a subtle criticism of researchers' treatment of the gene as an unquestioned "truth," a powerful sign that, when evoked in a scientific argument, provides a degree of legitimacy to statements about biological life.

By questioning the functional association between genes, and the diseases these genes claim to harbour, King and McClellan argue for an alternative approach to gene discovery in the study of disease from which "biological relevance must be established before a mutation can be causally linked to a disorder."[203] The problematic discovery of genes with no known function that characterized the Human Genome Project is a lesson learned for the new generation of genetic research. Employing sequencing technologies, King and McClellan propose that functional mutations can be identified by tracing the inheritance of disease alleles in affected families, as well as discovering additional functional mutations in unaffected family members. Just as King sought to discover the

[202] McClellan and King, "Genetic Heterogeneity," 215.
[203] Ibid., 216.

missing piece of the puzzle that was hereditary breast cancer—the heritable gene, the problem of more complex conditions can also be solved by finding the "missing hereditability"[204] of the disease.

Importantly, King and McClellan's argument reinforces the analytical viability of the Mendelian gene and Mendelian laws of inheritance, but responds to current debates about the functional role of genes and their clinical significance. Expanding Mendelian genetics from the study of single-sited gene disorders to more complex diseases, assumed to be multifactorial in nature, King and McClellan reinforce the causal role of the gene in the pathogenesis of disease. Responding to the non-determinist views of genetics, the authors acknowledge that "variable penetrance, epistasis, epigenetic changes, and gene-environment interactions will complicate these efforts," but playfully assert their research confidence by claiming that "it will be fun to sort out."[205] Just as King argued that the causal role of BRCA1 would be proven despite the "epidemiological complications" of breast cancer, the forward-looking statement presented in the essay asserts that the causal role of the gene will have to be proven again, in this new disease problem.

Moving beyond the discovery of "tautological" genes, that is, genes discovered without a proven function, King and McClellan claim that "the ultimate goal of gene discovery in complex disease is to identify and characterize biological pathways and processes critical to the disorder."[206] Notably, the quest to discover common "pathways" within and between diseases has altered how genetic mutations are "made" in current biomedical research initiatives. Re-imaging the gene as a node in a larger network, King and McClellan claim that "defining the ways in which biological networks for common

[204] Schorck et al., "Common vs. Rare Allele Hypothesis," 217.
[205] McClellan and King, "Genetic Heterogeneity," 216.
[206] Ibid., 216.

disease are impacted by mutation will contribute substantially to the understanding of their pathology and provide important targets for intervention."[207] In King and McClellan's version of the translational gene mutation, the source of disease is still tied to a singular, internalist cause: a dysfunctioning biological structure. The biological mechanisms that drive disease at the sub-cellular level of mutations acting in molecular pathways are causally linked to pathway-dependent drugs to treat them, and with the mutation then simultaneously reproducing both its biological and clinical relevance.

Translational researchers turn the Mendelian gene like a kaleidoscope, observing new shapes and patterns that were not in critical view in the practices of the New Genetics. Working from Rheinberger's dialectic between the epistemic and the technical components of experimental procedures, the Mendelian gene occupies a transient status between the *known* and the *unknown*: as a known object, like a good book, it can be read again and again for new insights (what is currently *unknown* or underemphasized). However, also like a good book, it can be referenced as an authoritative source on the state of knowledge in the life sciences (what is *known*). While Mendelian genes were the desired epistemic objects of the New Genetics, they are crafted from statistical knowledge of genetic risk, a point of interrogation for basic science researchers who argue that genes are defined based on their proven biological function. Consequentially, the Mendelian gene is re-defined in the post-genomic language of its "function" and mechanistic druggability, remaining an epistemic object in translational practices centered on the discovery of the functional gene mutations that characterize complex disease. However, the Mendelian gene also becomes a *medium* of investigation in post-genomic science, acting as a "technical object" to discover other *unknowables*: primarily, the molecular pathways shared between disease types.

[207] Ibid., 216.

Chapter 5. Translational Ontologies: Re-Assembling Disease Entities and the Breast Cancer Patient

5.1. A Cultural Reading of Disease: Between an Anatomical and Molecular Atlas of the Body

For us, the human body defines, by natural right, the space of origin and of distribution of disease: a space whose lines, volumes, surfaces, and routes are laid down, in accordance with a now familiar geometry, by the anatomical atlas. But this order of the solid, visible body is only one way—in all likelihood neither the first, nor the most fundamental—in which one spatializes disease. There have been, and will be, other distributions of illness.

-Michel Foucault, Birth of the *Clinic*[208]

But when we stratify these diseases and name them properly, these diseases will lose their geographic names.

-Chairman of Genomic Incyte, Randy Scott, in Interview with *Science*[209]

Developments in genetic knowledge and technologies have impacted the classification, management, and treatment of cancer in the clinic. Following the completion of the Human Genome Project, the use of increasingly sophisticated and cost-effective genetic sequencing technologies has become a routine practice in clinical cancer research, informing how hypotheses are formulated, experiments are conducted, and results are verified in the context of the clinical trial.[210] In the practice of histology, cancer has been diagnosed based on the observation of abnormalities at the microscopic level of tissues and

[208] Michel Foucault. *The Birth of the Clinic: An Archaeology of Medical Perception.* (New York: Routledge, 1976[1963]).

[209] Peter Gwynne and Gary Heebner. "Technologies in Cancer Research: Progress at the Molecular Level." *Science*, March 6th 2001.

[210] Nelson et al., "On Being Actionable," 2013.

cells. More recently, this has come to include a molecular tool-set and etiological framework that re-locates disease to the sub-cellular level of genes and molecular structures. The medical object of cancer, defined by tissue type, has increasingly come to be redefined in molecularized terms, a move that does not only signal to a new representational or classificatory practice in oncology, but also holds an ontological premise.

Historical, philosophical, and anthropological investigations of the "reality" of medical categories and objects have revealed the implicit cultural values that underpin objective, expert knowledge.[211] Michel Foucault's archaeological investigations of medical knowledge have been particularly insightful, demonstrating how medical facts and objects are formulated in relation to shifting regimes of thinking and acting on disease as a social category. In the preface to *the Birth of the Clinic*, Michel Foucault outlines the objects of the not-quite-archaeology, not-quite-genealogy: "this book is about space, about language, and about death; it is about the act of seeing, the gaze."[212] Foucault, a careful cartographer, charts the emergence of new geographies of disease with the development of pathological anatomy in the nineteenth century, describing how perceptual codes were developed to read the body and disease in the language of the clinic. Central to Foucault's project is demonstrating the interaction between perception and language, framing his analysis around the oppositional pairings of words/things, seeing/saying, and the invisible/visible

[211] There is an extensive body of research dedicated to anthropological and sociological investigations of ontology in science and medicine, including early works such as Emily Martin's "The Egg and the Sperm: How Science Has Constructed a Romance Based on Stereotypical Male-Female Roles." *Signs* 16 3 (1991): 485-501, and elaborations of actor-network theory such as Annemarie Mol's *The Body Multiple: Ontology in Medical Practice.* (Durham: Duke University Press, 2002). Ian Hacking's approach of 'historical ontology' has shed light on how medical knowledge, and in particular, psychiatric knowledge produces 'kinds' of people who self-identify with the medical classifications they are given. See: Ian Hacking. "The Looping Effects of Human Kinds." *Causal Cognition: A Multidisciplinary Debate.* (New York: Oxford University Press, 1995): 351-394; *The Social Construction of What?* (Cambridge: Harvard University Press, 1999).

[212] Foucault, *Birth of the Clinic*, XI.

to explain how the discursive development of clinical knowledge produced a new ontological order in medical practice. Employing literary theory, Foucault claims that the intimate relationship between words and things is expressed in a form of analogical reasoning in medicine, a way of determining the relations between symptoms and diseases, and from one disease to another. In the classificatory medicine that dominated medical practice in the eighteenth century, Foucault explains how disease-objects were viewed as "nosological essences" external to the body, possessing their own unique and essentialized form.[213] The clinical gaze is a perceptive apparatus that transforms how disease is perceived and classified, expressed in a new "fruitful analogy" that relates symptoms no longer as signs of disease as essentialized forms, but to the functional interactions in and between organs.[214]

Foucault explains how the act of reigning in the disease and fixing it in the corporal space of the body first appears with the practice of examining or "opening up" corpses in the medical autopsy, introducing a form of medical knowledge where life, and its normal processes, can be learned from observing the body in a state of disease and death: "It [disease] is no longer an event or a nature imported from the outside; it is life undergoing modification in an inflected functioning."[215] The medical cartography of the corpse was transposed onto the living body in the clinic, marking a shift from the "garden of species" where nosological disease roamed freely to a disease chained to the body in pathological anatomy: "it is no longer a pathological species inserting itself into the body wherever possible; it is the body itself that has become ill."[216] For Foucault, the emergence of clinical medicine possesses both epistemological and ontological implications, described as the

[213] Ibid., 100.
[214] Ibid., 100.
[215] Ibid., 153.
[216] Ibid., 136.

new relationship between "seeing" and "saying," and we might also add, "doing" disease.[217] The medical gaze moves to a new depth as disease is implanted below the surface of the skin, at the three-dimensional level, to the examination of tissues, and the functional interactions between organs.[218]

With special attention given to the spatialization and localization of disease, Foucault's medical geography relays the re-organization of medical experience to the level of historically-mediated perception. In contrast to the origin myth of clinical medicine as the advent of an empirical practice where symptoms are observed through objective observation, Foucault describes a form of medical thought taking place at the sensorial plane of "…colour, consistency, texture, [with] a preference for metaphor rather than measurement."[219] Applying a semiotic analysis to examine the connections between symptoms, disease categories, and bodies, Foucault explains how the clinic instead introduced a new structure of thought to medical practice, re-locating disease to the interior topography of tissues and organs. With the development of pathological anatomy, "…the whole relationship of signifier to signified, at every level of medical experience, is redistributed," culminating in a new relationship "...between the symptoms that signify and the disease that is signified, between the description and what is described, between the event and what it prognosticates, between the lesion and the pain that it indicates, etc."[220]

Cancer has been researched and treated according to its location within this topography of tissues. Histology, the modern practice of classifying disease by tissue-type and cell-type, is a direct extension of the "…medicine of organs, sites, [and] causes"[221] of

[217] Mol, *The Body Multiple*, 2002.
[218] Foucault, *The Birth of the Clinic*, 135-136.
[219] Ibid., 169.
[220] Ibid., xviii-xix.
[221] Ibid., 122.

pathological anatomy, initiated with Parisian medical practitioner Marie Bichat's physical observation of pathological tissues in the autopsy. In the practice of histology, the anatomical region of the tumour provides a primary site of origin for the disease—a beginning that can be returned to by the clinician if the disease undergoes metastasis, a term that denotes the process by which the disease "dis-places" itself and progressively moves to other regions of the body. The development of the disease ("pathogenesis"), expressed in a qualitative series of events, is traced to the originating anatomical site of the tumor. For example, lung cancer may spread to other parts of the body ("metastasis"), but it is the organ of the lung that acts as the biological-pathological anchor to order, classify, and treat the disease as the initial site of tumor formation.

