INTERDISCIPLINARITY IN TRANSLATIONAL MEDICINE: A BIBLIOMETRIC CASE STUDY

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By

Jonathan Young

Dissertation Committee:

Rich Gazan, Chairperson

Julia Patriarche

Nancy Reed

Liz Davidson

Bruce Shiramizu

DEDICATION

For Alicia and Annika

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ABSTRACT

Translational research (TR) is the process of bringing innovations from basic science into applied science, usually referring to the practice of medicine. It has been assumed that cross-disciplinary collaboration, or interdisciplinarity research (IDR), is essential to translation. Yet there is a gap in the literature regarding the interaction between interdisciplinarity and translation. If interdisciplinarity is highly correlated with translational research, this relationship would open up the possibility of using bibliometric techniques to help evaluate and target TR research.

This dissertation uses a bibliometric case study approach to explore the progression of three innovations through the published literature, in order to better understand the role of interdisciplinarity in translation and study the application of bibliometric methods to TR. The translational importance of the literature of these cases was determined by qualitative coding in collaboration with a physician consultant, while interdisciplinarity was operationalized by both a variety of bibliometric IDR indicators as well as through qualitative coding.

The results show that there is a weak correlation between interdisciplinary indicators and translational research, with a random forest prediction model able to correctly identify translational records with 69% accuracy using these indicators. The progression of records in the cases did not fit the theoretical linear model of translation, and better supports a balanced circular model. Multidisciplinary research is observed in some cases, but interdisciplinary work is rare. Interdisciplinary research did not appear to be a necessary or sufficient component of translation. The bibliometric diversity indicators of Integration and Diffusion are shown to be useful in identifying this distribution of information in practice. The use of subject categories to study

translational research is found to be useful, but several caveats are noted, including the overlap of translational research areas within overly broad subjects.

It is hoped that the results from this study will enable TR policymakers to fund research with more confidence, promote the kinds of cross-disciplinary information flows that are most likely to benefit translation, and better evaluate the performance of such research using appropriate bibliometric methods. Ultimately, this understanding will improve TR and aid in its major goal of improving the health of society.

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LIST OF ABBREVIATIONS AND SYMBOLS

BC: Bibliographic Coupling

The number of cited references in common between two articles.

BtS: Back to Sleep

Pediatric innovation to instruct parents to place infants on their back to sleep to reduce the risk of Sudden Infant Death Syndrome.

CC: Co-citation

The number of times two articles are cited together.

CTSA: Clinical and Translational Science Awards

National Institutes of Health funding program to promote translational research

EBM: Evidence-based Medicine

Approach to medical practice that emphasizes scientific methods to inform clinical decision-making through reasoned use of the medical literature

HPV: Human Papillomavirus Vaccine

Vaccine that confers immunity to strains of the Human Papillomavirus that are linked to causing several types of cancer.

IDR: Interdisciplinary Research

Research that involves the presence of ideas, methods, or data from two or more scientific disciplines.

MeSH: Medical Subject Headings

A controlled vocabulary used in the National Institute of Health's PubMed bibliographic database

NIH: National Institutes of Health

A United States federal agency that conducts and provides funding for biomedical research.

RCT: Randomized Controlled Trial

A research design that compares the results of medical interventions to randomly assigned subjects, where one intervention is the control, or standard of comparison.

SIDS: Sudden Infant Death Syndrome

The unexplained death of an infant under 1 year of age during sleep.

TcB: Transcutaneous Bilirubinometry

The measurement of bilirubin levels using a device that detects changes in light through the skin.

TR: Translational Research

Medical studies that aim to apply findings from basic science to improve medical care and human health.

WoS: Web of Science

A bibliographic database produced by Thomson Reuters that makes use of citation indexing.

CHAPTER 1. INTRODUCTION

1.0 Executive Summary

Biomedical research ultimately needs to benefit the health of society. However, due to a variety of barriers to the implementation and dissemination of beneficial innovations, this is challenging. The efforts to overcome these challenges have been collectively termed translational research (TR). Yet identifying translational research can also be difficult. One common but untested assumption is that cross-disciplinary collaboration, or interdisciplinarity, is essential to promoting the movement of innovations into health care practice. If interdisciplinarity is actually highly correlated with translational research, this relationship would open up the possibility of using bibliometric techniques to help evaluate and target TR research.

The literature shows that while interdisciplinary research (IDR) is a complex phenomenon that spans a considerable variety of activities, consideration of these complexities is mostly absent from the discussion of translational research. The major theoretical models of translational research do not address interdisciplinarity specifically. While many institutional evaluations of translational research provide qualitative analysis of cross-disciplinary collaboration, there are few comparative studies that look at the larger issue of how these collaborations matter across the entire process of translation, which spans many years and many institutions. And while a number of bibliometric indicators have been developed to identify IDR in the scientific literature, they have not yet been frequently used in the study of translational research, and so the usefulness of this approach remains unclear.

This dissertation seeks to answer the question of how interdisciplinarity affects the movement of biomedical innovations through the translational process. It uses a bibliometric case study approach to explore the progression of three innovations through the published literature, seeking to understand the role of interdisciplinarity in these cases and to draw generalizable statements from them. These innovations, chosen for meeting a number of practical and theoretical criteria, are: human papillomavirus (HPV) vaccination, the Back to Sleep campaign and transcutaneous bilirubinometry.

The translational importance of the literature of these cases was determined by qualitative coding in collaboration with a physician consultant, while interdisciplinarity was operationalized by both a variety of bibliometric IDR indicators as well as qualitative coding. The second research question is: what bibliometric indicators are most useful in measuring translational research? The indicators used in this study include co-authorship, similarity measures based on the journal subject categories of cited references (Integration), and network measures such as betweenness centrality. The cases were evaluated qualitatively to answer the question of how IDR interacts with TR, and the bibliometric indicators that are most correlated with translational importance will be identified.

The results show that there is a weak correlation between interdisciplinary indicators and translational research, with a random forest prediction model able to correctly identify translational records with 69% accuracy using these indicators, with Integration Score being most important. The progression of records in the cases did not fit the theoretical linear model of translation, and better supports a circular model. Multidisciplinary teams are seen in some types of translational work, exhibiting contextual and composite interdisciplinary research. Integrative, theoretical or methodological interdisciplinary is rare and does not seem to be crucial to translational research. Interdisciplinary research is therefore not a necessary or sufficient component of translation, but the distribution of information to diverse disciplinary audiences seems to be an important contributor to translation. The bibliometric indicators of Integration and Diffusion are shown to be useful in identifying this distribution of information in practice. A refined model is proposed that incorporates the contribution of multidisciplinary research to translation, proposes the bibliometric indicators most useful for identifying particular translational areas and fits the temporal qualities of the data. This model predicts that the balanced appearance of all four translational stages of research best facilitates translation along with contextual and composite multidisciplinary research. The use of subject categories to study translational research is found to be useful, but several caveats are noted, including the overlap of translational research areas within overly broad subjects.

The results from this study will enable TR policymakers to fund research with more confidence, promote the kinds of cross-disciplinary information flows that are most likely to benefit translation, and better evaluate the performance of such research using appropriate

bibliometric methods. Ultimately, this understanding will improve TR and aid in its major goal of improving the health of society.

1.1 General Background

Until the last half of the 20th century, the advancement of medical science was the province of scientist-physicians who did both research and treated patients. With the explosion of complexity in biomedicine from the new fields of molecular biology and genomics, and the increasing complexity of medical practice itself, now basic biomedical research is primarily the province of PhD scientists who never see actual patients, while many clinicians never participate in research. This disconnect has been called 'the valley of death' due to the chasm it presents to the transmission of biomedical innovation (Butler 2008). Indeed, the time it takes to overcome this barrier between medical research and medical practice and bring a new discovery to patients has been estimated to average 17 years (Balas and Boren 2000).

The approach to bridge this gap, to move basic science discoveries into clinical practice, has been called translational research or translational medicine (Lenfant 2003). The goal of translational research is clear: to ensure that discoveries in the laboratory make their way successfully to the clinic in the shortest time possible. However, the best implementation and evaluation of such efforts are not as obvious (Butler 2008).

One common theme that pervades the translational research literature is the need for a new approach to research, one that involves collaboration and multidisciplinary or interdisciplinary team approaches (Zerhouni and Alving 2006). But just as translational research includes a wide range of concepts, so too is interdisciplinarity not simply one type of collaboration. Researchers have described an entire taxonomy of interdisciplinarity, defining differences depending on the degree of integration, the purpose of integration, or the intellectual distance between the disciplines (Klein 2010a). However, at present there is no model for how interdisciplinarity works in translational research and it remains unknown if it even contributes to enhancing the process of translation.

To address these questions, an objective method of measuring the process of translation is needed. Currently, evaluation of TR is most often done by using qualitative surveys that ask

participants specifically about their collaborations and research. However, this methodology is not scalable or easily compared across settings, making it only applicable for the local evaluation of individual institutions. For instance, it would be impossible to use this methodology to identify gaps of translational research across an entire field.

Another method to measure interdisciplinary research is to analyze the content of published scientific papers using bibliometric techniques that attempt to operationalize and quantify IDR in various ways. As publications are one of the major outputs of the research process, this can be an effective means to measure successful research. Examples include measuring collaboration, the presence of multiple disciplinary factors, or knowledge integration (Schummer 2004; Besselaar and Leydesdorff 1996; Porter and Rafols 2009). There have been studies on how to measure the interdisciplinarity of fields, researchers, and how information moves across disciplinary boundaries (Gowanlock and Gazan 2012; Rinia et al. 2002; Shi, Tseng, and Adamic 2009; Porter et al. 2006; Porter, Roessner, and Heberger 2008a). Many of these methods could prove useful in measuring translational research, yet there have only been a handful of studies applying this type of bibliometric network analysis in the TR evaluation literature (Cambrosio et al. 2006; Jones, Cambrosio, and Mogoutov 2011).

The central question of this study is to fill this void by combining a qualitative analysis of interdisciplinarity in translational research with bibliometric analysis to advance the methodology of how to measure TR. As Lord Kelvin once said, “If you cannot measure it, you cannot improve it.” This study seeks to make a contribution to the measurement and improvement of translational research, for the benefit of medicine and society.

1.2 Core Concepts

Three major concepts underlie this dissertation: translational research, interdisciplinarity, and bibliometric evaluation. Here, in brief, these core issues will be discussed. They will be examined in greater depth in Chapter 2.

1.2.1 Translational Research

What exactly is translational research? Is all research in the biomedical domain translational? While the only clear consensus on the definition of translational research might be that it means many different things to different people, there are some common concepts(Woolf 2008). The NIH for the purposes of its grant awards has defined that

> translational research includes two areas of translation. One is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science (National Institutes of Health 2014)

Phrased this way, translational research seems easy, just three particular research foci of an applied science. However, the reason that this has become a topic of global interest is that this particular applied science (what might be broadly termed health science), in actuality spans a huge range of disciplines and specialties, from the basic sciences of cell and molecular biology to clinical sciences such as pediatrics to the social sciences of public health, education, and economics.

The word translation has two distinct meanings, either to transform or to transfer, both of which can be seen in the concept of translational research (Zucker 2009). One definition of translation, somewhat technical and commonly seen in mathematics or physics, is the movement of an object, the transfer of it from one point in space to another. In this sense, translational research is the movement of an idea, a biomedical innovation, from its origin in the basic sciences, to its implementation in the health care system. This is evident in Rubio's definition of translational research, which "expedites the *movement* between basic research and patient-oriented research" and "facilitates the *movement* between patient-oriented research and population-based research" (emphasis added) (Rubio et al. 2010). The second meaning of translate is to transform, such as the process of making words or concepts in one language understandable in another, as in to translate English into French. In this sense, translational research is the process of making an idea, couched in the language of the basic sciences, understandable in the language and setting of the health care system. This can be seen in Kelley's discussion of translational research as "interdisciplinary conversation" and the facilitation of a "common understanding of the problem and goals" (Kelley et al. 2012).

In both of these conceptions, whether translation is understanding or translation is movement, the context and players of translational research are not physical space or literal languages, but the disciplinary language and structure of science and health care. Therefore, translational research is by definition inherently interdisciplinary. It refers to both the movement of an innovation through and between these disciplines and the interdisciplinary communication that must occur to enable that movement. Countless authors refer to the need for collaboration between disciplines and departments and the need to train multidisciplinary investigators to foster translational research (Duyk 2003; Westfall, Mold, and Fagnan 2007; Maienschein et al. 2008; Woolf 2008; Rubio et al. 2010). They may disagree on the extent to which interdisciplinary collaboration will foster their varying conceptions of translational research, but all agree on the vague idea of interdisciplinarity being somehow important. Some have even said that "translational research requires interdisciplinary scientists" (Bentires-Alj et al. 2015). However, studies on the potential benefits of interdisciplinarity have shown that

> it is not merely the integration or combination of multiple disciplines that enable interdisciplinary research to produce breakthroughs. Rather, it is the nature of that combination – the characteristics of the cognitive integration of concepts from disparate disciplines in novel configurations – that would indicate the potential of a given interdisciplinary effort to achieve a scientific breakthrough (Alexander et al. 2013)

Indeed, given how difficult it can be to successfully conduct interdisciplinary research, which has been called a "wicked problem," it should not be suggested lightly (Norris et al. 2016). This brings us to the second concept of this study: interdisciplinarity, which has a rich and complex character.

1.2.2 Interdisciplinarity

Interdisciplinarity is the second core concept of this dissertation. How to define interdisciplinarity is the subject of decades of debate in many fields, but Klein provides a useful starting point:

> Interdisciplinarity is neither a subject matter nor a body of content. It is a process for achieving an integrative synthesis, a process that usually begins with a problem, question, topic, or issue. Individuals must work to overcome problems created by differences in disciplinary language and world view (Klein 1990)

The key aspects of this definition are the notion of process and the goals of integration and synthesis of the approaches of multiple disciplines.

Clearly, any discussion of interdisciplinarity needs to address disciplinarity. A discipline is a scientific construct that encompasses cultural, intellectual, and social features (Sugimoto and Weingart 2015). Intellectually, it is a method of scientific inquiry, a set of appropriate questions and methods to investigate them, agreed upon by a group of scientists. At the same time, it is a group of scientists, a social structure, a community whose membership is dispersed but still linked by channels of journal communications and gatherings at conferences. And it is a cultural grouping as well, as evidenced by the development of disciplinary language and shared history, as well as citation and publishing practices.

The progress of science has always been accompanied by specialization. While in the distant past scholars may have been able to contribute to advances in areas as disparate as optics, economics, astronomy, mathematics, and physics, as Newton did, that is very difficult today. The specialization and depth of knowledge in each area of science contributes to the development of disciplines. These disciplines are cognitive, social, and cultural institutions that develop their own language, social networks, and accepted methods of inquiry and problems of interest.

Interdisciplinarity, then, is any activity, any process that bridges the separation between disciplines. It includes the concept of team science, where a large group drawn from many different disciplines cooperates and collaborates to solve a larger problem, a classic example being an interdisciplinary effort like the Human Genome Project. However, it also includes the single researcher who in his own training and interests, bridges the intellectual and social divisions that separate disciplines, exemplified in medicine by the clinician scientist (Lander and Atkinson-Grosjean 2011). These differences encompass the range of interdisciplinarity that some have termed “big” versus “small” interdisciplinarity (see Rinia’s work for further discussion of this typology) (Rinia and Wetenschappen 2007). Later, the various classifications of interdisciplinarity will be discussed, but here it will suffice to state that interdisciplinarity is a general concept with a myriad number of presentations. These presentations can vary across a number of dimensions, including the mode of research, the amount of disciplinary synthesis, and the intended outcome of the research (Aboelela et al. 2007). Given the wide range of definitions,

in this study we will cast a broad net, and include in our definition of interdisciplinarity any research with any level of knowledge integration from multiple disciplines. This will include what is often termed multidisciplinary as well as interdisciplinary work.

1.2.3 Bibliometric Evaluation

The final pillar of this dissertation is the use of bibliometric evaluation methods. Bibliometrics is a field of study that analyzes the published output of the scientific process. By studying these outputs, it aims to build an understanding of what science is and how it works. It allows for the quantitative measurement of scientific output, productivity, and scholarly communication. Moed defines bibliometrics as applications that "extract, aggregate and analyse quantitative aspects of bibliographic information. As statistics related to scholarship are applied mainly in the sciences, the term scientometrics is also often used" (Moed 2006).

One of the key concepts of this method is the analysis of citations. Citations are references in a published article to other works. These two terms, citations and references, are often used in lay terminology as synonyms, but will be used in this work with more precise definitions, as defined by Price:

> It seems to me a great pity to waste a good technical term by using the words citation and reference interchangeably. I therefore propose and adopt the convention that if Paper R contains a bibliographic footnote using and describing Paper C, then R contains a reference to C, and C has a citation from R. The number of references a paper has is measured by the number of items in its bibliography as endnotes and footnotes, etc., while the number of citations a paper has is found by looking it up on some sort of citation index and seeing how many other papers mention it (Price 1970)

Commonly, citations are used when an author wishes to note the importance of some past work in relation to the current work. Occasionally, citations are used for other purposes as well, such as acknowledging social obligation, refuting previous work, or even for self-promotion through self-citation (Wouters 1999; Greenberg 2009). Cited references are usually presented in a prescribed style, which allows some databases to, with great effort, record the citations made by each article (Garfield 1964). Others attempt to use machine learning to automatically extract citation information, but at present there are still many errors with this method (Jacsó 2010).

In recent years, bibliometrics has reached new levels of visibility due to the development of well known metrics that use citations such as the Impact Factor and the h-index. These are based in the measurement of citations as indicators of influence. By counting the number of citations to either a journal, or an author, these two indicators have provided an easy method to evaluate scientific prestige and productivity (Hirsch 2005; Garfield 2006). Early on, researchers recognized the potential to measure scientific influence through citations, as explained by the sociological researchers Cole and Cole:

> The problem of assessing the "quality" of scientific publications has long been a major impediment to progress ... The invention of the Science Citation Index (SCI) a few years ago provides a new and reliable tool to measure the significance of individual scientists'contributions ... The number of citations an individual receives may be tabulated and used as an indicator of the relative scientific significance or "quality" of that individual's publication (Cole and Cole 1971)

Of course, Cole and Cole go on to list several concerns about this assumption, including disparity in field sizes, critical citations, equal weighting of citations, obliteration by incorporation, citation half-life and multiple author collaboration. The accuracy and ramifications of using these metrics is still debated, and the literature addressing these concerns is beyond the scope of this review, but what is clear is that these types of bibliometric indicators are part of the current, evolving practice of science (Seglen 1997; Jacsó 2001; Bar-Ilan 2008; van Eck et al. 2013).

One criticism of bibliometrics that should be mentioned specifically is that it by definition privileges publications as the most important marker of scientific activity, ignoring the many other avenues of communication and indicators of prestige that undoubtedly exist in the real world. This limitation needs to be especially considered in a study like this, where one of the major fields of study consists of the applied field of clinical medicine, where the professionals who use the literature may contribute little to its actual content, in contrast to the situation in the basic sciences.

1.3 Problem Statement and Purpose of the Study

Currently, interdisciplinary collaboration is widely assumed to be a crucial part of translational research, but little research supports or clarifies that assertion, and few studies have been done on measuring such research using bibliometric methods. If interdisciplinarity is a key component of translational research, the bibliometric methods currently being used to study interdisciplinarity should be able to be successfully applied to measure TR. This study will test that assumption. By understanding specifically how interdisciplinary research occurs in translational research and how to measure it, future translational research efforts can be designed around promoting the kinds of interdisciplinary interactions that aid translational research and those efforts can be evaluated more effectively.

1.4 Research Questions

1.4.1 How do interdisciplinary interactions affect translational research?

The primary question that needs to be answered is how interdisciplinarity appears in the translational research process. There are anecdotes and assumptions in the literature about how interdisciplinary work drives translation forward, but no one has yet proposed a detailed model of how interdisciplinary interaction works in the translational process. Are there interdisciplinary interactions in all stages of translation? Is translation the result of multidisciplinary efforts of large teams, each doing their own disciplinary part, or individual investigators with multidisciplinary training? Do the translational stages correlate with disciplines? Does interdisciplinary research correlate with more efficient translational progress?

1.4.2 What are appropriate bibliometric indicators of interdisciplinarity in translational research?

The secondary set of questions involves the quantitative measurement of translational research using bibliometric methods. Interdisciplinarity is assumed to be part of translational research by definition, but IDR encompasses a wide range of activities, and different bibliometric measures are considered to measure different types of IDR. Which are most appropriate for the measurement of translational research? Is co-authorship a useful indicator of

interdisciplinarity in TR? Is interdisciplinary content more or less important than the interdisciplinary impact of a work in measuring translation? Are indicators based on journal subject categories able to distinguish the interdisciplinary interactions seen in TR, or are spatial, network measures more useful?

1.5 Summary

Translational research is widely considered to be an important effort in restructuring the biomedical scientific process to improve health care. While the precise definition of translational research varies, it is widely believed that interdisciplinarity is a key component. However, few studies have explored the role of interdisciplinarity in translational research directly, especially in a way that allows for large scale analysis that supports comparison across domains.

This study aims to fill a gap in our knowledge of translational research by taking a bibliometric approach and exploring the role of interdisciplinarity in the translational paths of three biomedical innovations in the past 30 years. In doing so, it will begin to answer the question of how interdisciplinarity contributes to translation, and also the secondary question of how best to measure translation with bibliometric approaches. Answering these questions will improve translation by improving our understanding of where in the translational process interdisciplinary interactions are most effective, and will improve the methodology of evaluating and identifying translational areas and gaps in the literature.

CHAPTER 2. LITERATURE REVIEW

2.1 The Biomedical Literature

As this study is at its heart a bibliometric analysis of the biomedical literature, some background on the literature is warranted.

The biomedical literature is the published, official record of research and innovation, and a basic overview of the terms and concepts in this literature is worth reviewing here (Hersh2009). One distinction is between primary and secondary literature, where primary literature consists of original research, while secondary is analysis and commentary on that research. Several types of secondary literature are highly important in the medical literature: systematic reviews and clinical guidelines. Systematic reviews (and related meta-analyses) are studies that aim to come to a single conclusion by looking comprehensively at all the evidence on a clinical question. Clinical guidelines are the recommendations of a group of clinicians, usually associated with a professional organization, for the standard of care on a particular medical issue. These are cornerstones of the EBM movement, which looks to foster medical decision-making based on the highest available scientific evidence, the gold standard of which are randomized controlled trials (RCTs). These clinical trials, when involved in drug development, are classified into phases to denote the process of development, and proceed from Phase 0, preclinical pharmacokinetic studies, to Phase I safety trials, Phase II efficacy trials, Phase III effectiveness studies, and Phase IV postmarketing research. These are the stereotyped research models seen in most biomedical innovations, especially pharmaceuticals. Following this standard process, some have called for implementation and comparative or cost effectiveness studies, but these are less standardized(Westrich, Wilhelm, and Schur 2016; Sampson et al. 2016).

2.2 Translational Research: Background and History

In 2003, the US Institute of Medicine published an article titled “Central Challenges Facing the National Research Enterprise” that called attention to a problem in medical innovation that had been slowly growing more pressing since the first half of the last century: the “disconnection between the promise of basic science and the delivery of better health” (Sung et

al. 2003). The problem is simple: while the US spends millions on biomedical research each year, it takes a very long time for any discoveries resulting from these investments to impact the health of the population. Maienschein calls the need to solve this problem the "translational ethos," the perspective that implementation of biomedical discoveries into health practice is the ultimate measure of success (Maienschein et al. 2008). This has a high failure rate when viewed in this manner. The most frequently cited figure is 17 years from first publication of a new innovation to incorporation into medical practice. This is the result of a study by Balas on the implementation of a sample of medical innovations, such as influenza vaccines and beta blockers after myocardial infarction, from 1968-1997 (Balas and Boren 2000) . While there are uncertainties including variations based on medical field, making the 17 year figure at best a ballpark estimate, there is broad consensus that the process takes too long (Morris, Wooding, and Grant 2011). There is also broad consensus on some of the basic structural features of the biomedical research system that cause this problem, though which internal or external factors (career incentives, lack of interdisciplinary communication, onerous regulatory requirements, lack of convincing evidence, etc.) are the largest contributors is still a matter of debate (Beaulieu et al. 2008; Heller and de Melo-Martin 2009; Laan and Boenink 2012a).

Fifty years ago, medicine was advanced and practiced by physicians who both treated patients and conducted research (Butler 2008). With the advent of highly specialized, technical fields such as genomics and molecular biology, biomedical research has become the province of PhDs working in academic institutions, where the publication of high impact research articles is the currency of the realm. Medical practice, on the other hand, is conducted by physicians who are compensated for treating patients, and have little time to even keep up with the advancing literature, let alone conduct research. The rate of publication of literature relevant to primary care physicians has been estimated to exceed 7,000 articles a month, which would require a physician to spend over 30 hours of scanning time a *day* (Alper et al. 2004). The distance between these two ends of the biomedical research chain has been termed a chasm, even a "valley of death" (Butler 2008), and bridging that divide is the motivation behind the funding and study of translational research. While translation as a phenomenon has obviously been occurring well before this time, this "dysfunctional separation" is a much more modern phenomenon, and it is hoped that the funding and study of translational research will improve the rate of translation (Gilchrest 2015).

The discourse on translational research, as a specific term, is relatively recent: while the first occurrence of the term was in 1993, primarily within cancer research, the discussion only truly began in the early 2000s. Since then the use of the term in the literature has undergone exponential growth, and today there are several thousand articles per year using the term (Butler 2008; Laan and Boenink 2012a). This coincides with the development and implementation of the Clinical Translational Science Award program of the NIH, launched in 2006, which specifically aimed to fund translational science through promoting collaborations and multidisciplinary training (Zerhouni and Alving 2006). Other funding efforts have gone on to target community partnerships and health disparities through cross-cultural and minority research, also through promoting collaboration (Kataoka-Yahiro et al. 2015; Hedges, Shiramizu, and Seto 2011). While there is now broad consensus on the problem that translational research needs to address, there are still disagreements over the precise definition, barriers, and endpoints of translational research. As Gehr and Garner state in a survey of a number of translational programs there is "no one path for successful translation but a myriad of strategies" (Gehr and Garner 2016). Further, there is disagreement about whether translational research models should be descriptive, and show the current state of biomedical research, or prescriptive, to propose a possibly more efficient process.

The first theoretical model of translational research was proposed by an Institute of Medicine initiative started in 2000 (Sung et al. 2003). This is a three step model that defines translational research as the application of science to better human health. It identified two major barriers to this movement. They called these barriers, translational blocks, as they prevent the movement, or translation, of knowledge along the path to improving health. The first was a translational block restricting the use of new knowledge of disease mechanisms, or basic behavioral mechanisms, from being applied to human interventions (Czajkowski et al. 2016). The second was a block on the study of these new human interventions that kept them from becoming available for medical practice. These blocks, T1 and T2, include a variety of issues from a lack of clinical trial participants to regulatory practices to career disincentives and lack of funding. This first model made it clear that translational research is a broader term than both diffusion of innovations or knowledge transfer, as it encompasses not only the transfer and uptake of the mature innovation, but also its transformation as it moves from basic science into

clinical practice (Gervais et al. 2015; Knapp, Simon, and Sharma 2015; Bottorff 2015; Parston et al. 2015; Albrecht et al. 2016).

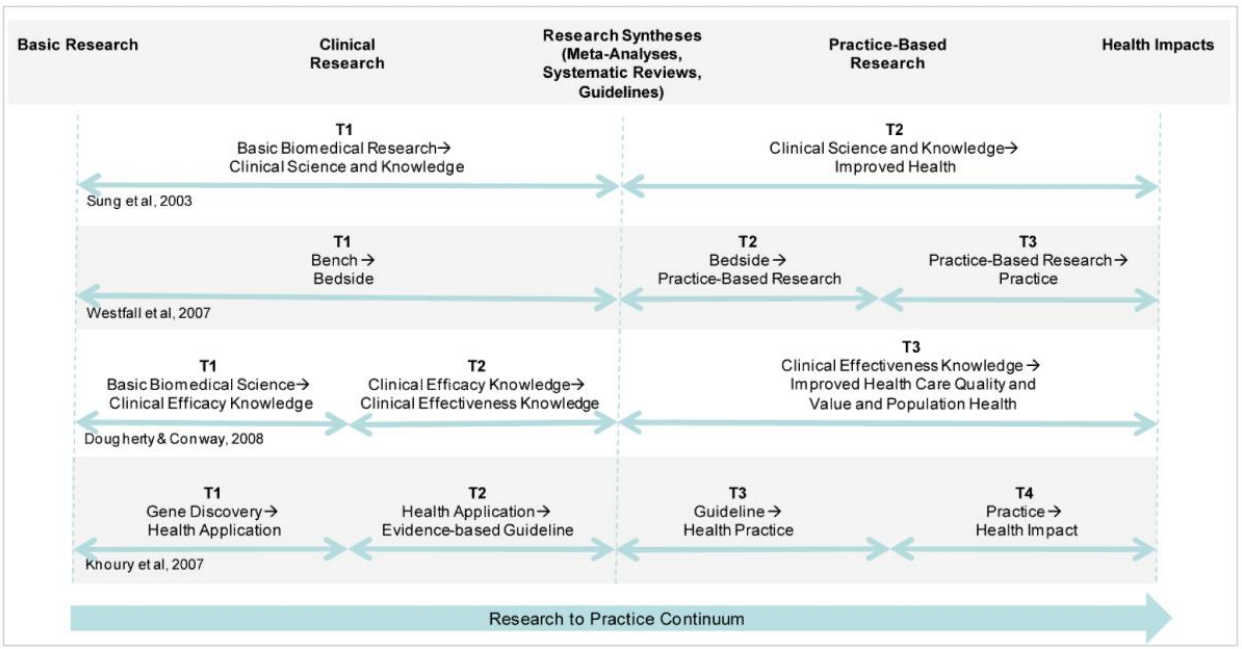
Westfall in 2007 proposed an expansion of this three step model to a four step model by the addition of a "practice-based research" step. This model leaves unchanged the first translational step from basic science to clinical science, but makes the claim that the leap from clinical knowledge to medical practice in thousands of outpatient, primary care settings across the country is unlikely without practice-based research that addresses the problems of implementation and dissemination of innovations (Westfall, Mold, and Fagnan 2007). Dougherty and Conway proposed a similar four step model, identifying the T1/T2/T3 blocks as barriers to research in clinical efficacy, effectiveness, and implementation (Dougherty and Conway 2008). Khoury described the translational research process as a continuum with four distinct phases, using T1-4 to label these phases rather than barriers (Khoury et al. 2007). Recently it has been proposed that the T3-T4 gap is actually the greatest barrier to translation (Sampson et al. 2016). Each of these models, aligned to show their similarities, is shown in Figure 2.1.

Trochim et al. argued that these phase-based models lack clear signposts of progress and proposed a process marker-based model that uses operational markers, such as the dates of first publication, clinical trials, or systematic reviews, to track the progress of translational research from basic to clinical to practice systems (Trochim et al. 2011).

Recently, Kelley et al. have argued for moving away from the linear model of research progressing from basic to clinical settings, and proposed a prescriptive, cyclical model where the phases of discovery, development, delivery, and outcomes are overlapping and all have roots in assessment and priority setting. This model drops the basic/clinical divide, and explicitly calls for interdisciplinary collaboration at all phases of translational research (Kelley et al. 2012). This has been supported by recent evidence showing that patient interaction is highly beneficial for basic science researchers involved in translation (Llopis and D'Este 2016). Similar recommendations were made by Hiatt and Breen in cancer research, calling for a "cross-disciplinary, multilevel framework" in research, where experts in social determinants, biological factors, psychological factors, and healthcare systems all collaborate at all stages of the translational process to correctly address the multifactorial issues (Hiatt and Breen 2008).

Lander and Atkinson-Grosjean proposed a lemniscate model of TR, as a result of their case study on the development of IRAK-4 diagnostic testing, where basic and clinical science continually exchange information (Lander and Atkinson-Grosjean 2011). These non-linear models are shown in Figure 2.2.

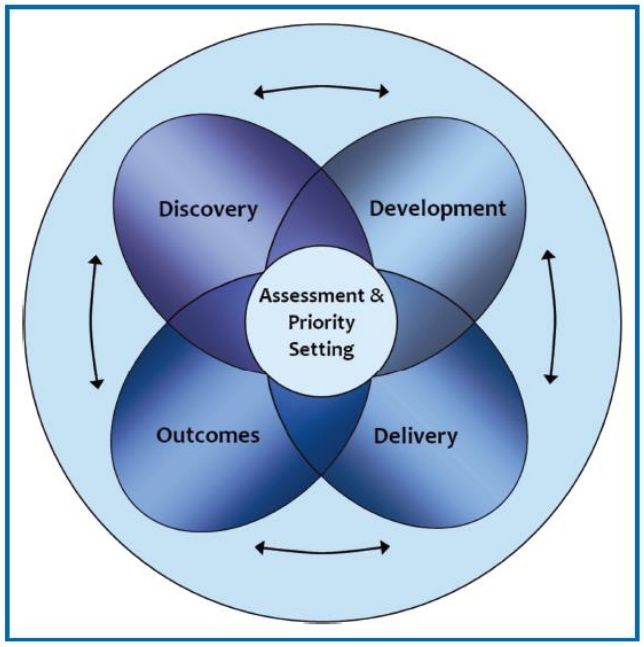
Figure 2.1. Linear Models of Translational Research



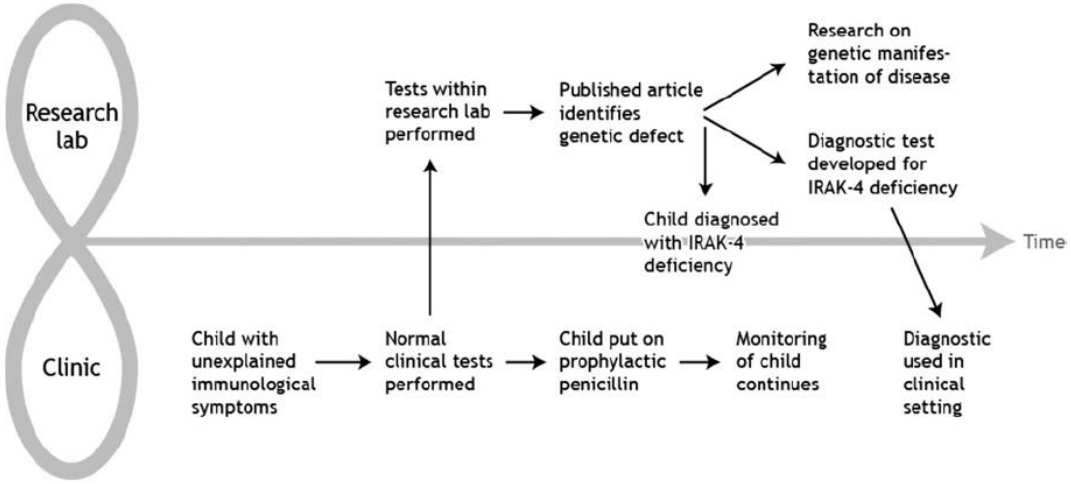
Reproduced from Trochim 2011

The four major iterations of the linear model of translational research are shown in order of complexity. The left to right arrow below shows the dominant translational motion from 'bench to bedside.'

Figure 2.2. Non-linear Models of Translational Research



Reproduced from Kelley 2012



Reproduced from Lander 2011

The TR model advanced by Kelley et al. (top), presents TR activities that are roughly equivalent to the T1-T4 activities in the linear models, but arranged in a radial fashion with no implied directionality. All are linked centrally by assessment and priority setting, which is absent in the linear models. Lander and Atkinson-Grosjean present a recurrent model, shown on the bottom left, where information flows continually between clinical and basic research, as supported by their case study details on the right.

These models show two trends. One is the clear progression and expansion of the scope of translational research. At the start, it dealt only with the process of bringing a basic science innovation (usually a new therapeutic drug) to market via government approval. This has progressed through additional iterations of the model to one where the scope of translational research extends from the basic science innovation to the research needed to show that it is improving health in a way that benefits society. This delineates a basic division between how translational research is defined. The more common understanding is that it is the bridging of a narrow gap preventing the implementation of a scientific discovery. The other is that it is a broad reconception of how biomedical science needs to work, a need to translate the concerns of all the disciplines involved in health care so that together they can develop solutions to health care problems (Maienschein et al. 2008; Laan and Boenink 2012a). While the major models are still framed in a linear, translation as movement paradigm, the expansion of the scope to questions of health impact allowed thinkers such as Kelley et al. to postulate that there might be a need for a more recurrent model of translation, one based more on communication and shared priority setting than the movement of a discovery through phases towards a defined endpoint. Early work in building a taxonomy of translational research models has been started by van der Laan and Boenink, and they propose three dimensions of variation: the location of the translational gap(s), the process of translation, and the cause of the gaps (Laan and Boenink 2012b).

However, all the models are highly abstract. As Trochim points out, none clearly help define the methods on which to base research evaluation. Yet, the evaluation of translational research is not an unexplored area.

2.3 Translational Research Evaluation

With the exception of Trochim's process marker model, none of the theoretical work described so far has explicitly addressed how to measure translational research. Of course, as agencies and institutions have begun to fund translational research, they are also highly interested in ways to measure whether such research is occurring. The NIH, since 2006, has been granting Clinical and Translational Science Awards (CSTA) with the explicit goal of the awards being to "integrate intellectual and physical resources essential to clinical and

translational science" (Zerhouni and Alving 2006). Naturally, being able to evaluate whether this integration is actually occurring is important (Leshner et al. 2013).

Traditional methods of evaluating TR have focused on institutionally centered reporting of various activities such as publications and partnerships (Kane, Rubio, and Trochim 2012). Rubio et al. describe such a method to demonstrate TR occurring in biostatistics research, consisting of three metrics: collaboration between researchers, publications, and methods development (Rubio et al. 2011). In analyzing this literature, it is clear that there is a notable trend of using qualitative methods to evaluate the interactions between researchers as evidence that they are conducting translational research (Schleyer, Teasley, and Bhatnagar 2005).

This is in keeping with the intent to measure all three stages of collaborative research described by Stokols et al: antecedents (the prior factors that enhance or inhibit collaboration), processes (the activities that contribute), and outcomes (the result of such collaboration) (Stokols et al. 2003). This type of local, contextual reporting can capture the personal interactions that are required for this type of research, measuring well the antecedents and processes. However, there are clear limitations as well, as it is costly and difficult to scale to allow for objective comparisons over time and between institutions, and some have proposed incorporating quantitative approaches for an improved measure of outputs and outcomes (Kagan et al. 2009). To address this Trochim et al. describe a mixed methods approach that uses a qualitative instrument to report on researcher activities and beliefs, including their perspective on transdisciplinarity and collaboration, while also reporting on publication and citation rates (Trochim et al. 2008). They conclude that the researchers in their study "value collaboration and transdisciplinarity." However, the evaluation of how interdisciplinarity may be involved in translation is still missing from the literature.

One aspect that is needed is to operationalize translation, which has commonly been done by using time as the output variable. Several studies have looked at the time lags of translation using various markers as a means to evaluate TR (Hanney et al. 2015). One was a study by Balas on nine different innovations (influenza vaccination, thrombolytic therapy, pneumococcal vaccination, diabetic eye examination, beta blockers after myocardial infarction, mammography, cholesterol screening, fecal occult blood test, diabetic foot care), measuring the time lag from their first landmark clinical trial to their implementation in clinical care, estimating 17 years

from publication to 50% adoption in clinical practice (Balas and Boren 2000). Trochim and Kane used data from clinical trial registrations to measure the delay in the implementation of trial protocols as a marker of translational efficiency (Kagan, Rosas, and Trochim 2010). In another study, the time from publication of an original study to incorporation in a systematic review was shown to average eight years (Trochim 2010). Grant agrees with this eight year time to incorporation, though estimates that effective incorporation of the clinically relevant research takes about 17 years (Grant et al. 2000). There seems to be a convergence of these estimates on this 17 year number, with other authors agreeing as well. For a more comprehensive review on time lags in biomedical publication, see Morris et al. (Morris, Wooding, and Grant 2011).

One area of evaluation that is still less studied is the measurement of interdisciplinarity as a proxy for translational research. This approach operationalizes translation not by the time to outcomes, but by the improvement of proximities between researchers (Molas-Gallart et al. 2015). Many of the institutional studies that have reported on translational research centers report how they establish infrastructure and incentives to promote interdisciplinary collaboration, but do not address how that has improved translation, outside of the assumption that the removal of communication barriers will improve TR (Berglund and Tarantal 2009). Researchers in the history of science have been doing case studies and narratives on the development of such major advances as molecular biology or magnetic resonance imaging, including the role of cross-disciplinary collaborations, but these have not been focused on identifying practical evaluation methods (Rosenberg 2009). Given that translational research must be interdisciplinary in some sense, by definition, it is reasonable to assume that some measure of interdisciplinarity might serve as an indirect measure of translational research. Before exploring this idea, first we should review the literature of interdisciplinarity to understand it in more detail.