The classificatory practices of pathological anatomy have impacted how cancer is treated. In the 1970s, the "War on Cancer" produced a vision of cancer as a singular enemy that could be attacked and ultimately destroyed using a "one size fits" all treatment: chemotherapy, a method comparable to a wartime blitz of chemical bombs being dropped on the body.[222] However, researching the biology of cancer under Nixon's administration, scientific researchers determined that cancer was actually a heterogenous collection of different diseases, and from which a single, universal treatment would likely not be found. As scientific understandings of cancer are marked by the concept of tissue heterogeneity, cancer activists have sometimes translated the heterogeneity of cancer tissue types into the language of social differences. For example, mainstream breast cancer movements have often targeted cancer as a gender-specific phenomenon, mobilizing essentialist notions of

[222] One oncologist analogizes chemotherapy to "carpet-bombing," a military technique deployed by both German and "allied" forces during World War II (Nathan 2007). Carpet-bombing is the practice of using B-52 bomber planes for intensive aerial bombing over a vast strip of "enemy" land, resulting in a high number of civilian casualties and general devastation. As Nathan explains, chemotherapy also has its casualties, describing it as an unsafe and ineffective technique that destroys as many healthy, non-cancerous cells as it does cancerous cells. David G. Nathan. "The Cancer Treatment Revolution." *Transactions of the American Clinical and Climatological Association* 118 (2007): 317–323.

femininity when advocating for research into the disease. This is illustrated in campaign slogans such as "Save the Boobies!", a statement that reduces the experience of breast cancer to the possession of organs that are valued for their sexual appeal, suggesting that it is not the woman, but her breasts that are valued.

In *the Birth of the Clinic*, spatial theory, literary theory, and semiotic analysis come together to produce a nuanced reading of disease as a discursive event, that is, as the product of shifting theoretical practices. Disease nominalisms—that is, the objects that populate medical thinking and form the basis of medical investigation, are formed by historically-specific modes of interpreting symptoms and treating diseases. Using Foucault's language, pathological anatomy is a theoretical framework that determines how the signifiers of symptoms are linked to the signified of disease. The emphasis on spatial narrativization in clinical medicine produces a view of the body as it is stratified by anatomical locales: it is a space composed of organs and tissues that act as sites for disease. Extending the geographic imaginary, the significance of the anatomical locale to the logic of disease can be related to philosopher Michel de Certeau's spatial analysis of urban landscapes in *the Practice of Everyday Life*. For de Certeau, the practice of systematic objectivity undertaken by city-planners produces the 'concept-city' or, "…a way of conceiving and constructing space on the basis of a finite number of stable, isolatable, and interconnected properties."[223] The central units of urban organization are "proper names," or, place-names such as streets, buildings, and other geographic locales. These "proper names" act as fixed and stable signifiers that direct action and order movement through the city.

[223] Michel Certeau. "Walking in the City," in *The Practice of Everyday Life.* Translated by Steven Rendall. (Berkeley: University of California Press, 1988). 94.

Relating the concept of the 'proper name' to the logic of disease, the anatomical locales of diseases like cancer—Breast, Ovary, Lung, etc.—designate, like a landmark, where to look as much as how to get to the disease. In the practice of histology, the proper name both captures and fixes the disease in an established locality—the organ—which gathers up the fragments of symptoms, and orders them in proximity to the anatomical locale. However, de Certeau claims that the order of the concept-city can be disrupted by the everyday practice of walking in the city, resisting the official 'text' of the city plan by taking short-cuts and using spaces for unintended purposes: "…these names make themselves available to the diverse meanings given them by passers-by; they detach themselves from the places they were supposed to define and serve as imaginary meeting-points on itineraries which, as metaphors, they determine for reasons that are foreign to their original value by may be recognized or not by passers-by."[224] De Certeau's counter-reading of the official "text" of urban space is useful for imagining how the spatial order of the body and disease may also come to serve alternative purposes for clinicians and patients in practice.

5.1.1. Unfixing the Disease Proper

The movement of molecular knowledge and technologies has altered how clinicians interact with the "proper names" of disease. Describing a shift from the Foucauldian "clinical gaze" to what he terms as an emergent "molecular gaze," the sociologist Nikolas Rose claims that clinical medicine is undertaken in the present with a new power to visualize "life itself" at the level of DNA.[225] For Rose, this new style of practice in the life sciences is the product of "molecularization," a process that "…strips tissues, proteins,

[224] Ibid., 104.
[225] Rose, *The Politics of Life Itself*, 14.

molecules, and drugs of their specific affinities – to a disease, to an organ, to an individual, to a species," and once unfixed from their anatomical locales, may then be "…be regarded, in many respects, as manipulable and transferable elements or units, which can be delocalized – moved from place to place, from organism to organism, from disease to disease, from person to person."[226] The process of molecularization proposed by Rose resembles de Certeau's vision of the 'concept-city,' a space where the signifiers of street-names and other locales come to have multiple significations for walkers. In the rhetoric of molecularization, the "affinities" between diseases, organs, and individual bodies with certain qualities and definitions are broken and "delocalized," and from which these biological units gain new signifying functions.

Current efforts to conceptualize and perform cancer at the molecular level are carried out under the banner of 'personalizing' cancer diagnosis and treatment. A research agenda endorsed by the National Institute of Health, personalized medicine makes the claim to pair the "right drug, with the right patient," proposing the use of targeted molecular therapies to individualize the treatment of cancer.[227] The process of individualizing disease includes employing genetic testing and sequencing technologies to pin-point the genes, molecular pathways, and other molecular properties of cancer tumors. These include the development of "smart drugs" which, compared to the "dumb drugs" of chemotherapy, are "…tumour-specific, targeted, highly-effective, and has little toxicity."[228] Speaking on behalf of the US-based pharmaceutical company Genomic Incyte that markets drugs for cancer, the chairman Randy Scott describes the potential of "personalized" approaches to cancer diagnosis: "But when we stratify these diseases and name them properly, these

[226] Ibid., 14-15.

[227] Elias Zerhouni. "Clinical Research at a Crossroads: the NIH Roadmap." *Journal of Investigative Medicine*, 54 4 (2006):171-173.

[228] Lisa Carey. "Old Drugs, New Tricks for Triple-Negative Breast Cancer." *The Lancet Oncology* 16 4 (2015): 357-359.

diseases will lose their geographic names." The geographic imaginary, and the view of disease as it is organized by anatomical locales, has come into question with the turn to personalized genomics in the mid-2000s. It is through the loss of their established classificatory power that the "proper names" of anatomical diseases permit the existence of a new form of signification, signaling towards the emergence of new disease entities.

The uptake of personalized medicine has been fueled by mounting public expectations about the potential of genetic medicine to better manage, treat, and ultimately cure most common diseases. In the aftermath of highly-publicized gene-centered initiatives such as the Human Genome Project, US publics have criticized genetic discoveries for their failure to provide improved treatments and cures for patients. The gap between basic science discoveries in genomics and their clinical application in the treatment of common diseases like cancer has become a rallying point for advocates of translational, personalized medicine. Translational science is one response to the long-standing call to "bridge the gap" between genomics and clinical medicine, operated under the premise of swiftly moving genomic discoveries from the laboratory "bench" to the waiting "bedside" of the patient. In the years following the Human Genome Project, translation research emerges as a new rationale for conducting biomedical research, producing scientific knowledge that is "…converging on a set of unifying principles that link apparently disparate diseases through common biological pathways and therapeutic approaches."[229] Translation, beyond being carried out as an economic or political agenda, is also an epistemological move that proceeds with new rules and conditions for knowledge-making.

Acknowledging the complex interaction between shifting disease categories and cultural values, the preceding section will examine how the object of disease is being understood and deployed by Stand Up to Cancer, a patient group advocating for

[229] Zerhouni, "the NIH Roadmap," 2003.

translational, personalized cancer research. A semiotic analysis of the materials published through Stand Up to Cancer will illuminate the rhetorical construction of cancer in the texts being analyzed, and how the objective of translational research is framed by the organization. With the move to 'delocalize' disease in translational research, the following analysis will provide insight into how patient activists are organizing themselves with the introduction of molecular definitions of disease. Previously, patient groups for cancer research have organized around an identification with anatomical diseases that affect certain members of the population. For example, 'breast cancer' is marked as a 'women's disease' even though men may also develop breast cancer. Close textual analysis of documents produced by Stand Up to Cancer will provide a vantage point to examine how the 'proper names' of the disease (breast cancer, lung cancer, ovarian cancer, pancreatic cancer, etc.) are performed by the organization, and which, as signifiers, may be evoked and rearranged to produce new forms of signification in the logic of translational, personalized medicine.