2.4 Interdisciplinarity

Interdisciplinarity is a commonly mentioned phenomenon, but its precise definition is often left ambiguous. As will be seen, the term interdisciplinarity has been used to refer to many different goals, processes, and outcomes, all of which are valid. This study will describe a taxonomy of IDR that is based on two axes, the goal and the level of interdisciplinary

integration, based on that described by Klein (Klein 2010a). The first axis, the goal of the interaction, can vary between theoretical and methodological intent.

Theoretical interdisciplinarity seeks to achieve a unity of understanding by combining the particular disciplinary views of a subject into one whole. One example of this is the famous metaphor of an elephant in a dark room. Each disciplinary researcher can feel a different section of the great animal, and may describe it differently, but they all are referring to a single thing that only a combined viewpoint can truly understand.

In contrast, methodological interdisciplinarity seeks a practical solution to a large problem that one discipline cannot encompass in its entirety. Rather than attempting to understand a question from multiple angles, this mode of interdisciplinarity aims to bring the tools and approaches of many disciplines to bear upon a problem. Consider the Manhattan Project or the Human Genome Project as examples of this type of IDR.

The taxonomy that has gained the most traction in discussions of interdisciplinarity is the multidisciplinary, interdisciplinary, and transdisciplinary classification system (Huutoniemi et al. 2010). This taxonomy essentially classifies interdisciplinary research on the basis of the amount of integration that occurs between the disciplines involved, making this the second axis of Klein's taxonomy. At one end of the spectrum is multidisciplinarity, which is considered the basic and most essential form of interdisciplinarity. Multidisciplinarity is the cooperation of two or more disciplines on a research problem, but with no interaction or synthesis occurring between them. The classic example of this is working in a parallel team setting, where each disciplinary team member works on the problem in parallel in their own way (Ameredes et al. 2015; Wooten et al. 2015). Another is encyclopedic publishing, much as in a journal special issue on a subject in which there might be a number of articles published on a topic from different disciplines, but each is still contained within its own silo. In multidisciplinarity, there are multiple disciplines present, but the amount of integration between them is zero.

As integration occurs, the research enters the realm of interdisciplinary work. This may occur as models, methods, vocabulary, or people interact with another discipline. This can span a wide range of possible interactions, from a single author borrowing a single theory from another discipline to apply to his own, to an integrated team that applies their disciplinary

perspectives to generate an entirely new way of approaching a problem. That last example approaches the other end of the spectrum, transdisciplinary research, where the disciplinary perspectives are subsumed into a single unifying approach that crosses all the disciplines. One possible example of this is the team-based approach to health care currently being advocated, where a team of specialists, each with their disciplinary perspectives, are consulted by a single, transdisciplinary health care provider, who incorporates the perspectives of each specialist into a single coherent health care plan (Fay et al. 2006).

Given the wide range of possible manifestations of interdisciplinarity, what would it mean to use it as a way to measure translational research? Very few TR articles deal with interdisciplinarity as it relates to the translational process (Choi and Pak 2007; Choi and Pak 2008). The literature of team science, how to organize and operate large multidisciplinary teams, does address it as a variable to the process of efficient operation, but does not focus on the translation of innovations (Fay et al. 2006; Hall et al. 2008; Disis and Slattery 2010; Stokols et al. 2010; Lakhani, Benzies, and Hayden 2012). And it should be remembered that IDR is not a panacea that is always positive, but has real costs to implement and can lead to poorer outcomes or more costly research than traditional research (Yegros-Yegros, Rafols, and D'Este 2015; Wang, Thijs, and Glänzel 2015; Bromham, Dinnage, and Hua 2016; Chen, Arsenault, and Larivière 2015). Even a field as closely linked to biomedical research as biostatistics requires a great deal of expertise to integrate into the research process (Perkins et al. 2016). And there is a dearth of research on the specific communication strategies necessary to facilitate the appropriate type of interdisciplinary communication to enhance translation (Treise et al. 2016). While there is a general sense that interdisciplinarity must be important in translation, there is a lack of specific detail about which types of interdisciplinarity are involved or important in each of the stages of translation. Knowing these relationships would allow more targeted interventions by policymakers and research institutes to drive translation both in their own efforts and across the entire field. As noted above, one prominent methodology to allow for a broader investigation of interdisciplinarity and translation is bibliometrics, which has been applied to both these fields, but rarely together.

2.5 Quantitative (Bibliometric) Measures of Interdisciplinarity

The roots of bibliometric citation analysis go back to the legal practice of citing precedent cases in court opinions and briefs. Bibliometrics is the scientific study of the published literature. Just as in the legal literature, in the scientific literature it is common practice to cite previous work that influenced the current work in some way. The history of bibliometric analysis in its current form goes back to before the 1960s and the development of the first citation database, the Science Citation Index (Garfield 1955; Garfield 1964). Thus, bibliometric analysis has traditionally been associated with the use of these bibliographic databases to study the science of science. Recently there has been an extension of research into other types of media such as web pages, expanding bibliometric study outside the published journal literature (Bar-Ilan 2008). Scientometrics is a related term that has been introduced to emphasize the focus of the field on studying scientific activity, and to indicate that it is not limited to bibliographic databases. Yet, as peer-reviewed journal publication remains the currency of the realm for scientific research, the use of citation-based databases is still at the center of scientometrics.

Although the assumption that a citation is an indicator of the influence of the cited work has been hotly debated for decades, a consensus has developed that at least on the average, when comparing articles within the same field, higher citations correlate with higher influence (Leydesdorff et al. 2016). Increasingly, institutions and governments are using bibliometric citation analysis in evaluation, although many continue to warn against their use without considering the consequences (Weingart 2005). The h-index is one of the most used indicators, a citation based indicator that encompasses both productivity and impact(Hirsch 2005). Yet, despite their ease and popularity, there has been much discussion about the limitations of bibliometric indicators such as the h-index and the impact factor, including the issue that they are dependent on the particular fields of the researcher or journal (Waltman 2016; Bornmann and Daniel 2007).

This caveat of field specific citation data is particularly important in the context of this study on interdisciplinary research (Waltman and van Eck 2015; Ruiz-Castillo and Waltman 2015). Because each field has its own average rate of citations, it can be very misleading to compare raw values (Waltman 2016). What can be an excellent number of citations in a field such as Mathematics, can be a very common number in the field of Biochemistry, simply due to

the differences in citation practices between the fields (Batista, Campiteli, and Kinouchi 2006). This means that doing bibliometrics on interdisciplinary research is particularly challenging.

Here we will review the work that has been done to date on the specific question of how to measure translational or interdisciplinary research using bibliometrics. While the history of bibliometrics applied to medicine is long, it has a less robust relationship with translational research (Thompson and Walker 2015). As mentioned above, the bibliometric measurement of translational research is most often focused on measuring either the scientific output (in terms of number of publications), the influence of that output (in terms of h-index, impact factor or simply the number of citations), or the degree of collaboration (as shown by co-authorship statistics). There have been relatively few studies that go beyond these indirect indicators to attempt to measure translation directly.

A handful of studies have attempted to measure translation by looking at the citation connections between basic and clinical journals (Cambrosio et al. 2006; Jones, Cambrosio, and Mogoutov 2011), or at the subject headings given to articles (Weber 2013). Cambrosio et al. have published several studies that attempt to define a "translational interface" between the journals of clinical medicine and basic science. They utilize previous work by Lewison and Paraje that proposes the ability of a term filter based on title words and journal addresses to classify journals into clinical, mixed, or basic science categories (Lewison and Paraje 2004). Using this method, along with semantic and citation networks, Cambrosio et al. show that between 1980 and 2000, an intermediate group of translational journals in cancer research emerged that has citation links to both basic and clinical journals (Cambrosio et al. 2006). Further work goes on to show that this translational interface is field specific, not a general feature of all translational research, as the journal level translational interface in cardiac journals is much less widespread, and is biased towards certain topics (Jones, Cambrosio, and Mogoutov 2011). This is important for documenting the rise of a transitional journal system in some fields, but leaves open the question of whether this interdisciplinary interface can be detected at the article level.

One of the only studies that examines the article level bibliometric features of translational research is Lauto and Valetin's work, which finds that translational research shows interdisciplinary diversity, a measure of the number and type of different subjects within a

study's cited references, 30% higher than standard research (Lauto and Valentin 2016). This study operationalizes translational research as being the product of translational labs, which may be a simplification of the diversity of research interests of most scientists. It also combines the work of these labs into one pool, which given the difference in citing behavior in various fields may introduce errors. Finally, it uses only the Integration Score to measure interdisciplinarity, which may not be the best bibliometric indicator in this field. But it does lend some weight to the assumption that interdisciplinarity is involved in translation.

Weber uses a different approach, making use of the National Library of Medicine's Medical Subject Headings (MeSH) classification system to identify articles as either clinical or basic science focused based on the presence of the broad terms Human, Animal, or Cell, and to then position a journal or topical aggregation of articles based on its proportion of articles containing each term. Weber considers translational research to be any movement of a field towards the Human side of the triangle over time, and shows in several topics how the focus of a field can shift towards and away from human oriented research over time (Weber 2013). While the assumption that the translational stage of a field can be determined by the proportion of articles which are concerned with humans or animals is questionable (it ignores the entire progression of clinical trial phases, for example, which are all done in human subjects), and under some models movement away from humans could still be translational, this is still a pioneering work in attempting to trace a translational path through the literature.

Recently, another study has attempted to quantify the bibliometric properties of translational medicine by taking another approach. Luwel and Wijk chose to define translational research as articles published in translational journals (Luwel and Wijk 2015). There are weaknesses to this strategy of defining translation, namely that there will be many articles published that do not fit the definition of translational research even in a translational journal. However, they did find that while these articles are not more interdisciplinary in subjects cited than those articles from similar journals, they did seem to incorporate more variability in author departments.

The bibliometrics of interdisciplinary research in general, outside of medicine, has a larger body of work. For a recent review which discusses the measuring of IDR, including bibliometric measurement, see Wagner et al. (Wagner et al. 2011) . As described by Wagner et

al., the two principle types of approaches to bibliometric measurement of IDR are the structural or the spatial approaches. This refers to how the measurement models the phenomenon of science itself. If the approach accounts for the external structure of the scientific system (such as the hierarchy of nations, institutions, scientific groups, journals and departments), then it is structural in nature. If it looks at the system as a whole, looking for relationships between authors, articles or journals without regard for their nominal structure, then it is a spatial technique. The structural approach has been more commonly used, while spatial methods have started to be described more recently. Both have their advantages and disadvantages, for while scientific structures such as journals and institutional departments can be misleading, as each can contain outlying members that do not conform to the norm, they also carry information that does matter in reality.

The first attempts to measure interdisciplinary research using bibliometrics were founded in the principle of looking at the reference list of an article as a measure of its knowledge base (Morillo, Bordons, and Gómez 2001). If that knowledge base is made up of articles from journals that matched the citing article's discipline, that citing article could be said to be monodisciplinary. If, on the other hand, they are made up of articles from journals outside that discipline, that article is showing signs of interdisciplinarity. This is the basis for the Citations Outside Category metric (Porter and Chubin 1985).

Another indicator that has been proposed is based on co-authorship (Qiu 1992; Porter, Roessner, and Heberger 2008a; Huang and Chang 2011). This has been widely considered by bibliometricians as a weak measure of interdisciplinarity, due to both the practical limitation of author affiliation or discipline being unlisted in bibliographic databases, and the more fundamental objection that IDR can occur within the work of a single author, though it would necessarily be absent from a co-authorship indicator (Porter et al. 2007; Wagner et al. 2011). These concerns, along with the difficulty of determining knowledge integration, has led to few bibliometric approaches using this co-authorship method. However, it still appears as a frequent target of both interventions and evaluations (Seely, Kram, and Emans 2015). There is even some concern that collaboration could be a misleading factor in increasing citation counts independently of the quality of the work (Bornmann 2016).

More complicated indicators have been proposed by Porter (Porter et al. 2006). While these are citation based indicators, related to citations within category, they attempt to account for the baseline frequency of citations occurring between fields as an indicator of disciplinary relatedness. In this way, they try to discount citations between highly related fields as less interdisciplinary than citations between very different fields. This is accomplished by weighting citations by the frequency of the citations between their two subject categories in a large sample of the database. Porter et al. use this indicator, which they call Integration, to show that while authors today are citing a larger number of disciplines compared to in 1975, they are actually citing closely related disciplines, as evidenced by a lack of a trend in the increase of the Integration score over time. This is likely caused by the creation of specialized subfields, rather than a general trend towards IDR (Porter and Rafols 2009). Work continues to improve this type of indicator, such as by applying it to patents or emerging fields of research, and to correct for inaccuracies caused by missing data (Kwon, Porter, and Youtie 2016; Mund and Neuhäusler 2015; Mugabushaka, Kyriakou, and Papazoglou 2016b; Mugabushaka, Kyriakou, and Papazoglou 2016a; Moreno, Auzinger, and Werthner 2016).

As many of these structural approaches make use of the Web of Science subject categories, it is worth taking a closer look at them here. The Web of Science database classifies journals in a top down manner into disciplinary categories, based on the judgement of staff catalogers using information such as journal title and citation information (Leydesdorff and Rafols 2009). These have been shown to not necessarily match well with unsupervised methods to cluster the database (Leydesdorff 2006). In one study, it was shown that the subject categories matched with citation clusters in approximately 50% of cases (Boyack, Klavans, and Börner 2005). Nevertheless, they are still used as a means to identify some information about the subject matter of journals and have been commonly used to investigate interdisciplinarity (Leydesdorff and Rafols 2009). Especially in aggregate measures, they can be useful, as errors in classification will tend to be random and unbiased, while accurate classifications will dominate.

Spatial approaches ignore the a priori arrangement of science, and look for spatial relationships in the literature directly. This includes clustering techniques based on co-citation, co-author, or term relationships (Chen et al. 2014; Gowanlock and Gazan 2012). Other

approaches include metrics based on entropy, or global measures of diversity and network coherence (Rafols and Meyer 2009). Another method is to use network connectivity principles, derived from social network analysis, to look for articles or authors who exhibit a high degree of betweenness centrality, which is a measure of how much a node serves as a bridge between two otherwise isolated groups (Leydesdorff and Rafols 2011). All these methods look for relationships or similarity between authors, journals, or articles without using the groupings given by the structure of science. Especially in extremely new or highly dynamic fields, or in small subfields that may not be recognized as a distinct discipline, these methods can identify relationships that might elude other approaches.

There remains no consensus on the best bibliometric measures of IDR, although citations are a central part of many approaches, and each is likely to be sensitive to different manifestations of IDR. Recently, Jensen and Lutkouskaya studied the articles produced in European scientific laboratories, testing for interdisciplinarity using some of these indicators, including both top-down and bottom-up metrics, and showed with principal component analysis that IDR can be described along four major dimensions relating to collaboration, disciplinary distance, interaction type, and knowledge diversity. Each IDR indicator, therefore, seems to be measuring a different, equally valid aspect of IDR (Jensen and Lutkouskaya 2013). Other studies have used both of these types of metrics to explore, for example, the interdisciplinary development of fields such as nanoscience (Stopar et al. 2015; Chen et al. 2014). However, as Wagner et al. concludes,

> Among those relying on bibliometrics techniques, it is clear that citation analysis in several forms is widely accepted as a basis upon which to develop measures of IDR in various groupings of research output, but it is not the only measure. Within this set of tools, there are many methods used to reveal the structure or variety of knowledge sources within science. Exploration of various measures will continue to be of interest to academic bibliometrics researchers. But for the purposes of indicator development for use in policymaking and research management, such a variety of approaches to IDR become a complication rather than a revelation (Wagner et al. 2011)

Thus, for evaluation purposes, it would be ideal to demonstrate which of the many IDR indicators is most useful for a given setting, and this has yet to be done in the study of TR.

2.6 Conclusions from the Literature

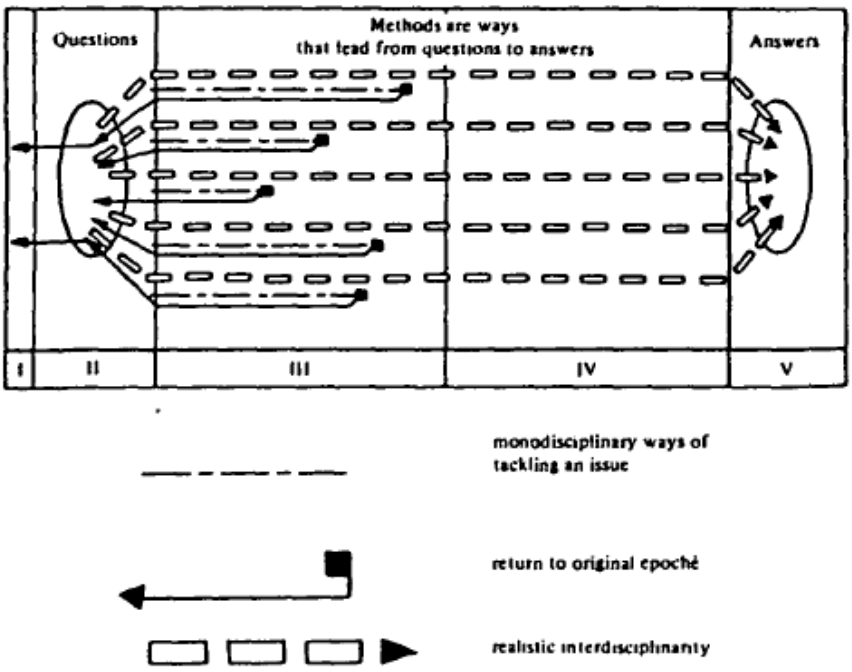
What we see in the literature are several lines of research that until now are mostly unconnected, but that share many underlying aspects. Interdisciplinarity is a widely dispersed area of study itself, but a consensus on several aspects of IDR has been described. Translational research theory has evolved from a narrow focus on barriers to clinical trials, to a discussion on the role of interdisciplinary communication and goal setting across the structure of biomedical science, but still remains vague on the nature of translation, and the role of interdisciplinarity. The definition of interdisciplinarity, as a process focused on achieving a synthesis that overcomes a problem too large for individual disciplines is very similar to the definition of translational research. Consider de Wachter's model of interdisciplinary research, shown in Figure 2.3, in relation to the models of translational research discussed earlier (Wachter 1982). Both show a process, a directionality from questions to answers, from innovation to implementation. But looking closer, linear translational models might be considered to orient their movement through disciplines, as if traveling in the vertical axis on de Wachter's model. This type of inconsistency in theory is part of why the consideration of interdisciplinarity in translational research remains an unanswered question.

There are common underlying forces at work in these areas, which might be expected due to their interrelations, perhaps originating from the practice of science, and they require careful consideration. The time lags observed in citation behavior, a well-studied aspect of bibliometrics, may be part of the cause of the translational time lags that occupy that field. Disciplinarity certainly plays a role in that, as evidenced by the known differences in citation lags based on whether citations are within fields or across disciplines. The literature as a whole therefore implies that any attempt to study translational research with bibliometrics will need to account for the particular context of how interdisciplinarity manifests within it. This is a complex and interrelated system, one which is difficult to study with methods of reduction. Bibliometric evaluation of translational research is almost non-existent, and while methods to detect interdisciplinary research have been growing in sophistication over the last decade, work still needs to be done to identify which indicators are most appropriate for TR.

This means that it is the appropriate time to conduct a study that will explore how the theories of interdisciplinarity can be applied to translational research, using the advances in

bibliometric techniques of the last decade to measure IDR and describe how translational research can be better measured.

Figure 2.3. de Wachter's Model of Interdisciplinarity



Reproduced from de Wachter 1982

This model of interdisciplinarity presents the process of interdisciplinarity as moving from questions to answers. The various disciplines involved are shown as lines in the vertical axis. The key activities are shown as monodisciplinary progress in phase III, which then return at various intervals to the question setting phase II, where disciplines collaborate to determine translations of the global questions into disciplinary language, which then can proceed via interdisciplinary research to reach global answers by using the contributions of all the disciplines.

CHAPTER 3. RESEARCH METHODS

3.1 Research Design

This study used a mixed methods design that combined qualitative case study methodology with bibliometric analysis. This is partially inspired by the call of Kane et al. for this type of research design to move translational research forward, as an example of

> case studies that can serve as essential evaluation components, with a 'case' defined as a drug, medical device, or a surgical process/procedure that has already been translated into clinical practice. FDA approval, Cochrane Reports, and Medicare/Medicaid approval serve as important marker points in successful translation. Once these cases and markers have been identified, evaluators engage in an activity that could be described as 'translational forensics,' in which they use publically available data sources such as literature reviews, patent records, and data mining in order to determine a genesis point for the cases. This information is then used to identify key participants, who are interviewed to document the entire story of the research translation from the initial discovery point(s) to clinical application(s). The interview data are analyzed and collated, relevant durations are calculated, and the TR pathways and timelines are depicted visually (Kane, Rubio, and Trochim 2012)

This type of approach was necessary to answer the interlinked questions of how interdisciplinarity affects translational research (requiring a contextually rich approach embedded in the particulars of each translational process), and how to identify and measure translation objectively (requiring quantitative bibliometric methods). This study traded off some contextual richness by using literature analysis instead of interview data to describe the story of the research path, in exchange for a greater breadth of comparison and increased generalization by including multiple case studies spanning years and institutions.