5.2. Patient Advocacy Groups in the Era of Translational Genetic Medicine: Stand up to Cancer (SU2C)

Patient advocacy groups in North America have long been active in raising public awareness and fundraising for research into a range of 'proper' cancers. These include initiatives in the 1990s such as Breast Cancer Action (BCA), an organization from San Francisco that continues to confront breast cancer as a political and systemic issue, rather than simply a health problem for one individual amongst many diagnosed with the disease

each year.[230] The Breast Cancer Action organization challenges the commercialization of breast cancer in a biomedical landscape where American health consumers continue to gravitate towards the "pink-washed" merchandise sold to promote research into the treatment of breast cancer.[231] This includes gendering breast cancer as a 'feminine' disease with the sale of pink ribbons, alongside pink-coloured electronics and kitchen appliances to show support for those affected by the disease, and to raise money for research into a cure. The pink-ribbon-effect functions to unite patients by recourse to the body, but not just any body—to an organ that is synonymous with the disease, and a disease that is correlated with defined populations designated "at-risk" for developing the condition (epidemiology). In the rhetoric of the pink-ribbon, the notion of breast cancer as a "women's disease" has enforced a heteronormative view of the cancer patient that reinforces dominant understandings of 'femininity' and survivorship at the exclusion of others.[232] The pink-ribbon is a powerful signifier in the politics of health activism, and as such, the ribbon can be analyzed for its rhetorical weight in public debates about what cancer is, who gets it, and how it should be treated.

[230] J. R. Osuch, K. Silk, C. Price, J. Barlow, K. Miller, A. Hernick, & A. Fonfa. "A Historical Perspective on Breast Cancer Activism in the United States: From Education and Support to Partnership in Scientific Research." *Journal of Women's Health* 21 3 (2012): 355-362.

[231] Laurie Gilmore Selleck. "Pretty in Pink: The Susan G. Komen Network and the Branding of the Breast Cancer Cause." *Nordic Journal of English Studies* 9 3 (2010): 119-138.

[232] In *the Cancer Journals* (1997), Audre Lorde critically examines her personal experience with breast cancer to reveal how racialized, heteronormative assumptions frame cultural and professional understandings of who a cancer patient is, and what the process of treatment and healing should look like. After her mastectomy, Lorde, a black woman, describes the pressure she felt from nurses to wear "pale pink" breast pads, a standard prosthetic that is designed to match a patient with a Caucasian skin tone (1997:42). Viewing herself and other cancer survivors as warriors, and the wounds from her mastectomy as "…an honourable reminder that I may be a casualty in the cosmic war against radiation, animal fat, air pollution, McDonald's hamburgers and Red Dye No. 2," Lorde challenges the optimistic progress narrative of status quo cancer research by bringing into question the very notion of the cancer survivor, and what constitutes the "acceptable" body of a cancer patient. Audre Lorde. *The Cancer Journals.* (San Francisco: Aunt Lute Books, 1997).

With the 'molecularization' of cancer, the pink-ribbon, and the dozen other coloured ribbons that exist for cancers defined by pathological tissue, have begun to unravel.[233] The movement of molecular knowledge into popular thinking about disease has influenced the practice of breast cancer activism. Further, the development of genetic testing technologies has helped to produce a new form of "biosociality," that is, the creation of new social identities and groups based on shared genetic diagnoses.[234] Founded in 1999, Facing Our Risk of Cancer Empowered (FORCE) is a patient group formed around a shared genetic mutation—BRCA1 and/or 2, for inherited breast and ovarian cancer. The discovery of a shared gene for two previously distinct medical conditions, breast cancer and ovarian cancer, linked the two diseases under one medical condition—hereditary breast and ovarian cancer (HBOC). The move to redefine the two diseases in molecular terms is demonstrated in a 2011 luncheon for breast and ovarian cancer entitled, "Tie the Ribbons."[235] The event title makes the argument that rather than viewing breast and ovarian cancer as two separate diseases, they should be considered one disease that shares the connection of having a mutation in either/both BRCA genes.

Forging together the pink ribbon for breast cancer and the teal ribbon for ovarian cancer, "Tie the Ribbons" reinforces the anatomical locale, but suggests that the coloured ribbons separating organs are not exclusive, and can come together under a genetic definition of disease. Observing that disease 'propers' are being challenged and recombined in current health activism, is it possible that there will come a day when there

[233] Encompassing the full spectrum of 30 official colour shades, the coloured ribbons used to promote cancer awareness and research range from "periwinkle" blue for stomach cancer to "orchid" pink for testicular cancer. For a complete list of all the ribbons for cancer, see: http://www.road2ca.com/assets/cancercolorchart.pdf.

[234] Rabinow, "Artificiality and Enlightenment: From Sociobiology to Biosociality," 1997.

[235] HudsonAlpha Foundation "Tie the Ribbons." Huntsville, Alabama. Accessed September 2016 https://support.hudsonalpha.org/tie-the-ribbons

is just one ribbon,[236] for one disease that had once been a collection of many different diseases, spoken to under many different names?

Founded in 2008, Stand Up to Cancer is a US-based patient-advocacy group for translational genetic cancer research. Stand Up to Cancer has since gained momentum as a transnational actor with the establishment of two sister organizations in Canada and the UK.[237] The organization showcases itself as a collaborative project between patient advocates, clinicians, and basic science researchers that seeks to raise funding for "high risk, high impact" translational research for a range of cancers.[238] Stand Up to Cancer occupies a unique position in the socio-historical landscape of cancer activism, emerging in an 'experimental culture' where genetic sequencing technologies are routinely employed to diagnose and treat disease entities on the molecular level. The emerging regime of "actionability" in translational research refers to the discovery of "…mutations that can be directly linked to a treatment, either a drug approved by the Food and Drug Administration (FDA) or an experimental therapy."[239] In the "FAQ" section of the US SU2C website, the translational ethos of the organization is embedded in a call for clinical applications of genetic knowledge:

> SU2C is founded on the belief that in the field of cancer research there is a solid foundation and sufficient understanding of the basic science of cancer, and with the technologies available, now is the time to take that understanding to the next level by translating this knowledge to the clinic—to real advances in patient care and cancer prevention.[240]

[236] The lavender ribbon is commonly used to represent "all cancers." However, this ribbon is an artefact of biomedical practices that acknowledge cancer as a diverse collection of anatomical cancer types.

[237] These international organizations are Stand Up to Cancer Canada and Stand Up to Cancer UK, respectively.

[238] "Why We're Different." Stand Up to Cancer. Accessed March 1st 2016 https://www.standup2cancer.org/why_were_different.

[239] Nelson et al., "On Being "Actionable," 406

[240] "FAQ." Stand Up to Cancer. Accessed March 1st, 2016 https://www.standup2cancer.org/faq

The statement poses a dichotomy between basic science and its clinical application, and between "real" (substantial) and what can be presumed are "less real" (insubstantial) advances in the domain of cancer therapeutics. The "belief" that the group puts forth mirrors a growing disenchantment among American publics with the progress of genetic medicine following from what has been termed as the "unfulfilled promises" of the Human Genome Project. The rhetorical weight of the statement is felt in the desired push to move from practicing science-for-science's sake in the generation of knowledge about genetic mutations and their functions, towards capitalizing on that investment in the form of new and improved treatments for patients. The science has been done and a foundation has been set, and now it is time for genetic medicine to "level-up", to make good on its promises.

In the practices of the New Genetics of the 1990s, genetic medicine has been formed around diagnostic testing for genes that are correlated with a heightened risk of disease. The routinization of genetic testing has produced a patient classification based on knowledge of genetic risk.[241] Emerging from discussions in the highly-active patient group FORCE, the term "previvors" is a label used amongst women to self-identify as BRCA carriers. Cancer previvors are described as "…individuals who are survivors of a predisposition to cancer but who haven't had the disease. This group includes people who carry a hereditary mutation, a family history of cancer, or some other predisposing factor." [242] Predictive genetic knowledge led to clinical programs centered on preventative measures, and genetic testing and screening, leading the way for the use of genetically-targeted therapies. Placing a stronger emphasis on therapeutic outcomes, translational cancer genetics advocates for the discovery of genetic mutations that respond to treatment.

[241] Gibbon, *Breast Cancer Genes and the Gendering of Knowledge,* 1997.

[242] "What is a Previvor?" FORCE. http://www.facingourrisk.org/understanding-brca-and-hboc/publications/newsletter/archives/2009winter/what-is-previvor.php (retrieved March 1st, 2016).

In the public rhetoric surrounding translating and personalizing cancer treatment, genetic medicine must not only speculate on, and predict disease, it must demonstrate its therapeutic use-value and perform the future it has long projected.

Led by "Dream Teams" composed of molecular biologists, oncologists, patient activists, and pharmaceutical actors, Stand Up to Cancer is one of many "bioclinical collectives" that are emerging as new configurations between practitioners of clinical medicine and basic science researchers.[243] The group lays out the values that drive these Dream Teams, including "…collaboration, innovation, acceleration, targeted therapy, and translational research," contrasting their organizing principles with the competitive ethos of what can be assumed to be the Human Genome Project: "Leaders from across disciplines, institutions, countries, and specialties are finally competing against cancer instead of each other, as research moves from bench to bedside to benefit patients more quickly."[244] While the Canadian and UK branches list fewer research projects (~3-4), the US branch has eighteen projects for research into the genetic biomarkers, molecular pathways, and targeted therapies associated with a number of common cancers. The cancers being researched retain their anatomical names: *pancreatic*, *breast*, *ovarian*, *uterine*, *colectoral*, *prostate*, and *endometrial cancers*, *melanoma*, cancers of the blood, as well as cancers that are not organ-specific, but designate affected populations as their referent: "childhood" cancers and "women" cancers.

The disease nomenclature employed by SU2C seems, at first glance, to fall in line with the common practice of classifying cancer by tissues. Does this nomenclature gesture to the anatomical sites where disease was implanted in the nineteenth century for an

[243] Pascale Bourret. "BRCA Patients and Clinical Collectives: New Configurations of Action in Cancer Genetics." *Social Studies of Science* 35 1 (2005): 41-68.

[244] "SU2C Scientific Research Teams." Stand Up to Cancer. Accessed http://www.standup2cancer.org/dream_teams/

anatomo-clinical gaze to extract and reveal, or are these 'proper names' actually doing something quite different? First, what does it mean not just to name, but to combine these proper names by placing them side by side, under the same research agenda—to read them like intersecting street names in the Translational City? What kind of a city have we entered, and what do the relations between these sign-posts lend to us as a kind of map, a walker's guide to move through the biomedical landscape?

The combination of disease propers signifies a new relation between disparate diseases in terms of their classification and treatment. Translational, personalized genomic does not efface the science of the tissues, but moves the clinical gaze to a new depth, at the seat of the gene—to functional molecular targets ("pathways") that may be treated with genetically-tailored pharmaceuticals. Does the disease proper refer to what it has claimed to represent, a "cancer of the breast," and this being somehow different than a "cancer of the lung," or has its referent changed, and how might we identify its new object? Reviewing the description of the research projects taking place under these propers ("breast, lung, etc.") on Stand Up to Cancer's website, nearly all cite research into at least two of the following: "molecules," "proteins," "genetic alterations," and "targeted drugs." The work of the translational Dream Teams is taking place in a biomedical space where cancer is molecularized and researched as a collection of diseases that share common genetic and molecular links.

The progress of translational research is fuelled by emergent visions of the potential of genetic medicine. STS scholar Sheila Jasanoff employs the concept of "sociotechnical imaginaries" to describe how histories, visions, and futures are operationalized in the everyday practices and large-scale projects of technoscience; these "imaginaries" can then act as sites to observe how science and the social order intersect and simultaneously "co-

produce" one another.[245] Similarly, science studies scholars have described how scientific press releases and newspapers employ a promissory logic (statements that play on promises, hope, and expectations) to describe the potential of the research being undertaken, examining the multiple ways that various actors (policy-makers, researchers, patient groups) draw on these affective structures to mobilize and legitimate scientific research.[246] In the hope/hype dynamic, patients come to take an active role in the biomedical innovation process through advocating and securing funding for research. Employing Jasanoff's concept of the "sociotechnical imaginary" alongside philosophical investigations of ontology, the following section will analyze the visions that Stand Up to Cancer draws on to frame the research being undertaken by their organization.

5.2.1. Presencing Things, Futures

Alongside a Mission Statement and Timeline that details milestones that the project has reached, The US Stand Up to Cancer website lists a short "Manifesto" that takes the style of free-verse poetry. While the Mission Statement details the research objectives of the project, the Manifesto provides a vantage point to examine the institutional values of Stand Up to Cancer, as well as how the organization positions itself amongst other actors and institutions in the biomedical landscape. Further, analysis is levelled at how Stand Up to Cancer not only engages with the linguistic representations of translational research and precision medicine that guides emergent bioclinical work in cancer genomics, but also how

[245] Sheila Jasanoff and Sang-Hyun Kim. "Containing the Atom: Sociotechnical Imaginaries and Nuclear Power in the United States and South Korea." *Minerva* 47 2 (2009): 119-146; Jasanoff, "The Idiom of Co-Production," 2006.

[246]For works that explore the hope/hype dynamic in genomics, see: Mike Fortun. *"Genomics Scandals and Other Volatilities of Promising," in Lively Capital: Biotechnologies, Ethics, and Governance in Global Markets, ed. Kaushik Sunder Rajan. (London: Duke University Press, 2012). 329-353.*. Carlos Novas. "The Political Economy of Hope: Patients' Organizations, Science, and Biovalue." *BioSocieties* 1 (2006): 289-305; Nik Brown. "Hope Against Hype—Accountability in Biopasts, Presents and Futures." *Science Studies* 16 2 (2003):3-21.

the poem, as a material artefact of scientific work, performs and fashions the futures and visions of genetic medicine. Drawing on Martin Heidegger's concept of the "four-fold world" as a heuristic device, it is possible to describe how the poem performs, or, presences the "things" (disease entities, actors, technologies) of the translational clinic, and how these "things" come to bear upon the future-reality envisioned by Stand Up to Cancer.

In "Language" and his later writings on technology, Heidegger discusses how technology can act as a gathering point for what he terms as the "four-fold world," that is, a phenomenological plane comprised of earth, sky, divinities, and mortals.[247] Heidegger makes the claim that concrete "things" do not pre-exist in a stable, observable reality, but are formed through an interaction between the four vectors of "earth," "sky," "divinities," and "mortals," and from which World is the context, or, reality-effect of these interactions. World, much like an actor-network, can be taken as a configuration of material things (earth/sky), people (mortals), spaces (earth/sky), and values (divinities) from which a concrete "thing" emerges as an artefact of the interactions between these elements. In the Manifesto, the potential and guiding ethos (divinities) of bioclinical work is summoned in the post-dreaming reality of translational research:

> We used to have such crazy dreams,
> The kind of dreams that brought us together, made us not mere mortals, but a movement.[248]

The opposition between "mortals" and "movement" can be seen in the light of transcending an individual, mortal life (a "mortal" subject) to connect with a "divinity," which for Heidegger, is a domain that encompasses value systems (in this case, the values underpinning a political movement). It is not just "mortals" and "divinities" who are being

[247] Martin Heidegger. "Language", In *the Norton Anthology of Theory and Criticism*. Eds. V. B. Leicht. (NY: W. W. Norton and Company, 2010) 991.

[248] "Manifesto." Stand Up to Cancer. https://www.standup2cancer.org/manifesto. Accessed March 1st, 2016. 1-2.

summoned, but also, a world of "things" that occupies the spatial plane of existence that Heidegger terms as "earth" and "sky":

> We used to dream we'd get to the moon.
> And we were crazy enough, fanatical enough, relentless enough, to get there.
>
> We dreamed we'd split the atom.
> Make smallpox and polio whisper from forgotten history books.[249]

In the "Manifesto," the group makes use of the popular trope of the relentless spirit of scientific progress ("crazy enough, fanatical enough, relentless enough"), and draws a parallel between the achievements of genetic medicine with major breakthroughs in the history of science and medicine: from the splitting of the atom to the eradication of smallpox and polio, to landing on the moon. But what function does naming these things and events have in the *Manifesto*, and for the purposes of SU2C at large? In "Language," Martin Heidegger describes the performative function of naming in his analysis of the Poem, *Winter Evening*:

> In their naming, the things named are calling into their thinging. Thinging, they unfold world, in which things abide and so are the abiding ones. By thinging, things carry out world. Thinging, things are things. Thinging, they gesture—gestate—world.[250]

By the repetition of "thing" and "thinging," Heidegger grants a processual movement and becoming to material objects through the performance of language. As the author of Heidegger's poem also summons tables, chairs, and plates, and wanderers ("mortals") to the scene of the winter evening, he explains how poetic language has the function of "bringing things to a nearness."[251] Heidegger's "things" do not pre-exist the observer in a stable, empirical reality, but must be "called" and presenced into existence. For Heidegger,

[249] Ibid., 1-2. 5-6.
[250] Heidegger, "Language," 992.
[251] Ibid., 991.

language cannot be reduced to a communicative or expressive function, and from which he makes the tautological claim, "language itself is language," arguing that language should be approached on its own terms, and not as the linguistic residue of a speaking subject.[252] Language holds a performative function. To name is to summon "things" to the present from a state of absence, and in what Heidegger terms as their "thinging," "…they gesture—gestate—world."

In the Manifesto, these "things"—atoms, disease entities, history books, are called forth from the distance of the scientific imaginary, here, represented as a "crazy dream," and are made to appear in the "nearness" of the present World. The stage is set for Stand Up to Cancer to perform and authorize a history of the scientific past in relation to the future of genetic medicine imagined, and in doing so, is able to connect its aims, efforts, and priorities within the order of things. The preceding lines of the stanza follow with:

> Make technology infinite, individual.
> Connect the world.[253]

The history of scientific progress is, here, moving in a linear and causal direction, and with precision medicine placed, as the next logical step, at the end of this line ("make technology individual"). "Technology," here, acts as the point of gathering that brings together "mortals," "world", "sky," and "divinities." It is technology, infinitely extending to connect the "individual" and the "world," that brings together the disparate parts of the World imagined by genetic medicine. However, this World has, and continues to face resistance:

> All the unbelievable and the impossible,
> all the can't do and the never will, we overwhelmed them, we overpowered them,
> we conquered them.
> They said no and we, well,
> We said yes.

[252] Ibid., 986.
[253] Stand Up to Cancer, "Manifesto," 3. 5-6.

We stood up.
We stood up and changed the world.

Stand up when everybody else sits down
Stand up when it's easier to turn away
Stand up for everyone who can't rise anymore

When the answer seems impossible, stand up
When the dream is right within our reach, stand up
When the powerful refuse your call, stand up

…This is where the end of cancer begins.[254]

It is not only the disease of cancer that is being "conquered," but also an unnamed "They" that has refused to engage with what has been formally thought of as "unbelievable" and "impossible" feats of scientific ingenuity. Who is this "They", and why are they always saying "No"? Are these the critics of genetic medicine? Taking account of the "crazy dreams" listed by the group that had also seemed, at one point, unimaginable, and their referents: novel cures for devastating diseases such as polio and smallpox, space-travel, and nuclear fission, it appears that the group is also seeking to conquer anti-scientific nay-sayers, non-believers, skeptics. With a retaliatory *Yes*, there is more hope than a "No." In Heidegger's excavation of *A Winter Evening*, the "call" is a generative act, an act of presencing. To name things—a chair, a table, an object of sensation, is to 'call' them forward into being "so that they may bear upon men as things."[255] In SU2C's poem, the group describes an inverse situation, one where "the powerful refuse your call," representing an act of silencing, inhibiting. The "powerful," most likely referring to institutional actors such as health-care policy makers, must be challenged, and from which the poem operates as a "calling" in itself: it brings the realities of patients to the present to be heard, and being heard carries the potential for suffering to end, and for treatment to be

[254] Ibid., 11, 4-6. 9-20, 30.
[255] Heidegger, "Language," 992.

actualized. The "Yes" put forward is to the hope of scientific innovation, to the technological promise, and to the future promised by genetic medicine. The future is a "beginning" that is also an "end," an end to cancer, and to waiting for treatment.