The motivation for this study design was to answer the research question of how to measure translational research, which cannot be addressed without both parts of this mixed methodology. One difficulty in studying translational research is that it is highly contextual, dependent on the specifics of the particular setting. Therefore, to understand the role that interdisciplinarity plays in it, it is essential to view the entire context, which is what case study methodology excels at. However, a good measurement tool is usable across settings, giving the ability to objectively compare measurement scores. This requires the quantitative methods of bibliometrics to show which metrics correlate with different aspects of translation. Without the case study method, these numbers would be ungrounded in the reality of what is occurring, and

without bibliometrics, any observations of interdisciplinary translational research would be difficult to generalize objectively. Both methods are necessary to answer this research question, and were used in this study.

3.2 Research Hypotheses

3.2.1 How do interdisciplinary interactions affect translational research?

Interdisciplinarity will likely be found at various stages of translational research, but there should be systematic differences between interdisciplinary research (IDR) at the basic sciences end of the translational process compared to that at the clinical end. The stages of translation that theorists have identified as T1-T4 may exhibit distinct phases of different types of interdisciplinarity. There will likely be both qualitative differences (such as whether the interaction can be described as multi-, inter-, or transdisciplinary) and quantitative differences (such as the proportion of cited references from different specific fields).

Previous work suggests that interdisciplinarity can reduce the time lag between an innovation's first description and its first highly cited article (Contopoulos-Ioannidis et al. 2008). Therefore, in this study, it might be expected that greater interdisciplinarity will lead to decreased time between translational markers. However, it is also known that poorly implemented or unnecessary interdisciplinarity is costly (Choi and Pak 2006).This necessitates the study of multiple examples of translation, and a mixed methods approach that can take into account the complexity and context of the data.

The linear model of translation would predict that the translational stages should appear in order, from T1 to T4. If this prediction is not validated, this would be evidence against the linear model of translation.

3.2.2 What are appropriate bibliometric indicators of interdisciplinarity in translational research?

Different bibliometric indicators of IDR will best measure different phases of translational research. As each indicator will be sensitive to certain types of interdisciplinary

interaction, if these interactions vary across the translational path, then the indicators that best identify translational research will vary accordingly.

It is expected that co-authorship will detect multidisciplinary team science research, but will fail at showing the translational contributions of single authors who have had multidisciplinary training (the training of which is one of the stated goals of the CTSA program) (Rubio et al. 2010). Indicators that are based on Web of Science (WoS) subject categories, such as the Integration score, may have difficulty identifying interdisciplinary research that occurs between clinical specialties or subgroups, which often all occur within one WoS subject, as is common when translating innovations to new populations or settings. Spatial indicators, such as betweenness centrality, should detect key articles or actors that first bring an innovation to a new research domain, but will not perform well if translational progress is not made in such a manner.

3.3 Research Procedure

The study method consisted of the following steps, from case selection through data analysis.

1) Selection of three case studies using defined criteria
2) Data collection of the highly cited journal literature of each case
3) Coding records into translational stages and roles
4) Calculating bibliometric indicators for each record
5) Prediction methods to quantify relationship between translation and IDR
6) Qualitative analysis using all above data

Table 3.1 shows the variables of interest, the measurements that are used to operationalize them, and the research questions each variable addresses.

Table 3.1. Variables and Measurements

	Variable	Level	Operational Measurements
1	Collaboration	Article	Co-authorship
2	Interdisciplinary Interaction	Article	Type of IDR
3	Interdisciplinary Distance	Article	Scope of IDR
4	Interdisciplinarity Knowledge Integration	Article/Innovation	Cited Reference Integration
5	Translational Role	Article	Translational Stage and Study Type
6	Translational Efficiency	Innovation	Time Between Translational Stages
7	Interdisciplinary Impact	Article	Citation Integration / Co-citation BC
8	Publication Impact	Article	Field Normalized Citations per year
9	Spatial Interdisciplinarity	Article	Bibliographic Coupling Betweenness Centrality
10	Discipline	Article	Web of Science Journal Subject Category

Research Question	Independent Variables	Dependent Variables
How does IDR affect TR?	2,3	5
Is TR advanced by team science or multidisciplinary researchers?	1	5
Does IDR lead to more efficient TR?	2,3	6
Do translational stages correlate with disciplinarity?	5	2,3
What are appropriate indicators for TR?	1,4,7,8,9	5
How well do IDR indicators measure IDR in TR?	1,4,7,9	2,3
Are IDR indicators better than influence indicators at measuring TR?	4,7,8,9	5
Are spatial indicators better than structural at measuring TR?	4,9	5
Is ID content better than ID impact at measuring TR?	4,7,9	5

An outline of the variables measured in this study and the research questions they address. IDR = Interdisciplinary research. TR = Translational research.

3.4 Case Study Selection

The cases selected were chosen based on several criteria. First, the domain of the innovation needed to be within pediatrics. The content expertise of the physician collaborating on this project is centered in pediatrics, and therefore the case studies were drawn from pediatric innovations that fall within this domain. While the precise boundaries that define an innovation are necessarily somewhat arbitrary, an operational definition was constructed for each that took into account the published literature and clinical relevance (Contopoulos-Ioannidis et al. 2008).

The cases needed to have an established history of publication that spans the translational process. In practice, since this process takes nearly 20 years on average, this means that the first description of the innovation should occur no later than the early 1990s. While this excludes those recent innovations that have not passed the clinical trial stage, this study is not able to

differentiate the wide variety of factors that may contribute to that result, and therefore this exclusion seemed appropriate. This provided a rough upper limit on the date of the innovation. There also needed to be at least one example of late stage, T4 published research on the innovation.

In addition, the publications that represent the translational process of the innovation must be contained within the time period that has accessible Web of Science coverage. As the University of Hawai'i has access to Web of Science from 1980 to present, this provides a lower limit on the date of the innovation to 1980. As WoS journal coverage is not complete in all years for all journals, the presence of 90% of landmark articles as suggested by the content expert was also required, which was determined by inspection of recent review articles on each case.

Cases were selected to cover a wide range of biomedical innovations. The translational process, while conceptually similar, may differ in detail depending on whether the innovation is a new pharmaceutical, biomedical device, or simply a change in clinical practice. Cases from these different types were selected to try to determine the similarities that cut across them. As there is no theory in the translational research literature predicting differences in interdisciplinary work depending on innovation type, three cases were chosen based on the recommended number of replications according to Yin's multiple case study methodology (Yin 2013).

As a reminder, case study selection is not equivalent to the selection of a representative sample for statistical generalization. Instead, it is akin to the selection of a set of *experiments*, not the samples within them. They are chosen to test theory, and any generalization will be through the testing and development of theory, not the description of a population.

3.5 Data Collection

In order to study the published output of translational research, a number of approaches could be considered. Commonly, the evaluation of individual researchers or institutions retrieves published works from curriculum vitae or academic websites. This offers the advantage of comprehensive retrieval, independent of the coverage of any limited subset of databases, but is a non-scalable, costly method that is difficult to use to analyze large datasets or entire fields. In contrast, information retrieval from a single database must always consider coverage and bias in its data collection, but has the potential of analyzing a larger dataset. For this study, as the objective is to follow innovations through the translational pathway, across multiple researchers and institutions, the second method is used.

For the choice of database, one key consideration is the availability of citation information. Most bibliographic databases do not record this information in a readily accessible format. Of those that do, three are foremost, Thomson Reuters Web of Science, Scopus, and Google Scholar. Google Scholar, while possibly containing the largest set of records, lacks an easy interface that allows for the extraction of data, and is widely considered to have considerable errors in its citation and bibliographic data (Jacsó 2010; Jacsó 2011; Rothfus et al. 2016). Between Web of Science and Scopus, while Scopus may have better coverage of non-English articles in the medical field, Web of Science has a much greater coverage of older (pre-1996) literature (Kulkarni et al. 2009). Other research shows that WoS is also superior for the accuracy of its journal subject categories (Wang and Waltman 2016). For the purpose of this study, which aims to trace the progress of innovations from their first description to their implementation, this temporal depth of coverage is important, with the understanding that there may be a bias towards Western medicine. While there may be additional records for each case that are missed by choosing to use a citation enhanced database rather than a specialized medical database such as PubMed, as the bibliometric research questions to be addressed here involve citation information, the tradeoff is necessary. This caveat is further reduced by the confirmation that the manually chosen landmark articles are almost all found in the Web of Science coverage.

3.5.1 Web of Science Record Retrieval

3.5.1.1 Case Study Records

Records were collected from Thomson Reuters Web of Science citation database using comprehensive keyword searches. The results were limited to the main publications types of Article and Review, which are the main publication types used for scholarly communication in the biomedical sciences. Only those records with at least three citations were included, in order to allow citation based comparisons to be done on the entire dataset. The Web of Science coverage provided by the University of Hawaii Libraries is from 1980 to present, though specific journals may have different levels of coverage over time. Full searches are shown in Appendix 7.1. The role of the content expert was to first provide a level of medical expertise to the retrieval of the case records, and subsequently to provide that same expertise to the coding of translational records. To verify the completeness of the search retrieval, the content expert was asked to create lists of landmark articles that prominently featured in the medical knowledge of each case, from review articles, textbooks, and systematic reviews. These lists are shown in Appendix 7.4.

Case 1: Human Papillomavirus Vaccination

Defining the innovation of a vaccine against human papillomavirus for the ultimate purpose of reducing the impact of the cancers caused by it was complicated by several issues. First, there were two major vaccines against HPV serotypes developed within the same general time period, the HPV2 and HPV4 vaccines. For the purpose of this study, it did not seem to be relevant to distinguish between the two, especially since most clinical guidelines do not treat them differently. Second, the use of the vaccine as a therapeutic intervention on patients already infected with HPV has been explored, but this study considers this a separate case, and therefore only includes articles on the prophylactic use of the HPV vaccine. Also, there is a large and rich literature on the precursor research that led to the HPV vaccines, such as the work developing virus-like particles (VLP), and the evidence that indicated that the HPV virus is causally linked to cancers. These areas of research, while essential for the innovation, were considered to not

meet the definition of translational research given above. Finally, studies have looked at the use of the HPV vaccine to improve health outside of the prevention of cancers, such as reduction of genital warts, and this study included all outcomes measures. The final definition of the HPV vaccine research used was:

Research on a prophylactic vaccine aimed at reducing disease resulting from infection by human papillomavirus strains.

The search strategy was constructed to do a full field search (to maximize recall at the cost of precision which would be regained upon manual inspection) in all Web of Science databases from 1980 to 2013, limiting the results to English language records and record types primarily cited in medical research (Article and Review). The search included multiple variants of the trade names of the vaccines (e.g. Gardasil, Cervarix). The search was compared to a list of landmark articles provided by a content expert to provide a baseline level of recall, and 100% of the landmark list was retrieved. The full search strategy is included in the Appendix. Those records that were determined to be possibly translational after manual inspection were used as a search in Web of Science to retrieve the records that cited them (citing records).

The initial search retrieved 6791 records that fit the algorithmic relevance criteria. These were analyzed for topical relevance to the case topic by manual inspection of title and abstract. Of these initial retrievals, 576 were determined to be topically relevant to the case. Topical relevance was defined as meeting the definition of the case given above. Examples of algorithmically relevant but non-topical results include studies on non-human animal models or studies of therapeutic, not prophylactic, interventions. The Web of Science ID of these records was then used as a search query to retrieve the citing articles in Web of Science that reference these 576 case records. 6437 citing articles were retrieved that cite the case records.

Case 2: Back to Sleep Campaign

Defining the innovation of promoting the placing of infants to sleep in the prone rather than supine or side positions to reduce the risk of Sudden Infant Death Syndrome in the first year of life presented several challenges. The extent to which basic research on the physiology of

infant sleep should be included, which was nominally motivated by SIDS, was difficult to determine. Further, whether to include population health studies on the rate of SIDS, regardless of sleep position, was also a question that could reasonably be asked. Ultimately, it was decided that given that the medical innovation was the sleep position advice, not the general study of SIDS, any research would need to include analysis of sleep position to be included in the case study. The final definition used was:

Research on infant sleep position aimed at reducing Sudden Infant Death Syndrome.

The search strategy was constructed to do a full field search (to maximize recall at the cost of precision which would be regained upon manual inspection) in all Web of Science databases from 1980 to 2013, limiting the results to English language records and record types primarily cited in medical research (Article and Review). The search was compared to a list of landmark articles provided by a content expert to provide a baseline level of recall, and 92% of the landmark list was retrieved. The full search strategy is included in the Appendix.

The initial search retrieved 1088 records that fit the algorithmic relevance criteria. These were analyzed for topical relevance to the case topic by manual inspection of title and abstract. Of these initial retrievals, 246 were determined to be topically relevant to the case. The Web of Science ID of these records was then used as a search query to retrieve the citing articles in Web of Science that reference these 246 case records. 2990 citing articles were retrieved that cite the case records.

Case 3: Transcutaneous Bilirubinometry

The major issue in defining the innovation of using a device to measure the concentration of bilirubin in the skin of a newborn to determine the risk of pathologic hyperbilirubinemia was the wide variety of implementations of the device. It was deemed that all devices that performed transcutaneous measurements of bilirubin levels would be included, while devices that merely provided "color guides" to aid in visual diagnosis of jaundice would be excluded. The final definition used was:

Research on any device measuring bilirubin levels using optical means for the purpose of reducing hyperbilirubinemia.

The search strategy was constructed to do a full field search (to maximize recall at the cost of precision which would be regained upon manual inspection) in all Web of Science databases from 1980 to 2013, limiting the results to English language records and record types primarily cited in medical research (Article and Review). The search was compared to a list of landmark articles provided by a content expert to provide a baseline level of recall, and 100% of the landmark list was retrieved. The full search strategy is included in the Appendix.

The initial search retrieved 1315 records that fit the algorithmic relevance criteria. These were analyzed for topical relevance to the case topic by manual inspection of title and abstract. Of these initial retrievals, 104 were determined to be topically relevant to the case. The Web of Science ID of these records was then used as a search query to retrieve the citing articles in Web of Science that reference these 104 case records. 887 citing articles were retrieved that cite the case records.

3.5.1.2 Reference Set Records

In order to provide a large set of articles that can be used to compare the average values of bibliometric indicators over the long time span examined by this study (1980 – 2013), three sets of data were collected: 1990, 2000, 2010. A one month period from that year (all December articles) was collected for each of the sets by performing a title search including all 26 initial letters followed with wildcard operators limited to English language articles. The size of the datasets are 39,860 (1990), 61,411 (2000), and 87,147 (2010) records. These records were then used to generate the subject category similarity matrix, discussed below.

3.6 Data Analysis

3.6.1 Qualitative Coding of Translational Research

In order to determine whether each record fit the definition of translational research, as well as classify whether it could be described as research in a particular stage of the translational process according to the process model, qualitative coding of the records was done using titles, abstracts, as well as full text when necessary.

Coding was performed by two coders, one a content expert and one a non-expert, in accordance with guidelines published by the Cochrane Library for Systematic Reviews (Higgins and Green 2011). Coding was done independently, using the Dedoose Collaborative Coding Software. Following independent coding, the coders discussed all disagreements until consensus was reached.

Codes were given to records using the code book shown in the Appendix on the Translational Stage of the record. When there were no clear indications in the title and abstract for the placement of a record in a particular code, a note was used to indicate that the full text record should be consulted during the consensus stage. Prior to the consensus making, 89.96% of records matched on Translational Stage and 86.58% of records matched on Study Type.

A stratified subset of the records of each case was chosen for full text qualitative review based on the highest times cited, and highest integration score, diffusion score, bibliographic coupling betweenness, co-citation betweenness, and number of authors. Also, key records in the history of each case were chosen, namely the first appearance of each translational stage, the first appearance of clinical trials or guidelines, and any other important record as determined by the content expert. These texts were reviewed for indications of interdisciplinary interaction and trends in author disciplinarity, using the coding book presented in the Appendix. A total of 82 full text articles were reviewed. A summary of the coding questions and examples are shown in Figure 3.1.

Figure 3.1. Full Text Qualitative Coding Method and Examples

	Qualitative Analysis of Full Texts Methodology		
Coding Question	Types of IDR	Definition	Example
Do authors show affiliation with multiple disciplines?		"Research that involves several fields"	Division of Adolescent Medicine; Division of Adolescent Medicine; Division of Infectious Diseases; Center for Epidemiology and Biostatistics; Division of Adolescent and Behavioral Health
Are methods used which are associated with multiple disciplines?	Composite Multidisciplinarity	"Complementary skills are used to tackle complex problems"	Gynaecological examination; PCR analysis; Vaccine adjuvant preparation; Colposcopy; Biopsy Lesion Typing
Are theories applied which are associated with multiple disciplines?	Contextualizing Multidisciplinarity	"Knowledge produced within other fields is taken into account when identifying research goals."	Theory of Planned Behavior; Pediatric Vaccination Practice
Are there indications of integration between disciplines?	Methodological, Theoretical Interdisciplinarity	"Active interaction across fields during the framing of research problems, execution of research, or analysis of results"	Intravascular/Extravascular Model of Transcutaneous Bilirubinometry

[1]

The questions posed to the qualitative coders of the full text sample of the dataset, definitions, and the types of IDR they address are shown here. An example drawn from the coding set for a positive identification of each question is shown in the final column.

[1](Bosschaart et al. 2012; Lakhani, Benzies, and Hayden 2012; Villa et al. 2005)

3.6.2 Bibliometric Analysis

Bibliometric analysis was done primarily using custom scripted Python code. Centrality measures were calculated with the Python igraph library (Csardi and Nepusz 2006).

3.6.2.1 Subject Similarity

In order to determine the degree which two subject categories are related, the approach used in this research is to measure the co-citedness of each subject pair in a large sample of the Web of Science literature.

The cited references of the reference set records were extracted and then matched by source name to a list of Web of Science sources by subject category. The frequency of the co-occurence of subject categories within cited reference sets was used to create a subject similarity matrix. Each vector of the co-occurence matrix was compared with the vector of other subject categories and the cosine similarity was calculated. If x and y are the count of co-occurences with subject i for each of the two vectors, their cosine similarity is given by:

$$\frac{\sum_i (x_i y_i)}{\sqrt{\sum_i x_i^2 \sum_i y_i^2}}$$

This yields a value between 0 and 1 (in positive space) that represents their similarity. Using this, a SCxSC similarity matrix was constructed to provide the similarities of all SC combinations.

Additional similarity matrices were created for each of the reference set years (1990, 2000, 2010) as well as a combined matrix using the pooled reference data.

3.6.2.2 Knowledge Integration Score

The integration score of a record was calculated based upon the number of cited references it contained, weighted by their similarity. This calculation was defined by Porter (Porter, Roessner, and Heberger 2008b). This metric takes into account the three aspects of diversity of a reference set: the number of different types, the proportion of those different types, and the amount of difference between those types.

Therefore, the integration score of a paper is calculated as follows:

For each subject category cited in the reference list, determine the normalized proportions of co-occurence with other subject categories. Multiply each subject category pair's proportions with their similarity in the SCxSC similarity matrix. Sum over all categories, and subtract from 1 to give a value between 0 and 1 that is 0 when all cited references are from a single subject category, and 1 when they are all from maximally dissimilar categories. Shown mathematically:

$$I = 1 - \sum_{i,j} s_{ij} p_i p_j$$

3.6.2.3 Interdisciplinary Diffusion Score

The diffusion score is a measure of the diversity of the citations to a given record. It is calculated in the same fashion as the integration score, but using the citations of an article rather than the cited references. The same formula is used as shown above, but the citing articles, rather than the cited references are used.

3.6.2.4 Betweenness Centrality

Betweenness centrality is a network measure of interdisciplinarity that does not depend on predetermined properties such as subject categories. It instead is a property solely of the position of the record in a network, most specifically how centrally located it is as a bridge *between* otherwise non-connected groups.

This is calculated by determining the shortest paths between every pair of nodes in the network, where the betweenness centrality of a given node is given by the sum of the number of those shortest paths that pass through it. This value scales with the size of the network, so it is normalized to provide a value from 0 to 1.

The two types of networks used in this study are the bibliographic coupling network and the co-citation network. They are networks that can show the relationship between records by creating links based on the strength of the co-occurrence of records. In the case of the bibliographic coupling network, that co-occurrence happens between the reference lists of the two records: how many references do these two records share? In the co-citation network, this co-occurrence happens within the reference lists of later records: how many times do these two records appear together in reference lists?