The reader is presented with the image of suffering and disillusionment, a biomedical waste land that bears resemblance to the disenchantment of modernism depicted by T.S. Eliot. The fight for cancer has been nearly exhausted, with some people "turning away" (Because they have given up?), and with others "sitting down" or "who can't rise anymore" because of exhaustion (From fighting for treatment? From fighting cancer?). In *A Winter Evening*, Heidegger explores the space between the world and things as "dif-ference," a space where "world" and "things" penetrate one another. When the author of a *Winter Evening* declares that "pain has turned the threshold to stone," Heidegger makes the claim that it is "pain" that acts like "dif-ference." Pain/dif-ference, compared to the threshold of a house (a doorway), separates inside and outside, but also invites a breakdown of these dualities as what is outside is brought inside, and the reverse:

> But what is pain? Pain rends. It is the rift. But it does not tear apart into dispersive fragments. Pain indeed tears asunder, it separates, yet so that at the same time it draws everything to itself, gathers it to itself. Its rending as a separating that gathers, is at the same time that drawing which, like the pen-drawing of a plan or sketch, draws and joins together what is held apart in separation. Pain is the joining agent in the rending that divides and gathers. Pain is the joining of the rift. The joining is the threshold. It settles the between, the middle of the two that are separated in it. Pain joins the rift of dif-ference. Pain is the dif-ference itself.[256]

Martin Heidegger positions "pain" as the threshold to dif-ference, to the bidding or "inviting" of world and things in language. How does "pain" summon, invite, demand, and transform? For Heidegger, pain is not reduced to a psychological sensation taking place within the secret interiority of the subject, but is simply what he terms as an "opening up"

[256] Ibid., 994.

to the world. Refuting an anthropocentric notion of pain relegated to the status of an object that is possessed by a transcendental subject, Heidegger seeks to explore the performative function of pain as dif-ference. Pain is both connection and disconnection, acting as an intimate relation between subject and object. How does "pain" manifest in Stand Up to Cancer's Poem? The poem continues:

> The moment is now and the time has come to stand up.
> One out of every two men
> One out of every three women
> will face these diseases we call cancer.
>
> Our sisters, our brothers, our fathers, our mothers,
> our husbands, our wives, our children.
> Our very best friends and those we've yet to meet.
>
> One person every minute, one person in a moment gets lost, gets stolen, gets taken away.[257]

The concept of tissue heterogeneity came into question with the re-stratification of disease based on shared genes in the New Genetics, and now, with the discovery of an increasing number of molecular pathways shared between cancer tissue types in translational research efforts. Stand Up to Cancer combines various gendered signifiers ("sisters," "brothers," "fathers," "mothers," etc.) to produce the vision of a collective fight against "these many diseases we call cancer." Gendered "risk" designations of disease (women + breast cancer; men + prostate cancer, etc.) are re-combined in the language of personalized medicine with the plural Cancer invoked ("these many diseases we call cancer"). The discursive relation between diseased organs, gender, and risk appears to come close to falling away, and what is left is pain. The poem continues:

> Unforgivable.[258]

[257] Stand Up to Cancer, "Manifesto," 7-9. 21-28.
[258] Ibid., 10. 29.

Pain, here, operates like dif-ference, a threshold that both "rips" and "joins" World and things. While technological hope unifies individual and world, it is disease that dis-joins this same world, and from which human life "gets lost, gets stolen, gets taken away." Disease-as-pain, is, simply, "unforgivable." It is both pain and hope that "opens up" the cancer patient to a medical space characterized by the play of differences—differences in diseases, in social categories, and therapeutic approaches.

The stanza "type-jumps"[259] from statements backed with experiential or "biographical" knowledge (a lament to loved ones lost) to statistical evidence of cancer mortality rates taken from the American Cancer Society ("one out of every two men…three women"), and to a rhetoric that resembles the notion that "life must be defended" and preserved at all costs as the devastation of disease affects even strangers ("those we've yet to meet"). Flowing from each sentence, "pain" connects these worlds (private life, institutional sites, and a social body) and temporarily unifies them. The unification is complete:

> When together we become a force unmistakable.
> A movement undeniable.
> A light that cannot dim.
>
> When we take our wild impossible dreams
> And make them possible
> Make them true
>
> When together we rise as one
> When we stand up
> When we Stand Up To Cancer.[260]

[259] Stephen Toulmin. *The Uses of Argument.* (Cambridge: Cambridge University Press, 1958).
[260] Stand Up to Cancer, "Manifesto,"
12-14. 31-39.

The technological dream put forward in the poem acts to mobilize persons affected by cancer into a “force unmistakable, / a movement undeniable.” The social categories of gender and kinship, and distinctions between the individual and the global community, between family members and strangers, and those between cancer Propers are transcended as the promise of “infinite” technology unifies these disparate entities.

The vision of genetic medicine that emerges from Stand Up to Cancer’s “Manifesto” draws on collective feelings of frustration with available treatments for cancer patients and hope in the progress of technology and science. The “Manifesto” makes the demand for scientific knowledge that does something, conjuring the ethos of translational research as a scientific enterprise that delivers genomic discoveries to the clinic. Actively resisting the nay-sayers or critics of genetic medicine who argue that genomics will not make good on it’s promise of improving cancer treatments, the critique extends upward to the level of “powerful” policy-makers and institutional agents who have not prioritized patients’ voices in the research process. The “Manifesto” calls the “forgotten” and “lost" patient subjects forward (sisters, brothers, mothers, fathers, and so forth) just as it calls forward events from the recent history of scientific innovation (the invention of smallpox and polio vaccines; splitting the atom, and the moon landing) to the present. These “things”—the subject-objects of medicine and science, perform the future of genetic medicine that the group would like to see come to actualization. The teleology of the poem connects a history of technological innovation with the hope in an “infinite” and “individual” technology that will lead to the cure of all cancers.

5.2.2. Un-tying, Re-tying, Throwing Out the Ribbons of Anatomical Disease?

The ‘molecularization’ of cancer has been approached as a shifting view of “anatomical” or “tissue-sited” diseases towards an understanding of disease at the

microscopic level of genes, molecules, and biological pathways. Drawing from the spatial theory and semiotics analysis of French post-structuralists Michel Foucault and Michel de Certeau, insights into the ontological basis of medical knowledge about cancer can be garnered from examining the relationship between the signifiers of biological units (tissues, organs, cells, genes, etc.) and the signified of diseases. De Certeau's concept of the "proper name," and its ordering function in the urban landscape, is particularly useful to examine how disease nominalisms, as proper names, are artefacts of classificatory practices that may also come to take on additional significations in practice.

In the present-day, the pink-ribbon for breast cancer, and the 29 other ribbons for cancer types, remain powerful cultural symbols that act as rallying points for patient activists working to improve the health of specific populations "at-risk" for certain cancers. The cancer awareness ribbons, as material artefacts of cancer research and activism, reflect medical and cultural ontologies constructed from knowledge of disease as a pathology of discrete biological tissues and organs. These disease categories are never neutral, but reflect cultural values ascribed to the populations designated at-risk for certain types of cancer. For breast cancer and other "women's diseases," these include dominant assumptions about sexuality and gender. The "delocalization" of disease does not eliminate the anatomical locale, but presents a situation in which disease propers take on new signifying properties.

Current cancer activist groups such as Tie the Ribbons and Stand Up to Cancer employ the "proper names" of anatomical disease as signifiers with a molecular disease referent. For example, "Tie the Ribbons" seeks to "tie" the awareness ribbons for breast and ovarian cancer to symbolize the genetic connection between the two diseases, reworking the anatomical locale to fit with a genetic definition of disease. However, the joining of the two propers symbolizes a new at-risk population, one that is defined not only

by shared gene mutations, but also by epidemiological factors such as age, gender, and ethnicity, amongst others.

For Stand Up to Cancer, the anatomical landscape of disease is much like a large city in transition. The street names might be the same, but the feel of the neighbourhoods is changing. By researching multiple proper cancers, the group seeks to carve up the populations at risk for disease, calling all "sisters,' 'brothers,' 'fathers,' 'mothers,' 'husbands,' 'wives,' 'children,' 'best friends' and "those we've yet to meet" together in a pluralistic understanding of what cancer is, who gets it, and how it should be treated. The group promotes a collective fight against capital 'C' Cancer, not cancers, challenging tissue heterogeneity and supporting an emergent view of disease as defined by shared molecular pathways that cut across proper cancers, tissues, and social bodies. While the molecular pathway forges bridges between anatomical diseases, patients diagnosed with a range of cancer propers (breast, ovarian, lung, colorectal, and so forth) are also brought together in translational research by shared pain and frustration.

Chapter 6. Conclusion: The Present-Futures of Genetic Cancer Research

In 1994, researchers celebrated the discovery of the "breast cancer gene," hailed as a milestone in the field of medical genetics that would lead to further knowledge of the genetic basis of cancer. The isolation of BRCA1, and one year later, BRCA2, significantly improved diagnostic practices for women genetically at-risk for hereditary breast cancer, leading to improved access to genetic testing and preventative procedures, counselling services, and the growth of patient support and activist communities for BRCA carriers. The discovery of BRCA1 and 2 is praised as a model of translational research, historicized as an early example of how genetic knowledge and technologies can be applied in a clinical setting to improve health outcomes.

However, this thesis argues that the label of "translational" research cannot be neatly applied to the discovery of the BRCA genes. Employed as a thought experiment, the theory of a gene for breast cancer combined evolutionary genetics, population genetics, and statistical and mathematical frameworks to designate a "statistically-likely" correlation between a rare gene mutation and a familial pattern of breast cancer. These elements can be taken as stylistic cornerstones of the New Genetics, a style of research initiated with the discovery of the first oncogene in the 1970s, and carried forward in biomedical practices devoted to the pursuit of rare, Mendelian genes in the 1990s.

Translational research emerges amidst criticisms of "statistical" genes by post-genomic researchers who content that the discovery of a gene must be foregrounded by its proven biological and therapeutic relevance to disease diagnosis and treatment. Patient advocacy groups in the post-genomic era of cancer research mirror these criticisms, drawing on feelings of disappointment and frustration with the slow "translation" of genomic discoveries in the laboratory into actual treatments for patients. Translational

research, centered on pairing drugs with functional gene mutations and the biological pathways they operate in, produces mechanistic knowledge about gene mutations that have a demonstrated therapeutic outcome. In the New Genetics, the idea of a disease-causing gene took center stage, eclipsing concerns about gene-to-gene and gene-environment interactions, alongside knowledge questions about what these genes "do" in terms of their clinical and biological functions. As a result, BRCA's role in DNA damage repair was overshadowed by aesthetic commitments to the Mendelian gene. The application of statistical modeling to the study of disease risk has aided in diagnosing hereditary breast cancer, but new and improved therapeutic options for BRCA carriers in still a work in progress, and from which surgery remains a common treatment option for BRCA patients. Importantly, it is only in the early 2000s that specific "rational" mutation-drug affinities have been identified for BRCA cancers, the products of which are still in a preliminary stage of development.