3.6.2.5 Field Normalization

As it is well established that different subject fields display significantly different citation behaviors, the state of the art of analyzing citations in bibliometric analysis is to normalize citation counts based on journal subjects.

The reference data set from 1990, 2000, and 2010 was used to calculate the baseline total citations and the rate of citations per year for each of the Web of Science journal categories. These values were then used to calculate the ratio for each record in the translational dataset for these two metrics based on the subject categories of its source journal. In the case of journals with multiple categories, the baseline values were averaged between all the listed subjects equally.

3.6.3 Prediction Methods

A variety of machine learning algorithms were applied to the bibliometric data to determine if any useful correlations could be found between translational stage and the bibliometric indicators. The data was split between training and testing groups using a predefined seed to enable replication. For case based predictions, the data was split within each

case. Stratified sampling was used for cases that had small numbers of records in certain categories. Analysis was done using the R programming language, making use of the RandomForest package (Liaw and Wiener 2002).

3.6.3.1 Decision Tree Learning

Decision trees are useful as predictive modeling tools because of several properties that make them easy to implement. They are scaling invariant, and are able to determine the most useful variables for prediction. Furthermore, they are intuitive and can aid in understanding the landscape of a dataset. However, they are vulnerable to overfitting, which is addressed by the use of random forests. Overfitting is the training of the learning algorithm to specific patterns of noise in the data, rather than to generalizable trends. It leads to predictors that do very well on the trained data, but poorly on other datasets.

3.6.3.2 Random Forests

Random forests use a bootstrap aggregation method to generate a large number of decision trees and approach a solution. Given a training set, a large number of random samples of the dataset are taken with replacement, each used to generate a decision tree. This leads to reduced overfitting, as the noise within the samples are averaged out over the multiple trees.

In this study, random forests of 5000 trees were generated. Variable importance was calculated by permuting the values of each variable randomly and calculating the change in the number of incorrect assignments after this change (change in classification accuracy).

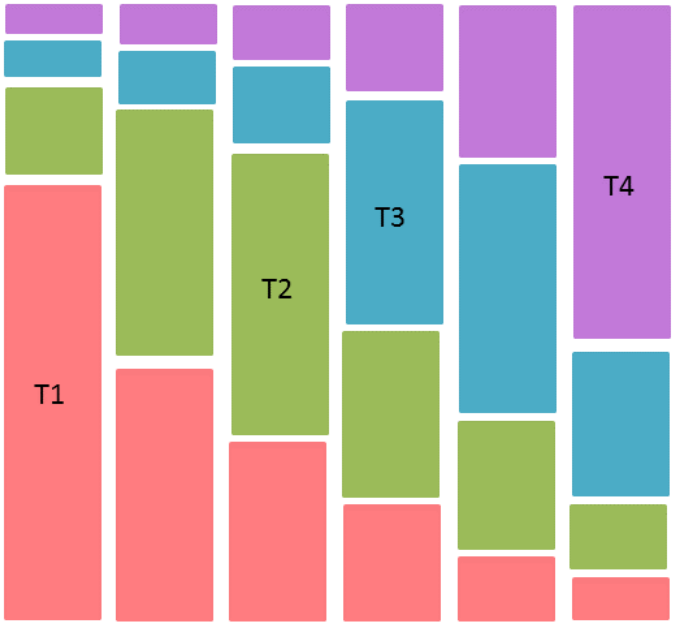
As a visualization aid, distances between data points were plotted in two dimensions using multidimensional scaling. This visualization method plots the proximity matrix of classification results for each data point in two-dimensional space while maintaining relative distance between points based on their relatedness.

CHAPTER 4. RESULTS AND DISCUSSION

4.1 Bibliometric Description of Cases

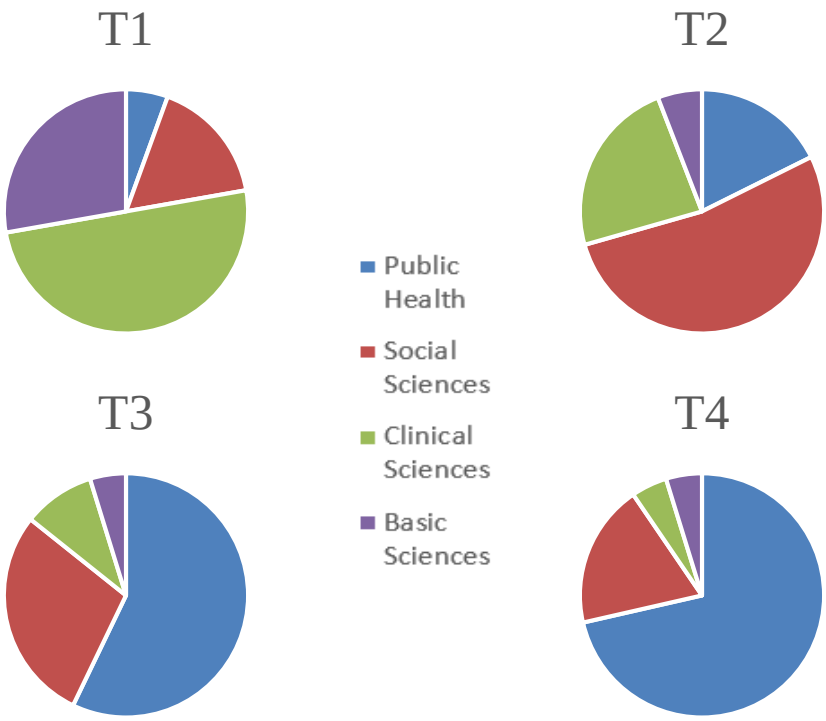
For each case, the bibliometric measures that describe the parameters of the dataset were calculated. These include the journal subjects and number of records over time, as well as the distribution of subjects among cited and citing references. This analysis aims to answer the research questions addressing whether translational stages correlate with disciplinarity. It also tests the basic assumptions of the linear model of translation. This model would be expected to show up in the data showing some basic patterns. As shown in Figure 4.1, the translational stages should be expected to appear roughly in order from T1 to T4. In real data, there will of course be expected to be some noise on the boundaries, but the centers of the distribution of each stage should be clearly in order. In addition, there should be a pattern of knowledge sources, where the stages progress from being based in basic sciences at T1, to clinical sciences, social sciences, and public health as the research moves to T4. This is idealized in Figure 4.2. This should be true for both cited references, and citing records, shown in Figure 4.3. This prediction comes out of the theory of translation positing that each stage serves as the predecessor and inspiration for the following stage. In bibliometric terms, this should manifest as citations flowing forward through the stages from T1 to T4.

Figure 4.1. Expected Translational Stages over Time



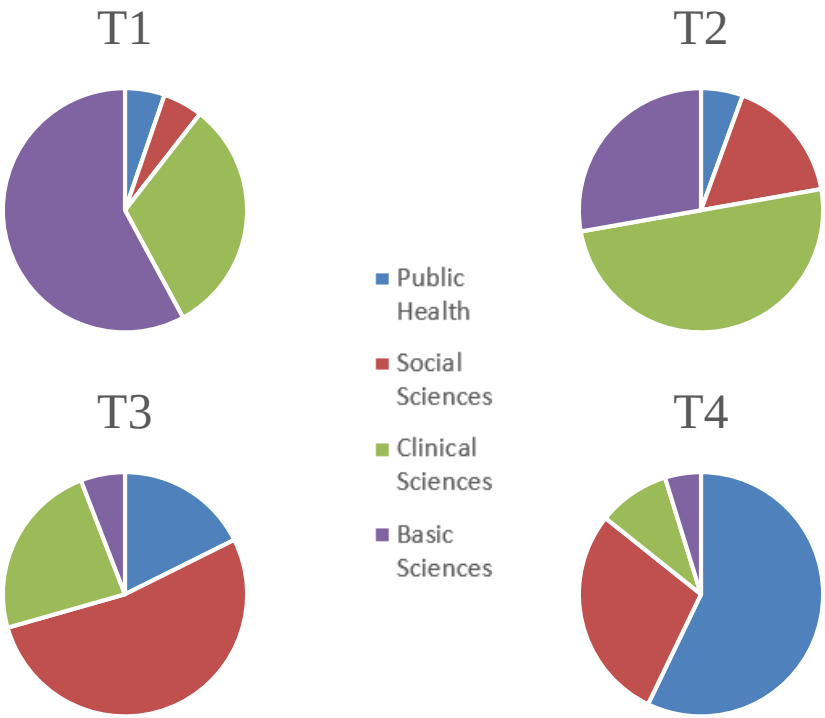
The expected results predicted by the linear translational model when shown as a proportion of total records over time within each stage. Each column represents some binned range of years, such as from 3 to 5 years. This follows from assuming each stage consists of a normal distribution of records centered at a time point in the linear sequence. Real data will be expected to deviate from this idealized data to some reasonable extent.

Figure 4.2. Expected Citing Subjects Distributions by Stage



The theoretically predicted proportions of the citing record subject distributions for the linear translational model. As the linear model proposes that each translational stage builds upon the work of its previous stage(hence cites), there should be a progression of the balance of subjects of citing records in each stage. Starting with basic sciences, there should be a movement towards clinical and social sciences in later stages.

Figure 4.3. Expected Cited Subjects Distributions by Stage



The theoretically predicted proportions of the cited reference subject distributions for the linear translational model. As the linear model proposes that each translational stage builds upon the work of its previous stage(hence cites), there should be a progression of the balance of subjects of cited references in each stage. Starting with basic sciences, there should be a movement towards clinical and social sciences in later stages.

In our data, the subject category frequency of the cases reveal the multidisciplinary nature of some innovations. HPV research spans many disciplines including basic science, clinical science, social science as well as public health, but curiously contains very few records in the field of Pediatrics, where the innovation must ultimately be implemented. The other two cases exhibit this range of subjects to a much lesser extent and TcB is basically monodisciplinary in its publications. For TcB, despite having the vast majority of its records published within clinical science (pediatrics and obstetrics/gynecology) there is still publication of most of the translational stages indicating that the clinical sciences can contain all stages of translation. This may be a contributing factor for the difficulty of bibliometric analysis of translation utilizing subject categories due to the potentially transdisciplinary nature of clinical medicine. This was entirely unexpected, as medical devices are often considered to be developed industrially, far removed from clinical practice. It would be expected that there would be publications in the basic sciences of physics, engineering, physiology, showing the fundamental evidence supporting the device. However, if this is the case, it is not apparent in the cited knowledge base. This may be an indication of a lack of deep evidence for the device, which may explain its lack of uptake.

The histograms of records over time for HPV and TcB show exponential increase in records as is common for publication patterns in growing fields, whereas the BtS dataset declines after a peak in 2000. This may indicate that BtS translation is nearing a close whereas the other two cases may be continuing.

A first order analysis of the cases is simply looking at the subjects of the journals that publish translational research. This is shown in Table 4.1 for each of the three cases. Differences in the pattern of subject categories is immediately apparent. The most common subject categories for the journals that publish HPV research are Immunology, Oncology, and Experimental Medicine. For the other two cases, the most common subject by far is Pediatrics, a clinical subject. In Back to Sleep, this is followed by a mix of public health, social science disciplines, and basic and clinical disciplines, whereas in TcB this is followed by many basic science fields. This is the first indication that translational research seems to look very different in each of these cases. HPV seems to be dominated by the basic sciences, TcB by clinical and basic science, and Back to Sleep by clinical and social sciences.

Table 4.1. Journal Subject Categories

Case	Subject	Records
HPV		
	Immunology	198
	Oncology	150
	Medicine, Research and Experimental	131
	Public, Environmental & Occupational Health	96
	Infectious Diseases	84
	Obstetrics & Gynecology	74
	Medicine, General & Internal	73
	Virology	73
	Microbiology	42
BtS		
	Pediatrics	39
	Public, Environmental & Occupational Health	10
	Medicine, General & Internal	8
	Obstetrics & Gynecology	6
	Medicine, Legal	4
	Clinical Neurology	4
	Nursing	3
	Cardiac & Cardiovascular Systems	2
	Pathology	2
TcB		
	Pediatrics	64
	Obstetrics & Gynecology	16
	Medicine, General & Internal	11
	Medicine, Research and Experimental	7
	Otorhinolaryngology	5
	Surgery	5
	Radiology, Nuclear Medicine & Medical Imaging	3
	Hematology	3
	Endocrinology & Metabolism	3

The number of subject categories of the source journals for the translational records in each of the three cases. Single source subject categories are shown, journals with multiple subject categories were counted for each of the subjects given.

4.1.1 HPV Vaccine Case

There were 576 topically relevant records associated with the HPV vaccine innovation. Of these, 493 were coded as fitting the definition of translational research. The count by stage were: T1 39, T2 101, T3 212, T4 132, and nine were coded as belonging to multiple stages.

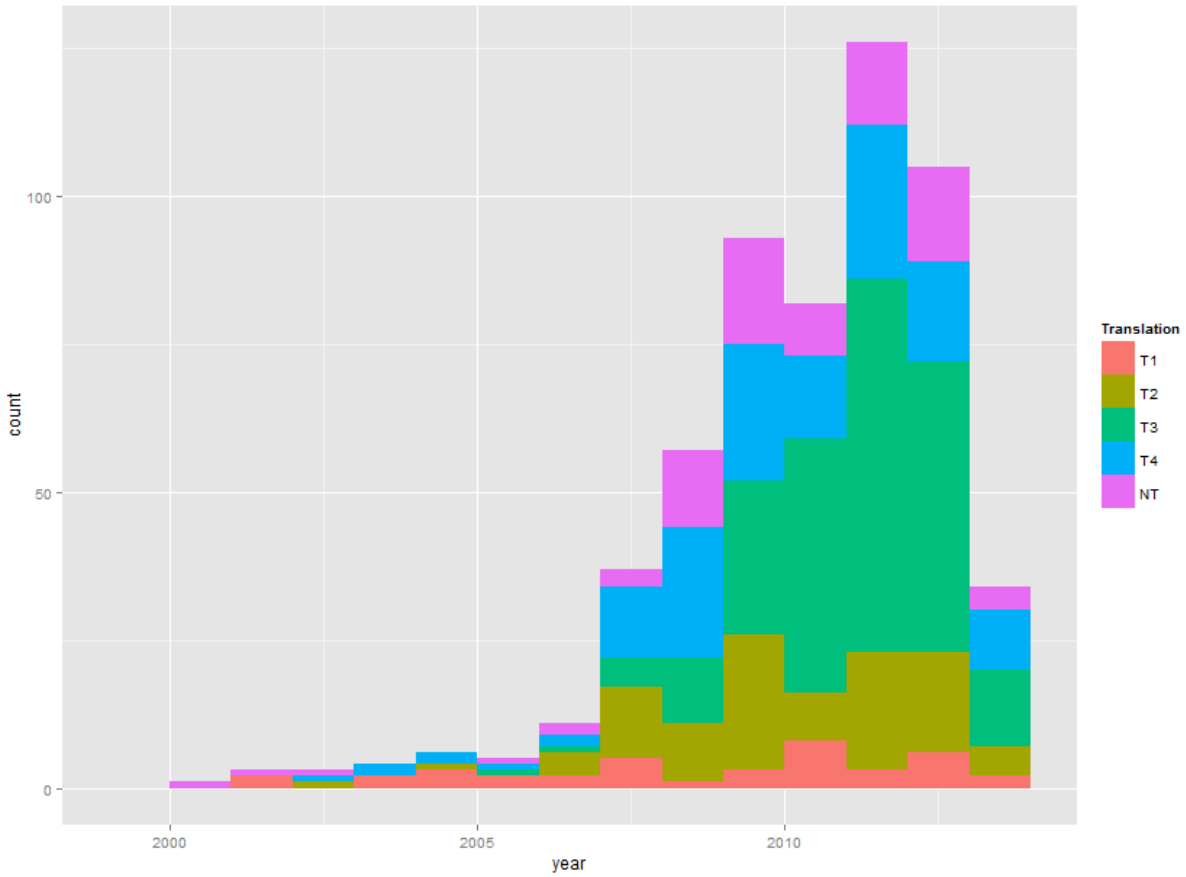
The HPV records selected for this case start in 2000, and increase rapidly after 2006. The highest ten journal categories are shown in Table 4.2. There is a wide range of subjects in the top ten journal subjects including basic science, clinical science, and social science subjects. However, the majority of the subjects are basic science focused, the exceptions being Public Health, Obstetrics, and Internal Medicine. Breaking this down into the types of translational record in Table 4.2 reveals a surprising result. The initial hypothesis that T1 research would show a large amount of basic science subjects, T2 and T3 would show more clinical subjects, and T3 and T4 would show more social sciences, is not supported by this result. While T1 shows a predominance of basic science subjects, T2 is found in public health journals, while T3 and T4 show a return to the basic science of Immunology journals. This unexpected result shows that T3 and T4 research may happen in basic science journals, though it is unclear from this data whether they can occur without drawing upon social sciences in their knowledge base.

Table 4.2. HPV Journal Subject Categories by Translational Stage

Stage	Subject	Records
T1	Immunology	20
	Oncology	10
	Medicine, Research and Experimental	8
	Infectious Diseases	8
	Microbiology	6
	Obstetrics & Gynecology	5
	Pediatrics	4
	Psychology, Developmental	3
	Biotechnology & Applied Microbiology	3
	Public, Environmental & Occupational Health	3
T2	Public, Environmental & Occupational Health	88
	Immunology	55
	Medicine, Research and Experimental	49
	Pediatrics	46
	Medicine, General & Internal	25
	Psychology, Developmental	18
	Obstetrics & Gynecology	18
	Oncology	17
	Infectious Diseases	15
	Health Policy & Services	11
T3	Medicine, General & Internal	30
	Immunology	29
	Pediatrics	16
	Oncology	14
	Medicine, Research and Experimental	13
	Infectious Diseases	12
	Obstetrics & Gynecology	10
	Microbiology	7
	Biotechnology & Applied Microbiology	7
	Public, Environmental & Occupational Health	5
T4	Immunology	42
	Medicine, Research and Experimental	32
	Oncology	23
	Public, Environmental & Occupational Health	22
	Infectious Diseases	21
	Medicine, General & Internal	17
	Health Care Sciences & Services	15
	Health Policy & Services	9
	Obstetrics & Gynecology	8
	Microbiology	7

Counts of journal subject categories in the HPV case based on the translational stage coded for each record. Single source subject categories are shown, journals with multiple subject categories were counted for each of the subjects given. Records coded with multiple translational stages were omitted (1.8% of records).

Figure 4.4. HPV Case - Number of Records by Translational Stages by Year

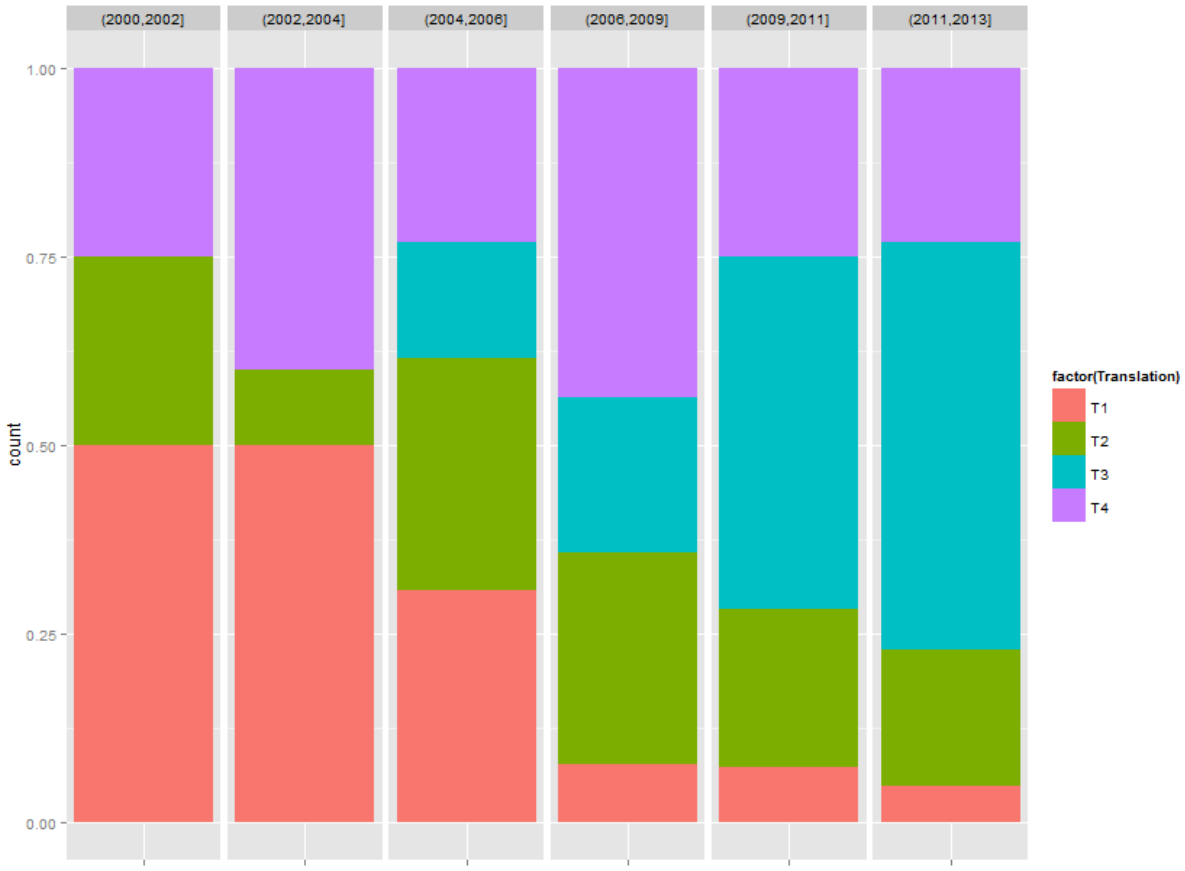


The number of records in the HPV dataset are plotted in a histogram. Colors indicate translational stage coded for each record, stacked cumulatively to show total number.