Further, framing the discovery of BRCA1 and 2 as a model of translational research reinforces the "technological imperative" in medicine, a situation in which medical interventions in matters of health and disease take recourse to genetic explanations and their technical counterparts; this includes the new wave of sequencing technologies that are poised for clinical use. While acknowledging developments in non-deterministic, environmental, and developmental studies of cancer with the advancement of epi-genetics, the turn to translational research occurs in a space where genomic explanatory schemas and technologies still hold a privileged position in medicine and society. This is demonstrated in the continuation of the major tenets of germ theory that were carried through to studies of cancer viruses, and later, the New Genetics, such as: reinforcing a singular disease etiology, and an internalist view of disease that positions the body as a machine that can be repaired and restored to an optimized state.

6.1. Discursive Formation, Stylized Thought

There is a general trend in cancer research towards "molecularization," a process from which "life itself" is re-defined at the level of molecules, genes, proteins, atoms, and other sub-cellular entities. In the 1990s, advances in genetics incited concerns over genetic determinism, expressed in the works of social scientists writing about the power of the genetic knowledge to reinscribe social categories such as race, gender, ethnicity, and kinship. Examining the trajectory of genetic cancer research from the discovery of BRCA1 and 2, this thesis argues that the discovery of the "breast cancer gene" must be situated between two co-existing thought styles: the New Genetics and Post-Genomics.

Molecularization, rather than being a totalizing movement, is enmeshed in heterogeneous, as well as historically and contextually-specific biomedical practices. The "molecular" is continually re-made within the bounds of the "thought styles" that researchers are working in during a given socio-historical moment. Stylized knowledge is mediated by the rules, norms, and values of the knowledge collective, resulting in the formation and transformation of objects produced within these collectives. Ludwik Fleck's concept of the "thought style" offers insight into how scientists are socialized to accept certain norms and values that set the precedent for everyday and experimental work in the laboratory, and from which scientific developments proceed from engagements, and challenges to collective knowledge.

While Fleck provides a theoretical framework for examining the mutation of scientific facts and objects, Michel Foucault's concept of the "discursive formation" provides a mechanism by which stylistic change is achieved. As Foucault explains, the discursive formation is not a synonym for an "ethos" or "worldview," but is an active principle describing the "dispersion," or, separation of discursive elements into different

categories for understanding.[261] Foucault outlines the purpose of critically examining these discursive divisions:

> We must also question those divisions or groupings with which we have become so familiar…These divisions—whether our own, or those contemporary with the discourse under discussion—are always themselves reflexive categories, principles of classification, normative rules, institutionalized types; they, in turn, are facts of discourse that deserve to be analyzed beside others; of course, they also have complex relations with each other, but they are not intrinsic, autochthonous, and universally recognizable characteristics.[262]

Espousing a constructivist view of how reality and its categorization schemas are relative and mutable, Foucault reminds us of the importance of questioning the relationship between knowledge, truth, and the social order. Analyzing discursive divisions includes scrutinizing the pre-packaged terms of the "molecular," "gene," "cancer," "translational," "genetic," "and "post-genomic," remembering that these are not stable categories that depict a fixed phenomenon in-the-world, but that these concepts are tied to certain knowledge practices, expectations, and values. Just as anthropologists have debated the use-value of the "culture" concept, leading to heated debates in the 1980s over what it's purpose should be, if any, in the future of the discipline, researchers in the "hard sciences" also debate what scientific concepts mean to them, continually revising and occasionally obliterating certain knowledge claims from existence. Innovations in the life science are often highly publicized, and come to perform in the "truth regime" of Western biomedicine. To examine the shifting status of scientific knowledge claims is to pose a direct challenge to the certitude of this knowledge, and to question their bearing on understandings of disease, illness, and social identity.

[261] Ibid., 37.
[262] Ibid., 21-22.

6.2. Hope, Hype, Expectations—Disappointment?: Affective Assemblages of Translational Research

Social scientists have highlighted how values, promises, and expectations contribute to the practice of science, not just in the form of the "social reception" of a scientific finding, but in the inventive process itself. Describing the discovery of a molecular pathway that regulates gene changes in the fruit-fly Drosophilia, the anthropologist Mike Fortun explains how the pathway—named by researchers as the German word for amazement—"toll," is representative of the affective conditions of all knowledge production. Fortun goes on to claim that "...scientific change is affective as much as it is cognitive, instrumental, experimental, and institutional."[263] In other words, the identification of a scientific problem is not the act of steadily uncovering more and more of the "truths" hidden in the natural world, blindly, and without purpose. Rather, scientific problems are problems that scientists think are worth solving. Beyond the laboratory, the fruits of these problem-solving tasks—scientific discoveries, are also subject to the evaluation of the public. Ludwik Fleck describes how scientific facts flow back-and-forth between the laboratory and the public, taking on a quality of "emotive vividness," that is, a "self-evident" value.[264]

Beyond acting merely as cut-and-dry policies that scientists adhere to, translational research agendas interact with social values to produce technoscientific visions, that is, futuristic narratives that scientific collectives and patient activist organizations draw on to frame research projects and to secure funding for genomic initiatives. Acknowledging the power of patient activist organizations to shape basic science research through funding

[263] Mike Fortun. "What Toll Pursuit," in *Post-Genomics: Post-Genomics: Perspectives on Biology after the Genome*. Eds. Richardson, Sarah S., and Stevens, Hallam. (US: Duke University Press, 2015). 35.

[264] Fleck, *Genesis*, 117.

efforts, it is important to examine how patient activists engage with research policies that promote certain experimental questions and frameworks for thinking about, and intervening in disease. Following the immense hype and promise of the Human Genome Project, a discourse centred on disappointment in genetic medicine emerged with critics citing the limited progress of genomic research towards improving the diagnosis and treatment of common diseases. While social scientists have examined how hope and a culture of optimism surrounding genetic technologies play a significant role in biomedical innovations, this thesis argues that the reverse state—disappointment and frustration, is an affective structure that patient advocacy groups such as Stand Up to Cancer draw on to mobilize research and securing funding in translational genomics. However, rather than challenging the progress narrative of genetic medicine, these criticisms reinforce it, proposing that the delivery of technological developments in genomic medicine to waiting-patients in the clinic only needs to be improved.

Translational science promises to increase and speed up the delivery of basic science discoveries to the public, a value that influences how gene mutations are discovered. For basic science researchers, epidemiologists, and clinicians working on the shared problem of "hereditary breast cancer" in the 1990s, the gene was the limit of epistemic possibility, imagined in the vision of researchers and the general public alike as the basic unit on which "life itself" was built. The pristine object of the gene may have eclipsed concerns about the biological function of genes, including the mechanism of DNA damage repair. Building on Rheinberger's theory of experimental systems, the historians Mody and Lynch remind us of the fluctuating, indeterminate nature of "epistemic things," and experimental assemblages themselves. Rare Mendelian genes, rather than being discarded from critical view, now act as investigative sites for translational researchers interested in uncovering mechanistic knowledge about biological pathways.

Examining the "retrospective hypothesis"[265] of BRCA as a translational research initiative, this thesis argues that the discovery of BRCA1 and 2 cannot be conflated with translational experimental procedures that operate under their own set of rules and values. These narratives of technoscientific progress re-write the past from the threshold of the present, assigning intentionality to actors and actions operating under a different set of discursive constraints, and imprinting a contemporary vision of scientific research on the past. By examining the contexts in which the theory of a gene for breast cancer was formulated, and in which the BRCA genes were discovered, this thesis seeks to destabilize the BRCA story as a progress narrative with the intent of revealing the emergent values and visions in present-day translational science.

[265] Foucault, *Archaeology*, 21.

References

Ackermann, Edith. "Piaget's Constructivism, Papert's Constructionism: What's the Difference." Future of Learning Group Publication 5, 3 (2001): 4.

Adams, Vincanne; Michelle Murphy, and Adele Clarke. "Anticipation: Technoscience, Life, Affect, Temporality." *Subjectivity* 28 (2009): 246-265.

Angier, Natalie. "Vexing Pursuit of Breast Cancer Gene." *New York Times*, July 12th, 1994.

BioPortal. "Pathway Ontology," Accessed at https://bioportal.bioontology.org/ontologies/PW.

Bourret, Pascale. "BRCA Patients and Clinical Collectives: New Configurations of Action in Cancer Genetics." *Social Studies of Science* 35 1 (2005): 41-68.

Bourret, Pascale; Peter Keating, and Alberto Cambrosio. "From BRCA to BRCAness: Tales of Translational Research," in *Breast Cancer Gene Research and Medical Practices: Transnational Perspectives in the Time of BRCA.* Eds. Gibbon, Sahra; Joseph, Galen; Mozersky, Jessica; zur Nieden, Andrea; Palfner, Sonja. (New York: Routledge, 2014). 175-193.

Brown, Nik. "Hope Against Hype—Accountability in Biopasts, Presents and Futures." *Science Studies* 16 2 (2003): 3-21.

Cambrosio, Alberto, and Peter Keating. *Biomedical Platforms: Realigning the Normal and the Pathological in Late Twentieth-Century Medicine*. (London: MIT Press, 2003).

Carey, Lisa. "Old Drugs, New Tricks for Triple-Negative Breast Cancer." *The Lancet Oncology* 16 4 (2015): 357-359.

Center for Disease Control and Prevention. "Genomics Translation." Accessed online at http://www.cdc.gov/

Childs, Barton. *Genetic Medicine: A Logic of Disease*. (Baltimore: JHUP Press, 2003).

Chedd, Graham. "The Molecular Roots of Cancer." *New Scientist*, June 29th, 1972.

Clark, Lauren. “A New Era in Cancer Research.” *Spectrum*, Winter 2011. Para. 11.

Clarke, Adele; Janet K. Shim; Laura Mamo; Jennifer Ruth Fosket. “Biomedicalization: Technoscientific Transformations of Health, Illness, and US Biomedicine.” *American Sociological Review*, 68, 2 (2003): 161-194.