The distribution of the translational stages over time is shown in Figure 4.4. The majority of the initial records are T1, T2, and T4. A large number of T3 records appear after 2010. Non-translational records are evenly distributed across the years. Here is a result in the data that applies to the question of whether the linear translational model is supported. While there is no clear dominance in the early years for T1 research, T3 and T4 research does appear in later years in great number. This is shown more clearly by looking at the relative distribution of the stages over time. This seems to support the linear model, as expected for a pharmaceutical type product that has gone through the classic sequence of clinical trials. However, this does not necessarily mean that translation has been a success in this case. Based on uptake studies, the number of patients who actually receive the HPV vaccine is still very low, which means that there is still a problem in translation despite the traversal of all translational stages (Widdice et al. 2011; Centers for Disease Control and Prevention (CDC) 2011).

The relative distribution of translational stages in the HPV case is shown in Figure 4.5. T3 records are missing from the first six years and following that make up a greater proportion of the records. T1 records show the expected pattern, starting off as a high proportion of the records, and gradually diminishing over time. Similarly, T3 records begin absent, and gradually increase in proportion over time. However, there is no equivalent change in T2 records, and T4 records appear immediately along with T1 records at the start of the record. These T4 records appear to be predictive cost-effectiveness analyses that attempt to quantify the possible impact of the HPV vaccine in various populations.

Figure 4.5. HPV Case - Relative Distribution of Translational Stages over Time



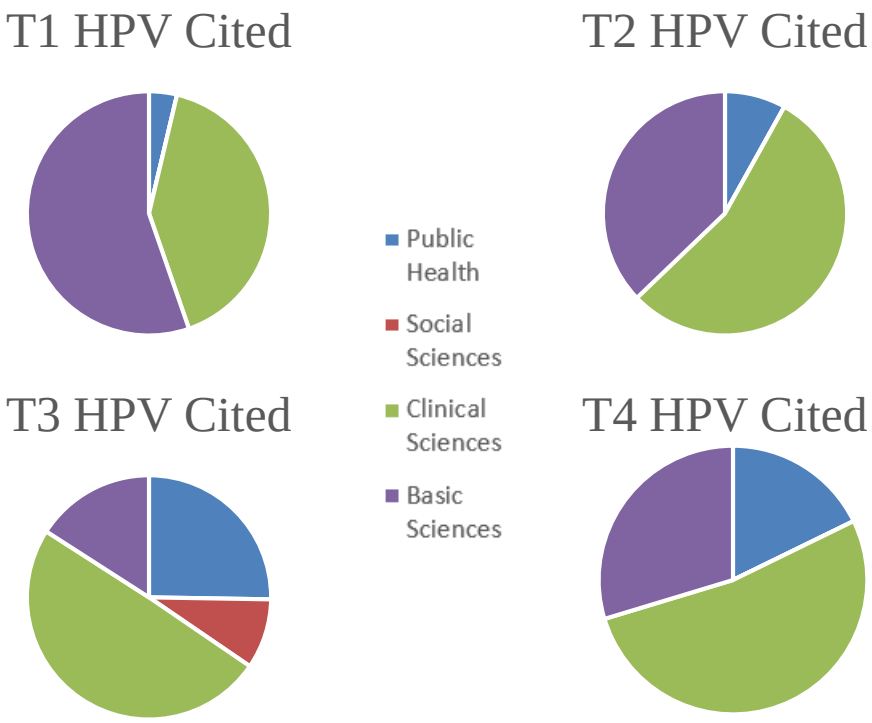
The relative counts of each translational stage within a portion of the dataset time frame, the number of records in each stage is shown as a proportion of the total number of translational records. For the HPV case, the time scale is divided into three year bins starting in 2000 with the first appearance of an HPV record in the dataset. Colors indicate each translational stage from T1 to T4.

Table 4.3. Subject Categories of Cited References in the HPV Case

Stage	Subject	Records
T1	Immunology	344
	Oncology	205
	Medicine, General & Internal	179
	Virology	156
	Infectious Diseases	149
	Medicine, Research and Experimental	139
	Microbiology	118
	Obstetrics & Gynecology	65
	Public, Environmental & Occupational Health	54
	Biotechnology & Applied Microbiology	50
T2	Immunology	662
	Medicine, General & Internal	656
	Oncology	480
	Infectious Diseases	379
	Medicine, Research and Experimental	292
	Public, Environmental & Occupational Health	284
	Microbiology	251
	Obstetrics & Gynecology	210
	Pediatrics	197
	Virology	100
T3	Public, Environmental & Occupational Health	1784
	Pediatrics	1166
	Medicine, General & Internal	977
	Immunology	637
	Oncology	544
	Psychology, Developmental	518
	Medicine, Research and Experimental	487
	Obstetrics & Gynecology	415
	Infectious Diseases	398
	Women's Studies	137
T4	Oncology	1054
	Medicine, General & Internal	909
	Immunology	896
	Infectious Diseases	664
	Public, Environmental & Occupational Health	590
	Medicine, Research and Experimental	493
	Obstetrics & Gynecology	299
	Microbiology	263
	Health Care Sciences & Services	251
	Health Policy & Services	148

Subject categories of the cited references in the HPV case, organized by the assigned translational stage of the source record. Subject categories were determined by matching source names in the cited references to reference set journal names.

Figure 4.6. HPV Cited Subject Proportion By Stage



The distribution of the top 10 most common cited reference subjects in the HPV case for each translational stage. The subject categories were grouped into four broad categories for easier visualization. The absolute numbers of categories are shown in Table 4.3.

One caveat of looking at journal subject categories is that while articles may be published in journals labeled with a certain subject, the subject of the article may differ. This can be mitigated by studying not the journal subject, but the subjects of the cited references of the article, which can be presumed to form the knowledge base of the research.

The top cited 10 subject categories cited by the HPV dataset for each translational stage are shown in Table 4.3. This is shown in graphical form in Figure 4.6. The cited subjects for the T1 records align closely with the source journal subjects, and are unsurprisingly focused on basic science categories. The cited reference subjects of the T2 records clarify the surprising result found in the source journals, revealing that while many of the records may have appeared in journals with some public health focus, the knowledge base of these T2 records are still primarily located in the basic and clinical sciences, as expected by the original hypothesis. The T3 records also confirm the expected pattern, drawing upon public health and showing the new appearance of social sciences such as Women's Studies. T4 records show a return to basic sciences in their cited references, although near the end of their top 10 subjects there is the conspicuous appearance of the expected categories of Health Policy and services.

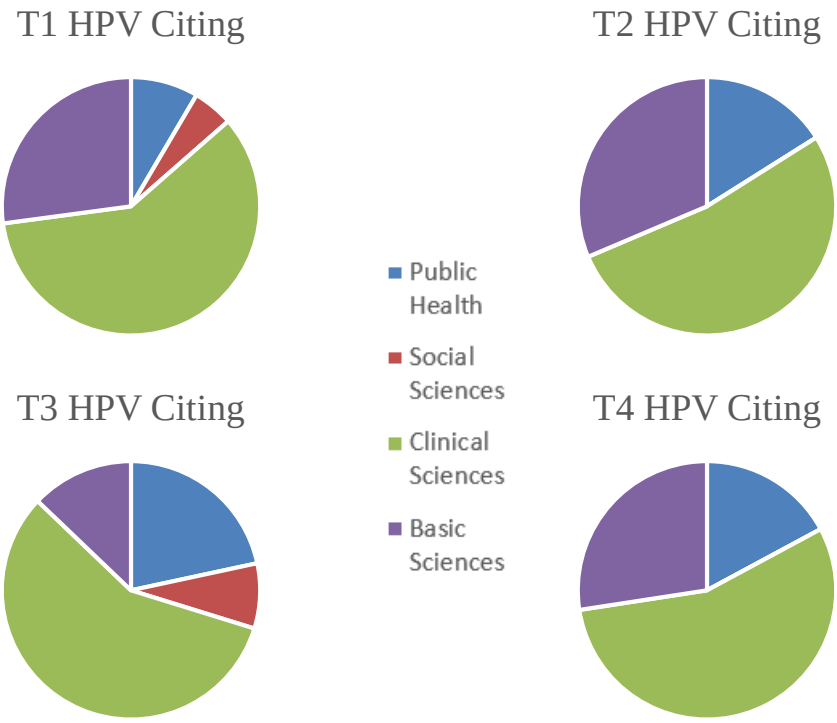
The same treatment can be done for the records that cite HPV records. This is a measure of the subjects that the translational research has the most impact on. The 10 most commonly citing subjects are shown in Table 4.4, and in graphical form in Figure 4.6. This impact is seen to be similar to the knowledge base of cited references, which is not unexpected, but there are also some notable additions. Pediatrics appears in the T2 and T3 lists, which is the expected clinical output of the HPV innovation. Public health is a major citing area for all the stages, which is also understandable.

Table 4.4. Citing Article Subject Categories of HPV Case by Translational Stage

Stage	Subject	Records
T1	Infectious Diseases	12
	Oncology	10
	Obstetrics & Gynecology	9
	Immunology	9
	Public, Environmental & Occupational Health	5
	Microbiology	4
	Multidisciplinary Sciences	3
	Biotechnology & Applied Microbiology	3
	Pharmacology & Pharmacy	2
	Urology & Nephrology	2
T2	Infectious Diseases	28
	Public, Environmental & Occupational Health	22
	Immunology	20
	Oncology	16
	Pathology	12
	Medicine, Research and Experimental	10
	Pediatrics	9
	Statistics & Probability	7
	Mathematical & Computational Biology	6
	Pharmacology & Pharmacy	5
T3	Public, Environmental & Occupational Health	62
	Infectious Diseases	61
	Oncology	53
	Immunology	31
	Psychology, Developmental	26
	Pediatrics	25
	Medicine, General & Internal	24
	Obstetrics & Gynecology	20
	Microbiology	10
	Health Care Sciences & Services	7
T4	Infectious Diseases	51
	Oncology	24
	Immunology	24
	Public, Environmental & Occupational Health	20
	Obstetrics & Gynecology	13
	Health Care Sciences & Services	10
	Pathology	9
	Microbiology	9
	Medicine, Research and Experimental	8
	Biotechnology & Applied Microbiology	7

The 10 most common subjects among the citing articles of the HPV case records. Subjects were determined by matching to journal names. Single subjects are given, journals with multiple subjects were assigned to all matching categories.

Figure 4.7. HPV Citing Record Proportions by Stage



The distribution of the top 10 most common citing subjects in the HPV case for each translational stage. The subject categories were grouped into four broad categories for easier visualization. The absolute numbers of categories are shown in Table 4.4.

Table 4.5. Journal Subject Categories for Back to Sleep Case by Translational Stage

Stage	Subject	Records
T1	Pediatrics	36
	Clinical Neurology	11
	Neurosciences	10
	Obstetrics & Gynecology	6
	Immunology	3
	Microbiology	2
	Infectious Diseases	2
	Respiratory System	2
	Medicine, Legal	1
	Medicine, General & Internal	1
T2	Pediatrics	39
	Medicine, General & Internal	11
	Public, Environmental & Occupational Health	9
	Obstetrics & Gynecology	4
	Medicine, Legal	3
	Behavioral Sciences	1
	Health Care Sciences & Services	1
	Psychology, Developmental	1
	Primary Health Care	1
	Rehabilitation	1
T3	Pediatrics	49
	Public, Environmental & Occupational Health	9
	Medicine, General & Internal	8
	Obstetrics & Gynecology	6
	Nursing	5
	Health Policy & Services	1
	Psychology, Developmental	1
T4	Pediatrics	17
	Medicine, General & Internal	5
	Medicine, Legal	3
	Public, Environmental & Occupational Health	3
	Health Care Sciences & Services	1
	Infectious Diseases	1
	Health Policy & Services	1
	Obstetrics & Gynecology	1
	Immunology	1
	Pathology	1

Counts of the 10 most common journal subject categories in the Back to Sleep case based on the translational stage coded for each record. Single source subject categories are shown, journals with multiple subject categories were counted for each of the subjects given. Records coded with multiple translational stages were omitted (5.8% of records).

4.1.2 Back to Sleep Case

There were 266 topically relevant records associated with the Back to Sleep innovation. Of these, 208 were coded as fitting the definition of translational research. The count by stage were: T1 55, T2 59, T3 65, T4 29, 13 were coded as belonging to multiple stages.

The distribution of journal subject categories publishing Back to Sleep research is shown in Table 4.1. While a majority are in the pediatric subject, there is also considerable number of records in public health and some basic sciences, as mentioned above. The breakdown of the records by translational stage is shown in Table 4.5. Here it is clear that the largest subject of the journals publishing all the stages of translation for this innovation is Pediatrics, which is a clinical subject. It spans from T1 to T4 as the highest occurring subject. There is even a lack in the T1 records of what could be considered basic sciences, with Neurosciences being the most common that fits that category, but even then it is outweighed by Clinical Neurology. Public health is seen in T3 and T4, as well as social sciences such as Legal Medicine and Health Policy. Is the basic science orientation of the early stage research hidden within the Pediatrics subject? To determine this, the cited reference subjects can be studied to see the knowledge base of the records.

The cited reference subjects of the Back to Sleep records is shown in Table 4.6. This is shown in graphical form in Figure 4.8. Here it is shown that while there is the appearance of some basic science subjects in the T1 cited references, such as Physiology and Respiratory, there remains a predominance of cited references within the Pediatrics subject. This indicates that in some cases, clinical subjects can contain the entirety of the translational process without reference to other fields. This may be a product of the nature of this innovation as a type of clinical behavior modification that originates within the field of medicine. Given the time constraints on clinician researchers mentioned in the literature review, it would be expected that there might be a trend towards knowledge remaining within the field, rather than drawing upon other sources.

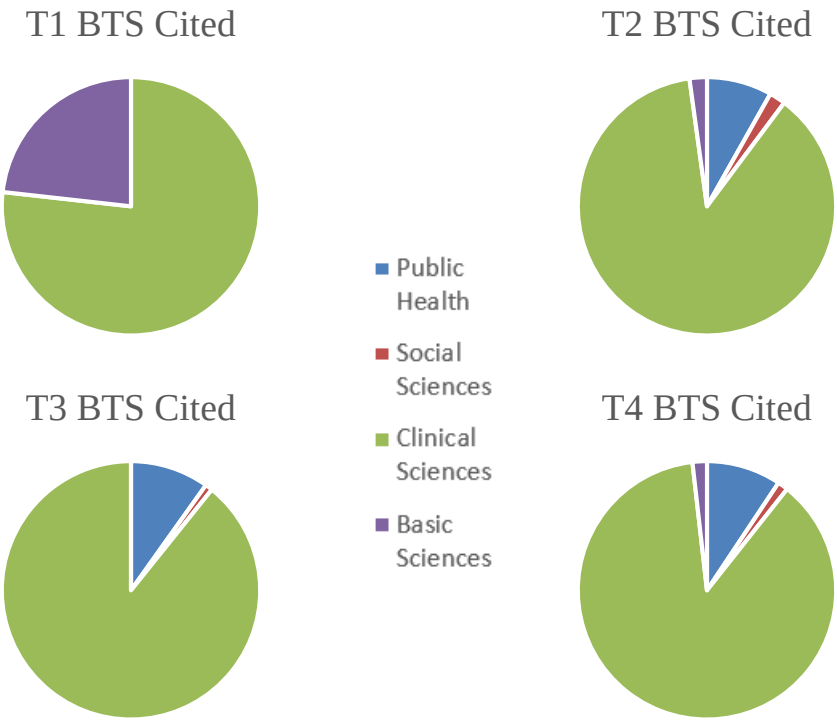
This trend continues in the Back to Sleep citing subjects as shown in Table 4.7, and in graphical form in Figure 4.9. One new subject that appears in all the stages in the citing records is the Public Health subject, which shows the impact that this innovation has had on public health.

Table 4.6. Cited Reference Subject Categories of Back to Sleep Translational Stages

Stage	Subject	Records
T1	Pediatrics	857
	Medicine, General & Internal	183
	Clinical Neurology	171
	Neurosciences	163
	Physiology	103
	Respiratory System	85
	Obstetrics & Gynecology	75
	Sport Sciences	66
	Critical Care Medicine	48
	Pathology	44
T2	Pediatrics	1088
	Medicine, General & Internal	462
	Public, Environmental & Occupational Health	165
	Obstetrics & Gynecology	68
	Clinical Neurology	64
	Neurosciences	44
	Medicine, Legal	41
	Surgery	39
	Pathology	33
	Endocrinology & Metabolism	15
T3	Pediatrics	682
	Medicine, General & Internal	334
	Public, Environmental & Occupational Health	104
	Obstetrics & Gynecology	40
	Nursing	14
	Health Policy & Services	8
	Clinical Neurology	8
	Health Care Sciences & Services	7
	Psychology, Developmental	6
	Multidisciplinary Sciences	5
T4	Pediatrics	289
	Medicine, General & Internal	200
	Public, Environmental & Occupational Health	52
	Obstetrics & Gynecology	25
	Pathology	13
	Medicine, Legal	8
	Endocrinology & Metabolism	7
	Neurosciences	6
	Immunology	5
	Health Care Sciences & Services	5

Subject categories of the cited references in the Back to Sleep case, organized by the assigned translational stage of the source record. Subject categories were determined by matching source names in the cited references to reference set journal names.

Figure 4.8. Cited Reference Subject Categories of Back to Sleep Records by Stage



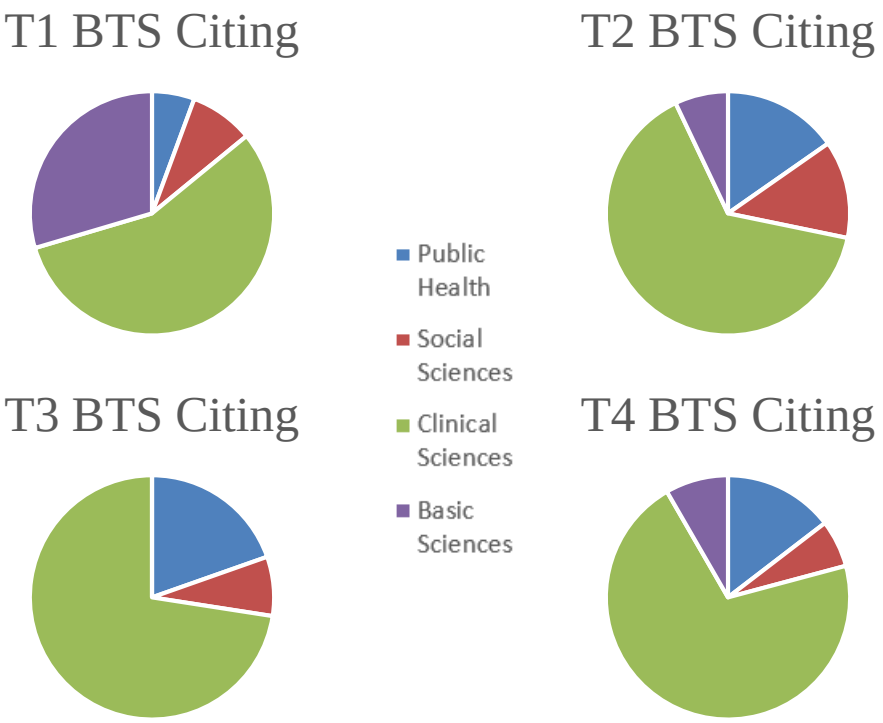
The distribution of the top 10 most common cited reference subjects in the Back to Sleep case. The subject categories were grouped into four broad categories for easier visualization. The absolute numbers of categories are shown in Table 4.6.

Table 4.7. Citing Article Subject Categories of BtS Case by Translational Stage

Stage	Subject	Records
T1	Pediatrics	19
	Respiratory System	9
	Medicine, General & Internal	7
	Obstetrics & Gynecology	7
	Multidisciplinary Sciences	6
	Physiology	6
	Neurosciences	6
	Public, Environmental & Occupational Health	4
	Clinical Neurology	4
	Critical Care Medicine	3
T2	Pediatrics	32
	Public, Environmental & Occupational Health	13
	Obstetrics & Gynecology	12
	Medicine, Legal	8
	Pathology	4
	Clinical Neurology	4
	Statistics & Probability	3
	Medicine, General & Internal	3
	Psychology, Developmental	3
	Mathematical & Computational Biology	3
T3	Pediatrics	37
	Medicine, General & Internal	19
	Obstetrics & Gynecology	15
	Public, Environmental & Occupational Health	13
	Health Policy & Services	4
	Psychology, Developmental	3
	Clinical Neurology	3
	Medicine, Legal	3
	Health Care Sciences & Services	3
	Multidisciplinary Sciences	2
T4	Medicine, General & Internal	15
	Pediatrics	9
	Obstetrics & Gynecology	6
	Public, Environmental & Occupational Health	5
	Medicine, Legal	3
	Neurosciences	2
	Cardiac & Cardiovascular Systems	2
	Clinical Neurology	2
	Pathology	2
	Health Care Sciences & Services	2

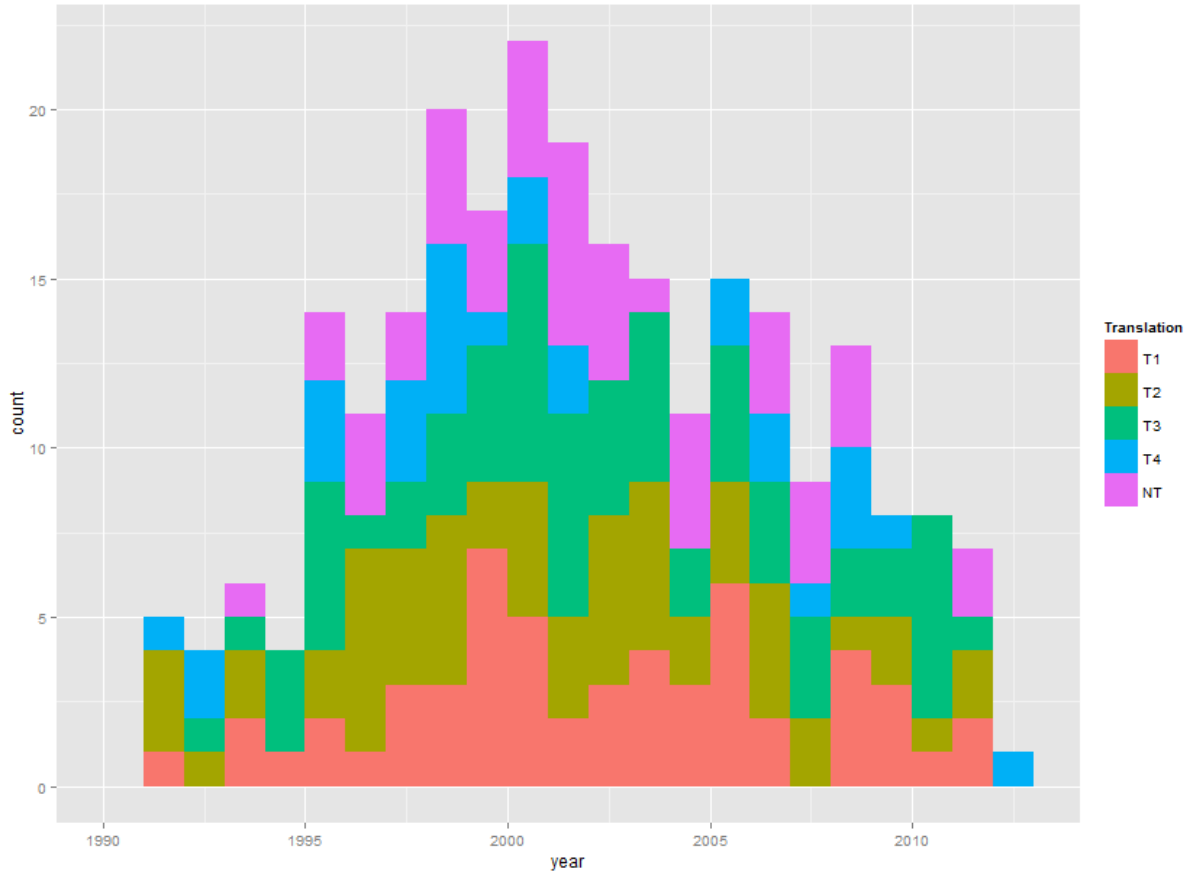
The 10 most common subjects among the citing articles of the Back to Sleep case records. Subjects were determined by matching to journal names. Single subjects are given, journals with multiple subjects were assigned to all matching categories.

Figure 4.9. Citing Article Subject Categories of Back to Sleep Records by Stage



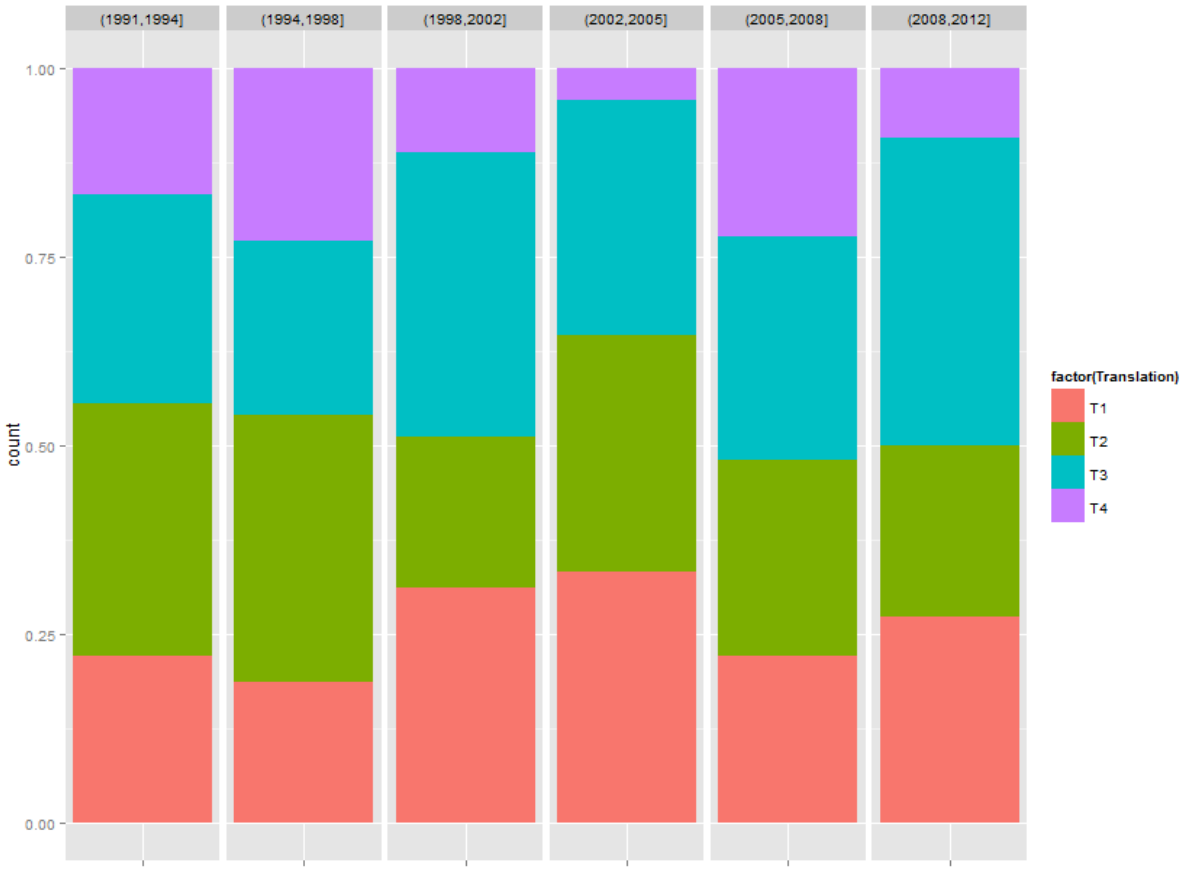
The distribution of the top 10 most common citing subjects in the BTS case for each translational stage. The subject categories were grouped into four broad categories for easier visualization. The absolute numbers of categories are shown in Table 4.7.

Figure 4.10. Back to Sleep Case - Number of Records by Translational Stages by Year



The number of records in the Back to Sleep dataset are plotted in a histogram. Colors indicate translational stage coded for each record, stacked cumulatively to show total number. NT indicates records that have been coded as not translational.

Figure 4.11. BtS Case - Relative Distribution of Translational Stages over Time



The relative counts of each translational stage within a portion of the dataset time frame, the number of records in each stage is shown as a proportion of the total number of translational records. For Back to Sleep, the time scale is divided into 4 year bins starting in 1991 with the first appearance of a Back to Sleep record in the dataset. Colors indicate each translational stage from T1 to T4.

The distribution of the translational stages over time for BtS research is shown in Figure 4.10. The BtS records start in 1991 and increase in 1995, then decline after 2006. From the first year of the dataset, all of the translational stages are present and in relatively equal number throughout the time frame.

This pattern is shown more clearly in Figure 4.11. It shows the relative frequencies of each translational stage and all are present in each of the time periods throughout the progress of the Back to Sleep innovation. This is in clear contrast to the HPV pattern, where T3 research is lacking in the initial years. How is it possible for T3 research, which is defined as being studies on implementation and dissemination, to appear alongside the other early research? This may be due to studies that measured the initial rates of Back to Sleep guidance being presented, before and after the public health campaign. In effect, the BtS studies begin in the clinical setting, rather than the basic science setting.

While calculating the time points of the translational process has been shown here to be an unanswerable question, given the coincidence of all stages appearing at once, it might open the possibility of using a different metric of translational efficiency.

4.1.3 Transcutaneous Bilirubinometry Case

There were 104 topically relevant records associated with the Transcutaneous Bilirubinometer innovation. Of these, 91 were coded as fitting the definition of translational research. The count by stage were: T1 44, T2 36, T3 1, T4 4, six were coded as belonging to multiple stages. Unfortunately this case had a very small number of records in T3 and T4 stages, but this could not have been predicted before data collection, and it provides valid information about the distribution of translational research.

The journal subject categories publishing TcB translational research are shown in Table 4.8. Nearly all consist of subjects in pediatrics or closely related clinical fields.

Table 4.8. TcB Journal Subject Categories by Translational Stage

Stage	Subject	Records
T1	Pediatrics	12
	Obstetrics & Gynecology	3
	Immunology	1
	Medicine, General & Internal	1
	Medicine, Research and Experimental	1
T2	Pediatrics	30
	Obstetrics & Gynecology	6
	Medical Laboratory Technology	4
	Medicine, General & Internal	2
	Pathology	1
	Medicine, Research and Experimental	1
		1
T3	Pediatrics	1
T4	Medical Laboratory Technology	2
	Medicine, General & Internal	1
	Pediatrics	1

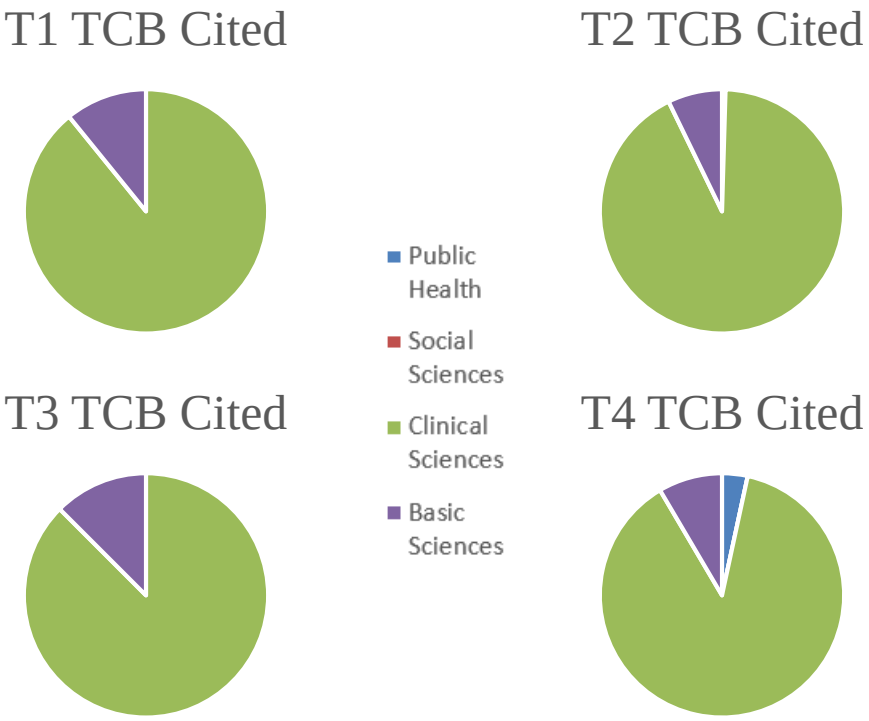
Counts of journal subject categories in the TcB case based on the translational stage coded for each record. Single source subject categories are shown, journals with multiple subject categories were counted for each of the subjects given. Records coded with multiple translational stages were omitted (6.5% of records).

Table 4.9. Subject Categories of Cited References in the TcB Case

Stage	Subject	Records
T1	Pediatrics	635
	Obstetrics & Gynecology	58
	Medical Laboratory Technology	58
	Medicine, General & Internal	57
	Medicine, Research and Experimental	16
	Biochemistry & Molecular Biology	13
	Primary Health Care	8
	Radiology, Nuclear Medicine & Medical Imaging	7
	Pathology	7
	Optics	7
T2	Pediatrics	807
	Medicine, General & Internal	77
	Obstetrics & Gynecology	74
	Medical Laboratory Technology	60
	Medicine, Research and Experimental	17
	Clinical Neurology	9
	Tropical Medicine	8
	Pathology	7
	Public, Environmental & Occupational Health	5
	Nursing	5
T3	Pediatrics	13
	Medicine, General & Internal	4
	Obstetrics & Gynecology	3
	Medical Laboratory Technology	2
	Pharmacology & Pharmacy	1
	Medicine, Research and Experimental	1
T4	Pediatrics	46
	Medicine, General & Internal	4
	Medical Laboratory Technology	3
	Public, Environmental & Occupational Health	2
	Obstetrics & Gynecology	2
	Immunology	1
	Medicine, Research and Experimental	1

Subject categories of the cited references in the TcB case, organized by the assigned translational stage of the source record. Subject categories were determined by matching source names in the cited references to reference set journal names.

Figure 4.12. TcB Cited Subject Proportion By Stage



The distribution of the top 10 most common cited reference subjects in the TCB case for each translational stage. The subject categories were grouped into four broad categories for easier visualization. The absolute numbers of categories are shown in Table 4.9.

In Table 4.9 the highest 10 subjects of cited references in the TcB dataset is shown. This is shown graphically in Figure 4.12. The vast majority of subjects in all the stages are from Pediatrics. This is an indication of the difficulty of using Web of Science subject categories to identify translational research, as the entire process can take place within the single subject of a clinical medicine field. Further, in this case, unlike in the Back to Sleep case, there is little obvious difference in the other subjects between the stages, although this may be an artifact of the small dataset for TcB.

The subject categories of the records that cite the TcB dataset are shown in Table 4.10 and graphically in Figure 4.13. The largest citing areas are in clinical medicine such as Pediatrics and Internal Medicine. There is little citing activity in policy areas or social sciences or public health, which may be due to the lack of late stage translational research in this case.

The number of publications in the TcB case is shown in Figure 4.14. This dataset shows a small number of publications for the decades of 1990 until 2005 at which point there is an increase in the number of publications. The majority of all publications consist of T1 and T2 translational research with only a handful of publications from other translational stages appearing.

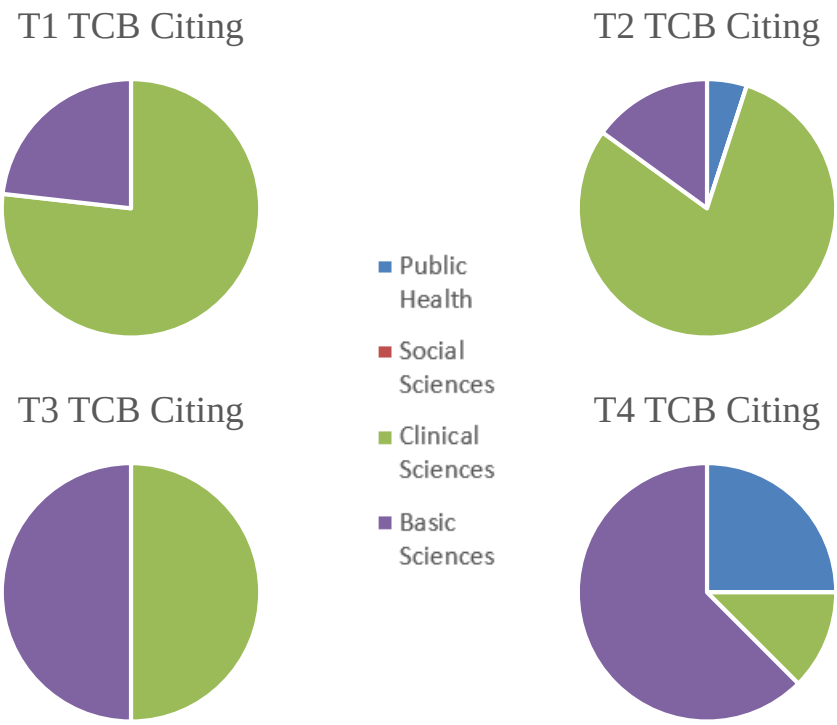
The predominance of T1 and T2 translational research is shown in Figure 4.15. Also, note the larger time periods in this case which are five years compared to the three and four years of the other cases, as the TcB innovation covers a larger time span. Despite this longer time frame, the lack of T3 and T4 research suggests a major problem here with effective translation.

Table 4.10. Citing Article Subject Categories of TcB Case by Translational Stage

Stage	Subject	Records
T1	Pediatrics	14
	Medicine, General & Internal	13
	Obstetrics & Gynecology	12
	Medical Laboratory Technology	5
	Medicine, Research and Experimental	3
	Gastroenterology & Hepatology	2
	Nutrition & Dietetics	2
	Immunology	2
	Tropical Medicine	2
	Chemistry, Analytical	1
T2	Medicine, General & Internal	10
	Pediatrics	9
	Obstetrics & Gynecology	9
	Nutrition & Dietetics	3
	Public, Environmental & Occupational Health	2
	Nursing	2
	Gastroenterology & Hepatology	2
	Medical Laboratory Technology	1
	Statistics & Probability	1
	Mathematics, Interdisciplinary Applications	1
T3	Pharmacology & Pharmacy	1
	Medicine, Research and Experimental	1
T4	Medical Laboratory Technology	3
	Public, Environmental & Occupational Health	2
	Immunology	1
	Medicine, General & Internal	1
	Medicine, Research and Experimental	1

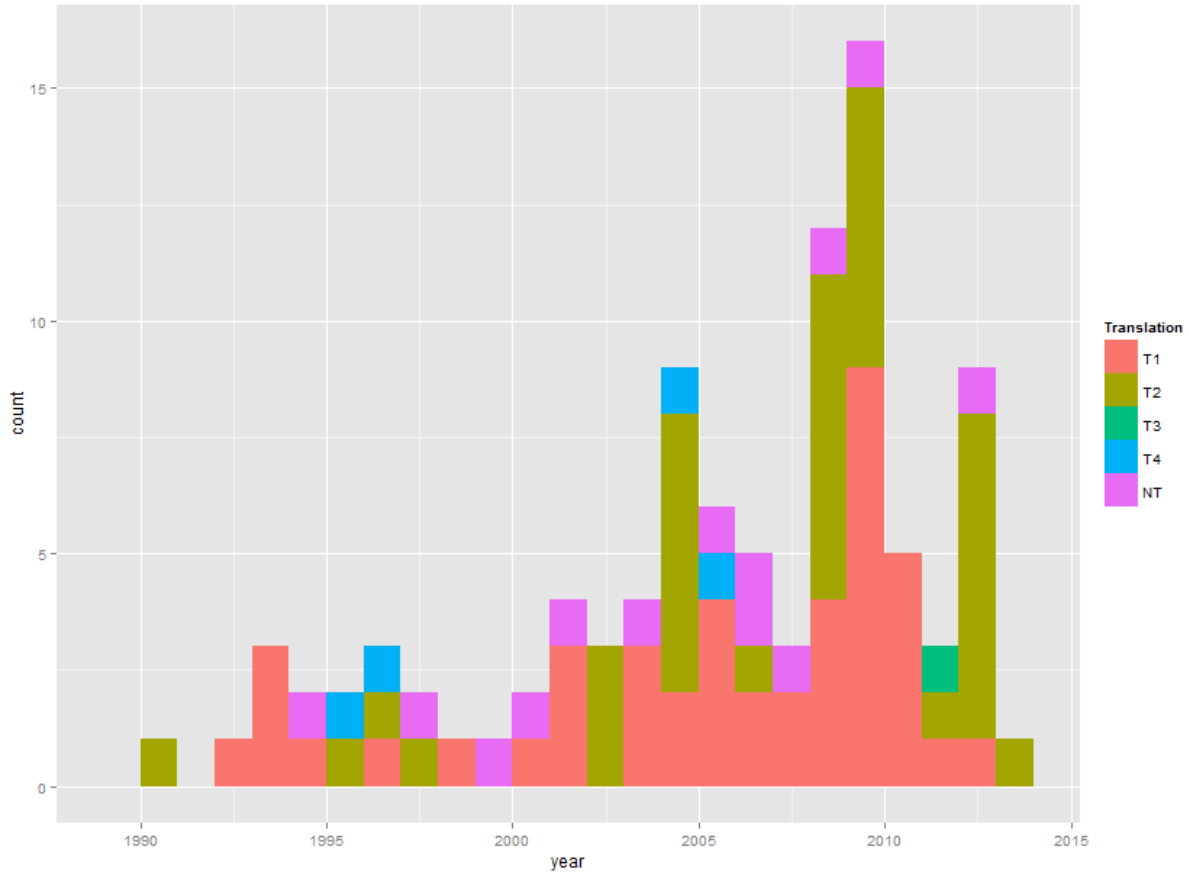
The 10 most common subjects among the citing articles of the TcB case records. Subjects were determined by matching to journal names. Single subjects are given, journals with multiple subjects were assigned to all matching categories.