Collins, Francis. “Medical and Societal Consequences of the Human Genome Project” *New England Journal of Medicine* 341 (1991): 33.

Condit, Celeste M., and Deirdre M. Condit. "Blueprints and Recipes: Gendered Metaphors for Genetic Medicine." *Journal of Medical Humanities* 22, 1 (2001): 29-39.

Conrad, Peter. “Medicalization and Social Control.” *Annual Review of Sociology*, 18 (1992): 209-232.

"A Mirage of Genes." *Sociology of Health & Illness* 21, 2 (1999): 228-241.

De Certeau, Michel. “Walking in the City,” in *The Practice of Everyday Life*. Translated by Steven Rendall. (Berkeley: University of California Press, 1988). 91-130.

DNA Learning Center. “Mary-Claire King.” Accessed April 12th, 2015, https://www.dnalc.org/ view/16055-mary-claire-king-.html.

Dreifus, Claudia. “A Never-Ending Genetic Quest: Mary-Claire King’s Pioneering Gene Work, From Breast Cancer to Human Rights.” *New York Times*, February 9th, 2015.

Dupre, John. “The Polygenomic Organism” in *Post-Genomics: Perspectives on Biology after the Genome.* Eds. Richardson, Sarah S., and Stevens, Hallam. (Durham: Duke University Press, 2015). 56-72.

Finkler, Kaja, Cecile Skrzynia, and James P. Evans. “The New Genetics and its Consequences for Family, Kinship, Medicine and Medical Genetics.” *Social Science and Medicine,* 57 (2003):403-412.

Fleck, Ludwik. *Genesis and Development of a Scientific Fact*. (Chicago: University of Chicago Press, 1979[1935).

FORCE. “What is a Previvor?” Accessed March 1st, 2016 http://www.facingourrisk.org/understanding-brca-and-hboc/publications/newsletter/archives/2009winter/what-is-previvor.php

Fortun, Mike. “Genomics Scandals and Other Volatilities of Promising,” in *Lively Capital: Biotechnologies, Ethics, and Governance in Global Markets*, ed. Kaushik Sunder Rajan. (London: Duke University Press, 2012). 329-353.

“EverythingXNothing,” in *Promising Genomics: Iceland and DeCODE Genetics in a World of Speculation*. (Berkeley: University of California Press, 2008).

Foucault, Michel. *The Birth of the Clinic: An Archaeology of Medical Perception.* (New York: Routledge, 1976[1963]).

The Archaeology of Knowledge. (New York: Vintage Books, 2010[1969]).

Friedberg, Errol C. “DNA Damage and Repair.” *Nature* 421, 6921 (2003): 436-40.

Fujimura, Joan. “The Molecular Biological Bandwagon.” *Social Problems* 35, 3 (1988):261-283.

Crafting Science: A Sociohistory of the Quest for the Genetics of Cancer. (Cambridge: Harvard University Press, 1996).

Galison, Peter, and Lorraine Daston. “Epistemic Virtues” in *Objectivity*. (Cambridge: MIT Press, 2007). 39-41.

Geertz, Clifford. *The Interpretation of Cultures.* (New York: Basic Books Inc., 1973).

Gibbon, Sahra. *Breast Cancer Genes and the Gendering of Knowledge: Science and Citizenship in the Cultural Context of the ‘New Genetics.’* (London: Palgrave Macmillan, 1997).

Goodman, Nelson. “Words, Works, Worlds.” *Erkenntnis* 9, 1 (1975): 57-73.

Green, Eric; James Watson, and Francis S. Collins. “Human Genome Project: Twenty-Five Years of Big Biology.” *Nature* 526, 7571 (2015): 29-31.

Griffiths, AJF; JH Miller, and DT Suzuki. “Penetrance and Expressivity,” in *An Introduction to Genetic Analysis*. 7th edition. (New York: W. H. Freeman, 2000).

Gwynne, Peter, and Gary Heebner. “Technologies in Cancer Research: Progress at the Molecular Level.” *Science*, March 6th, 2001.

Hacking, Ian. “An Indeterminacy in the Past,” in *Rewriting the Soul: Multiple Personality and the Sciences of Memory* (New Jersey: Princeton University Press, 1995). 241-250.

“The Looping Effects of Human Kinds,” in *Causal Cognition: A Multidisciplinary Debate.* (New York: Oxford University Press, 1995): 351-394.

The Social Construction of What? (Cambridge: Harvard University Press, 1999).

Hall, J., M. Lee, B. Newman, J. Morrow, L. Anderson, B. Huey, and M. King. “Linkage of Early-onset Familial Breast Cancer to Chromosome 17q21.” *Science* 250, 4988 (1990): 1684- 689.

Hallowell, Nina. “Doing the Right Thing: Genetic Risk and Responsibility.” *Sociology of Health and Illness* 21, 5 (1999): 597-621.

Hamer, Dean H., Stella Hu, Victoria L. Magnuson, Nan Hu, and Angela ML Pattatucci. "A Linkage between DNA markers on the X Chromosome and Male Sexual Orientation." *Science* 261, 5119 (1993): 321-321.

Hanahan, Douglas. "Rethinking the War on Cancer." *The Lancet* 383, 9916 (2014): 558-563.

Haraway, Donna. “Situated Knowledges: The Science Question in Feminism and the Privilege of Partial Perspective.” *Feminist studies* 14, 3 (1988): 575-599.

“Gene,” in *Modest_Witness@Second_Millennium. FemaleMan©_Meets_OncoMouse™: Feminism and Technoscience.* (New York: Psychology Press, 1997). 131-172.

Heidegger, Martin. “Language,” in *the Norton Anthology of Theory and Criticism*. Eds. V. B. Leicht. (NY: W. W. Norton and Company, 2010). 982-998.

Hofmann, Bjorn. “Is There a Technological Imperative in Health-Care?” *International Journal of Technology Assessment in Health Care* 18, 3 (2002): 675-689.

HudsonAlpha Foundation. “Tie the Ribbons.” Huntsville, Alabama. Accessed September 2016 https://support.hudsonalpha.org/tie-the-ribbons

Huebner, Robert J, and George J. Todaro. "Oncogenes of RNA tumor viruses as determinants of cancer." *Proceedings of the National Academy of Sciences* 64, 3 (1969): 1087-1094.

Hustchinson, Ezzie. “Alfred Knudson and His Two-Hit Hypothesis.” *The Lancet Oncology* 2, 10 (2001): 642-645.

International Council for Science. Accessed at https://www.icsu.org/most-recent

Jasanoff, Sheila. “The Idiom of Co-Production” in *States of Knowledge: The Co-Production of Science and the Social Order*. (London: Routledge, 2006). 1-12.

Jasanoff, Sheila, and Sang-Hyun Kim. "Containing the Atom: Sociotechnical Imaginaries and Nuclear Power in the United States and South Korea." *Minerva* 47, 2 (2009): 119-146.

Keating, Peter, and Alberto Cambrosio. "The New Genetics and Cancer: The Contributions of Clinical Medicine in the Era of Biomedicine," *Journal of the History of Medicine and Allied Sciences* 56, 4 (2001): 321-352.

Khoury, M.J. M. Gwinn, P. W. Yoon, N. Dowling, C. A. Moore, and L. Bradley, L. “The Continuum of Translation Research in Genomic Medicine: How Can We Accelerate the Appropriate Integration of Human Genome Discoveries into Health Care and Disease Prevention?” *Genetics in Medicine* 9, 10 (2007): 665-674.

King, Mary-Claire. “’The Race’ to Clone BRCA1.” *Science* 342 (2014): 1462-1465.

King, Mary-Claire, Joan H. Marks, Jessica B. Mandell and The New York Breast Cancer Study Group. “Breast and Ovarian Cancer Risks Due to Inherited Mutations in BRCA1 and BRCA2.” *Science New Series* 302, 5645 (2003): 643-646.

King, Mary-Claire, and Allan Wilson. “Evolution at Two Levels in Humans and Chimpanzees.” *Science* 188, 4184 (1975): 107-116.

Kingman, Sharon and Ian Anderson. Nobel Prizewinners Celebrate with a Baseball Match.” *New Scientist*, October 14th, 1989.

Kleinman, Arthur; Leon Eisenberg, and Byron Good. “Culture, Illness, and Care: Clinical Lessons from Anthropologic and Cross-Cultural Research.” *Annals of Internal Medicine* 88, 2 (1978): 251-258.

Knudson, Alfred. “Mutation and Cancer: Statistical Study of Retinoblastoma.” *Proceedings of the National Academy of Sciences* 68, 4 (1971): 820-823.

Koenig, Barbara. “The Technological Imperative in Medical Practice: The Social Creation of a “Routine” Treatment,” in *Biomedicine Examined*. Eds. Lock, M., and Gordon, D. (Netherlands: Kluwer Academic Publishers, 1988). 465-496.

Krush, Anne. "Contributions of Pierre Paul Broca to Cancer Genetics.” Transactions of the Nebraska Academy of Sciences and Affiliated Societies Paper 316 (1979).

Kuhn, Thomas. *The Structure of Scientific Revolutions*. (Chicago: Chicago University Press, 1970[1962]).

Latour, Bruno, and Steven Woolgar. *Laboratory Life: The Construction of Scientific Facts.* (Princeton: Princeton University Press, 1979). 23-30.

Leigh Star, Susan, and James R. Griesemer. "Institutional Ecology Translations' and Boundary objects: Amateurs and Professionals in Berkeley's Museum of Vertebrate Zoology.” *Social Studies of Science* 19, 3 (1989): 387-420.

Lemonick, Michael D. “Designer Babies.” *Time*, January 11th, 1999.

Levi Strauss, Claude. *The Savage Mind* (London: Weidenfeld and Nicholson, 1966[1962]).

Lippman, Abby. “Prenatal Genetic Testing and Screening: Constructing Needs and Reinforcing Inequities.” *American Journal of Law and Medicine* 17, 1-2 (1991): 19.

Lock, Margaret. “Eclipse of the Gene and the Return of Divination.” *Current Anthropology* 46, S5 (2005): S47-S70.

Lorde, Audre. The *Cancer Journals*. (US: Aunt Lute Books, 1997).

Macdonald., Marcy E., Christine M. Ambrose, Mabel P. Duyao, Richard H. Myers, Carol Lin, Lakshmi Srinidhi, and Glenn Barnes. "A Novel Gene Containing a Trinucleotide Repeat that is Expanded and Unstable on Huntington's Disease Chromosomes." *Cell* 72, 6 (1993): 971-983.

McClellan, Jon, and Mary-Claire King. “Genetic Heterogeneity in Human Disease.” *Cell* 141, 2 (2010): 210.

McClellan, Jon M.; Ezra Susser, and Mary-Claire King. “Schizophrenia: A Common Disease Caused by Multiple Rare Alleles.” *The British Journal of Psychiatry* 190, 3 (2007): 194-199.

McHale, Laurie. “Putting the Puzzle Together: In the Jigsaw World of Human Genetics, UW Professor Mary-Claire King Found a Crucial Piece that Helps Solve the Mystery of Breast Cancer.” University of Washington Alumni Association, Accessed April 10th 2016 http://www.washington.edu/alumni/columns/sept96/king1.html.

Miki Yoshi, Jeff Swensen, Donna Shattuck-Eidens, P. Andrew Futreal, Keith Harshman, Sean Tavtigian, Qingyun Liu, Charles Cochran, L. Michelle Bennett, Wei Ding, Russell Bell, Judith Rosenthal, Charles Hussey, Thanh Tran, Melody McClure, Cheryl Frye, Tom Hattier, Robert Phelps, Astrid Haugen-Strano, Harold Katcher, Kazuko Yakumo, Zahra Gholami, Daniel Shaffer, Steven Stone, Steven Bayer, Christian Wray, Robert Bogden, Priya Dayananth, John Ward, Patricia Tonin, Steven Narod, Pam K. Bristow, Frank H. Norris, Leah Helvering, Paul Morrison, Paul Rosteck, Mei Lai, J. Carl Barrett, Cathryn Lewis, Susan Neuhausen, Lisa Cannon-Albright, David Goldgar, Roger Wiseman, Alexander Kamb and Mark H. Skolnick. “A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1.” *Science* 266, 5182 (1994): 66-71.

Martin, Emily. “The Egg and the Sperm: How Science Has Constructed a Romance Based on Stereotypical Male-Female Roles.” *Signs* 16 3 (1991): 485-501.

Mendel, Gregor. “Experiments in Plant Hybridization.” 1856.

Mody, Cyrus, and Michael Lynch. "Test Objects and Other Epistemic Things: a History of a Nanoscale Object." *The British Journal for the History of Science* 43, 3 (2010): 429.

Mol, Annemarie. *The Body Multiple: Ontology in Medical Practice*. (Durham: Duke University Press, 2002).

Moyer, Virginia, on behalf of the U.S. Preventive Services Task Force. “Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement.” *Annals of Internal Medicine* 160 (2014): 271-281.

Nathan, David G. “The Cancer Treatment Revolution.” *Transactions of the American Clinical and Climatological Association* 118 (2007): 317–323.

National Cancer Institute. “National Cancer Act of 1971,". Accessed April 12 2016 https://www.cancer.gov/about-nci/legislative/history/national-cancer-act-1971.

“NCI Thesaurus,” National Cancer Institute, 2016. Accessed at https://ncit.nci.nih.gov/ncitbrowser/.

National Institute of Health. “Understanding our Genetic Inheritance. The U.S. Human Genome Project: The First Five Years (1991-1995)”. NIH Publication No. 90-1590 (1990): 1-85.

Nelson, Nicole; Alberto Cambrosio, and Peter Keating. “On Being "Actionable": Clinical Sequencing and the Emerging Contours of a Regime of Genomic Medicine in Oncology.” *New Genetics and Society* 32 4 (2013): 405-428.

Novas, Carlos. “The Political Economy of Hope: Patients’ Organizations, Science, and Biovalue.” *BioSocieties* 1 (2006): 289-305.

Osuch J. R., K. Silk, C. Price, J. Barlow, K. Miller, A. Hernick, & A. Fonfa. “A Historical Perspective on Breast Cancer Activism in the United States: From Education and Support to Partnership in Scientific Research.” *Journal of Women's Health* 21 3 (2012): 355-362.

Pier G. Natalia, Maria R. Nicotra, Aldo Bigotti, Irene Venturo, Dennis J. Slamon, Brian M. Fendly, and Axel Ullrich. "Expression of the p185 encoded by HER2 oncogene in normal and transformed human tissues." *International Journal of Cancer* 45, 3 (1990): 457-461.

Park, Alice. “Lessons from the Woman Who Discovered the BRCA Cancer Gene.” *Time*, June 2nd, 2014.

PlosBiology. “Other Article Types.” Accessed March 2016 at http://journals.plos.org/plosbiology /s/other-article-types

Polanyi, Michael. *Personal Knowledge: Towards a Post-Critical Knowledge.* (Chicago: University of Chicago Press, 1974[1958]).

Press, Nancy; Jennifer R. Fishman, and Barbara A. Koenig. “Collective Fear, Individualized Risk: The Social and Cultural Context of Genetic Testing for Breast Cancer.” *Nursing Ethics* 7, 3 (2000): 237-249.

Rabeharisoa, Vololona, and Pascale Bourret. “Staging and Weighting Evidence in Biomedicine: Comparing Clinical Practices in Cancer Genetics and Psychiatric Genetics.” *Social Studies of Science* 39, 5 (2009): 701.

Rabinow, Paul. “Artificiality and Enlightenment: From Sociobiology to Biosociality,” in *Essays on the Anthropology of Reason*. Eds. Ortner, Sherry; Dirks, Nicholas B., and Eley, Geoff. (Princeton: Princeton University Press). 91-111.

Rapp, Rayna. “Chromosomes and Communication: The Discourse of Genetic Counseling.” *Medical Anthropology Quarterly* 2, 2 (1988):143-157.

Testing Women, Testing the Fetus: The Social Impact of Amniocentesis in America. (New York: Routledge, 1999).

Rheinberger, Hans-Jörg. "Consistency From the Perspective of an Experimental Systems Approach to the Sciences and Their Epistemic Objects." *Manuscrito* 34, 1: 307-321.

Road2ca. Accessed March 1st, 2016 http://www.road2ca.com/assets/cancercolorchart.pdf

Rose, Nikolas. *The Politics of Life Itself*. (Princeton: Princeton University Press, 2007).

Rubio, D. M., E. E. Schoenbaum, L. S. Lee, D. E. Schteingart, P. R. Marantz, K. E. Anderson, and K. Esposito. “Defining Translational Research: Implications for Training.” Academic Medicine: *Journal of the Association of American Medical Colleges* 85, 3 (2010): 470.

Schork, NJ; SS Murray; KA Frazer, and EJ Topol. “Common vs. Rare Allele Hypothesis for Complex Diseases.” *Current Opinion in Genetics and Development* 19, 3 (2009): 212-219.

Schully, S. D., C. B. Benedicto, E. M. Gillanders, S. S. Wang, M. J. Khoury. “Translational Research in Cancer Genetics: The Road Less Traveled.” *Public Health Genomics* 14 (2011): 1-8.

Segal, Judy. *Health and the Rhetoric of Medicine*. (Carbondale: Southern Illinois University Press, 2005).

Shute, Nancy. “How Being Ignored Helped a Woman Discover the Breast Cancer Gene.” *NPR*, March 27th, 2014.

SPIEGEL. “Interview with Craig Venter: 'We Have Learned Nothing from the Genome.'” *SPIEGEL*, July 29th, 2010: 4.

Sunder Rajan. “Genomic Capital: Public Cultures and Market Logics of Corporate Biotechnology.” *Science as Culture* 12, 1 (2010): 87-121.

Sunder Rajan, Kaushik, and Sabina Leonelli. “Introduction: Biomedical Trans-actions, Postgenomics, and Knowledge/Value.” *Public Culture* 25(3), 71 (2013): 463-475.

Stand Up to Cancer. “Why We’re Different.” Accessed March 1st, 1016 https://www.standup2cancer.org/why_were_different

“FAQ.” Accessed March 1st, 2016 https://www.standup2cancer.org/faq

“Manifesto.” Accessed March 1st, 2016 https://www.standup2cancer.org/manifesto

“SU2C Scientific Research Teams.” Accessed M2016 http://www.standup2cancer.org/dream_teams/

Stehelin, Dominique; Harold E. Varmus; J. Michael Bishop, and Peter K. Vogt. "DNA Related to the Transforming Gene (s) of Avian Sarcoma Viruses is Present in Normal Avian DNA." *Nature* 260 (1976): 170-173.

Toulmin, Stephen. *The Uses of Argument*. (Cambridge: Cambridge University Press, 1958).

Turner, Nicholas; Andrew Tutt, and Alan Ashworth. “Hallmarks of 'BRCAness' in Sporadic Cancers.” *Nature Reviews Cancer*, 4, 10 (2004): 814-819.

Venkitaraman, A. R. “Cancer Susceptibility and the Functions of BRCA1 and BRCA2.” *Cell* 108 (2001): 171-182.

Wade, Nicholas. “Scientists Complete Rough Draft of Human Genome.” *New York Times*, June 26th, 2000.

“A Decade Later, Genetic Map Yields Few New Cures.” *New York Times*, June 12, 2010.

Wonderling, D., P. Hopwood, A. Cull, F. Douglas, M. Watson, J. Burn, & K. McPherson. “A Descriptive Study of UK Cancer Genetics Services: An Emerging Clinical Response to the New Genetics.” *British Journal of Cancer* 85, 2 (2001): 166.

Wooster R1., Bignell G., Lancaster J., Swift S., Seal S., Mangion J., Collins N, Gregory S, Gumbs C., Micklem G. “Identification of the breast cancer susceptibility gene BRCA2.” *Nature* 378 6559 (1995): 789-92.

Zerhouni, Elias. “Clinical Research at a Crossroads: the NIH Roadmap.” *Journal of Investigative Medicine* 54, 4 (2006): 171-173.

“The NIH Roadmap.” *Science* 302, 5642 (2003): 63-72.