Figure 4.13. TcB Citing Record Proportions by Stage



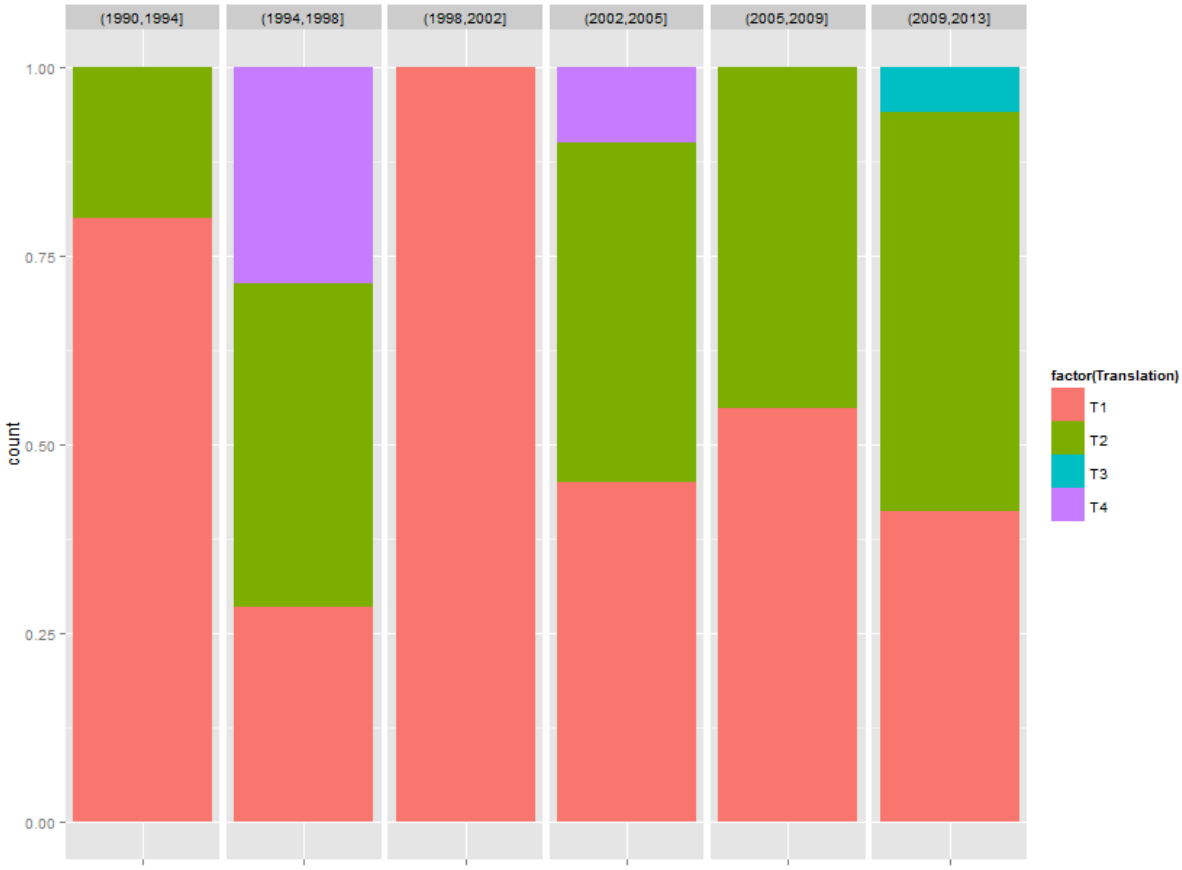
The distribution of the top 10 most common citing subjects in the TCB case for each translational stage. The subject categories were grouped into four broad categories for easier visualization. The absolute numbers of categories are shown in Table 4.10.

Figure 4.14. TcB Case - Number of Records by Translational Stages by Year



The number of records in the TcB dataset are plotted in a histogram. Colors indicate translational stage coded for each record, stacked cumulatively to show total number.

Figure 4.15. TcB Case - Relative Distribution of Translational Stages over Time



The relative counts of each translational stage within a portion of the dataset time frame, the number of records in each stage is shown as a proportion of the total number of translational records. For the TcB case, the time scale is divided into five year bins starting in 1990 with the first appearance of a TcB record in the dataset. Colors indicate each translational stage from T1 to T4.

4.2 Qualitative Analysis of Cases

The cases presented here were selected as examples of different types of medical innovations within the last several decades. While much of the funding and attention of the biomedical industry is on pharmaceutical development, there are many innovations that greatly impact health care that are not of this form. Therefore, the inclusion of the Back to Sleep campaign was aimed at investigating the translational model for a purely information innovation, while the transcutaneous bilirubinometer was chosen as a medical device. The HPV vaccine was included as the example of a pharmaceutical product.

The differences between these cases were stark. Not only did they publish in different venues, almost every bibliometric indicator differed between the cases. Translational medicine therefore should not be considered a single field of study, as some might interpret given the existence of journals of 'translational medicine,' but instead as a process that can apply to any aspect of medicine.

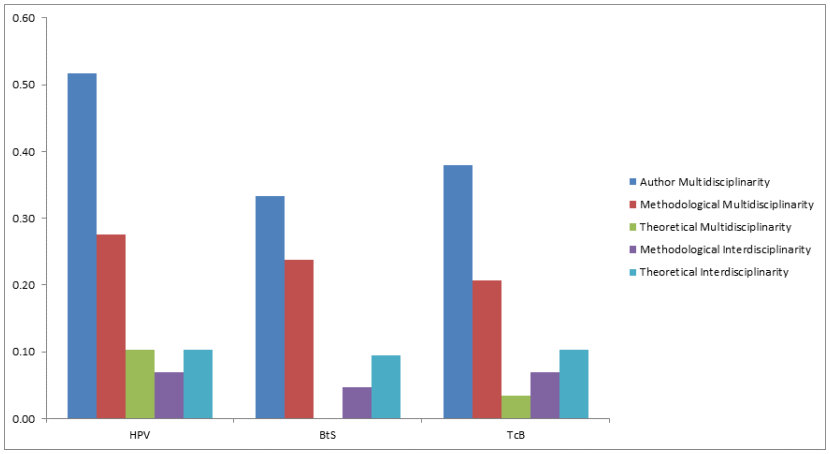
The results of the qualitative coding of the full text subset of the data, summarized by case and translational stage, is shown in Figure 4.16.

Figure 4.16. Qualitative Full Text Interdisciplinary Coding Summary

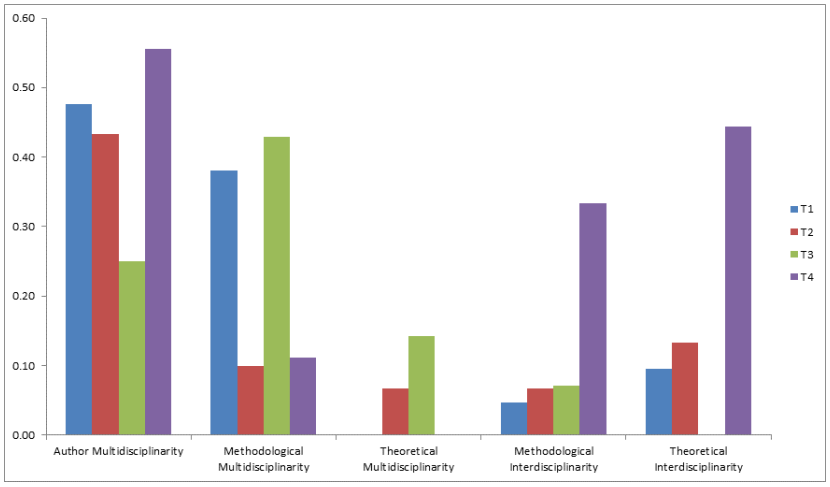
A

	HPV	BtS	TcB	T1	T2	T3	T4
Author Multidisciplinarity	0.52	0.33	0.38	0.48	0.43	0.25	0.56
Methodological Multidisciplinarity	0.28	0.24	0.21	0.38	0.10	0.43	0.11
Theoretical Multidisciplinarity	0.10	0.00	0.03	0.00	0.07	0.14	0.00
Methodological Interdisciplinarity	0.07	0.05	0.07	0.05	0.07	0.07	0.33
Theoretical Interdisciplinarity	0.10	0.10	0.10	0.10	0.13	0.00	0.44

B



C



Results of the coding of 84 full text articles selected from the dataset and coded for types of interdisciplinarity is shown as a proportion of records in panel A. The proportion of the sample articles that were coded for each type of interdisciplinarity is shown by the Case (B) or the translational stage (C) of the record.

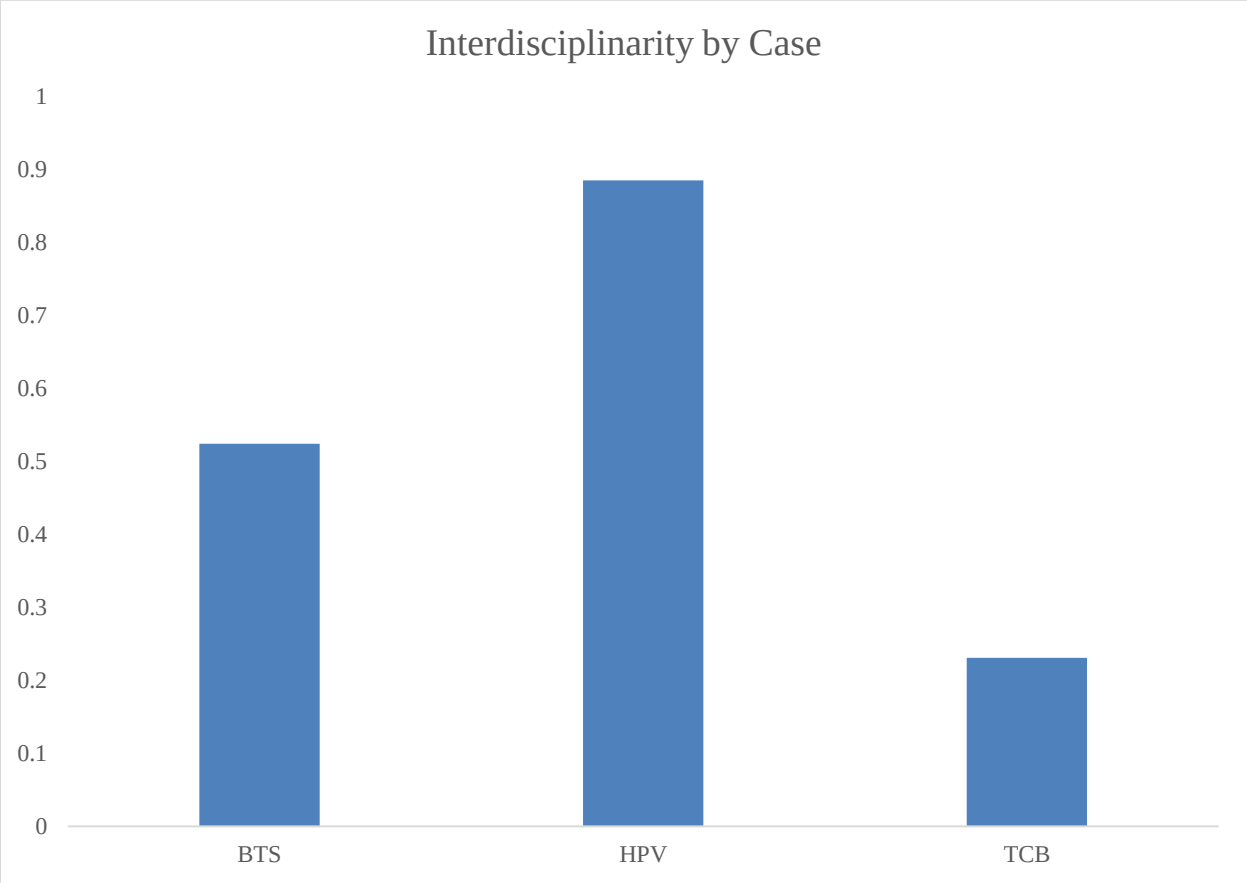
The HPV case exhibited a high degree of multidisciplinarity as defined by the nominal departments and backgrounds of the authors of the papers, as well as a high degree of multidisciplinarity in the methodological sense of research methods from various fields being combined independently in investigations. This is most iconically seen in the many large clinical trials reported in the HPV literature, where multiple authors from disciplines such as immunology, oncology, microbiology, and obstetrics co-authored the papers, and methods as diverse as molecular biological PCR and clinical visits were used. This also occurred primarily in the T1 and T2 stages, which is consistent with the way that clinical trials are conducted. Few showed evidence of the integration of disciplines that would characterize interdisciplinarity rather than multidisciplinarity.

In contrast, the Back to Sleep case showed a more balanced set of interdisciplinary studies, including several that took an integrative approach to combining disciplines. There was still a high degree of author multidisciplinarity, but this was not matched by the methodological multidisciplinarity seen in the T1/T2 HPV case, and this took the form of contextual multidisciplinarity, where studies were done in one discipline while another inspired their context or problem. This was seen in many public health type studies which used the innovation as a context, but made use of single disciplinary methods. The TcB case showed little of any type of multidisciplinarity or interdisciplinarity.

Across translational stages, the prevalence of author multidisciplinarity was little changed across the stages, while T2 and T3 research contained the most integrative interdisciplinary work (identified as methodological and theoretical Interdisciplinarity in the data), though it is still a small proportion of the total T2 and T3 translational work. This was analyzed further to identify any case specific trends.

Overall, there was wide variation in the amount of interdisciplinarity observed in each case. The presence of any type of interdisciplinarity is shown in Figure 4.17. It is clear that while the HPV case shows a large amount of interdisciplinarity, the TCB case shows very little, and the BTS case is intermediate.

Figure 4.17. Interdisciplinarity By Case



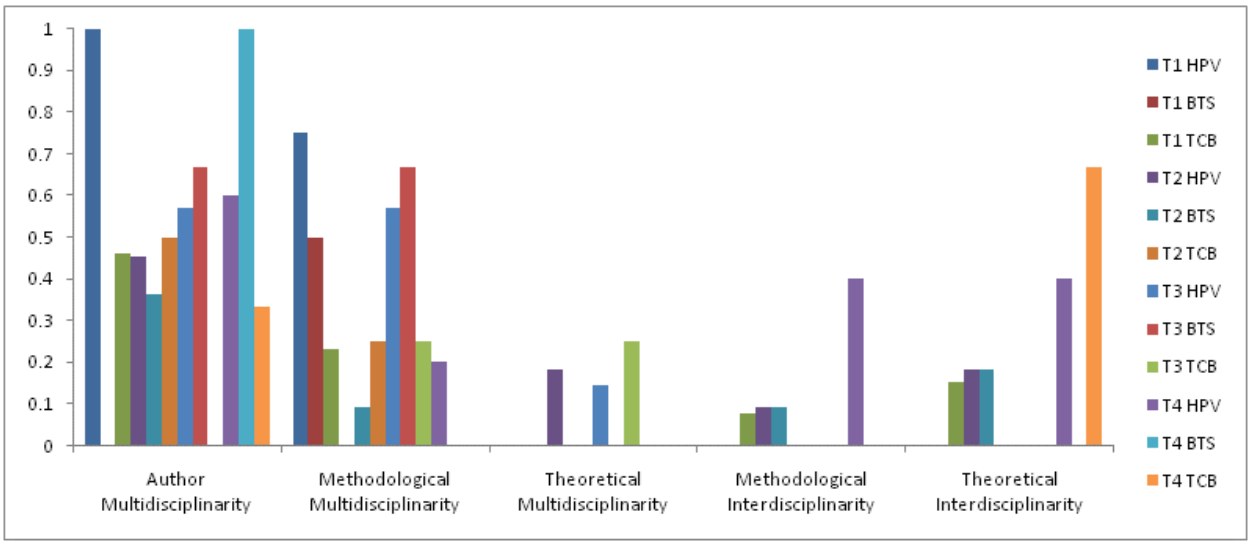
This graph displays the proportion of the full text records in each case that were classified as exhibiting at least one type of interdisciplinarity. The types of interdisciplinarity coded for were: Author Multidisciplinarity, Methodological Multidisciplinarity, Theoretical Multidisciplinarity, Methodological Interdisciplinarity, and Theoretical Interdisciplinarity. The full text records comprised a total of 73 records: 26 HPV, 21 BTS, 26 TCB.

Figure 4.18. Qualitative Interdisciplinarity Full Text Results By Case and Stage

A

	T1 HPV	T1 BTS	T1 TCB	T2 HPV	T2 BTS	T2 TCB	T3 HPV	T3 BTS	T3 TCB	T4 HPV	T4 BTS	T4 TCB
Author Multidisciplinarity	1	0	0.462	0.455	0.364	0.5	0.571	0.667	0	0.6	1	0.333333
Methodological Multidisciplinarity	0.75	0.5	0.231	0	0.091	0.25	0.571	0.667	0.25	0.2	0	0
Theoretical Multidisciplinarity	0	0	0	0.182	0	0	0.143	0	0.25	0	0	0
Methodological Interdisciplinarity	0	0	0.077	0.091	0.091	0	0	0	0	0.4	0	0
Theoretical Interdisciplinarity	0	0	0.154	0.182	0.182	0	0	0	0	0.4	0	0.666667

B



Results of the coding of 84 full text articles selected from the dataset and coded for types of interdisciplinarity is shown as a proportion of records in panel A. The proportion of the sample articles that were coded for each type of interdisciplinarity is shown by Case and Translational Stage of the record in panel B.

Figure 4.18 breaks down the qualitative coding of IDR types by stage within each case. As discussed elsewhere, a grave danger of combining datasets is the possibility of introducing spurious trends due to unequal distributions of subsets which differ. This breakdown reveals that the patterns assumed to be true in the pooled examples are not true across all cases.

First, observe the very low proportion of T1 records which demonstrate author multidisciplinarity in the TcB case. Whereas it was assumed that T1 research could be identified by this feature in the combined dataset, this is not true for this case, which consists of T1 research that does not follow the pattern of large clinical trials with teams of researchers, but instead consists of small laboratory studies of infant sleep patterns in the clinical setting.

Therefore, in contrast to the hypothesis that author multidisciplinarity would dominate at the T1/T2 stages, and interdisciplinarity would become more common at T3/T4, this is not observed as a general rule. Instead, it seems that certain areas of research, or cases in this study, may use multidisciplinarity more than other cases. And in terms of translational stages, the greatest amount of interdisciplinary integration, both methodological and theoretical, was seen across the cases in the T2 and T3 stages, with little occuring in T1 or T4.

4.2.1 HPV Vaccine Case

The full texts of 26 of the HPV records were analyzed for indications of interdisciplinary research. The questions asked during the analysis were whether interdisciplinarity was seen in the author affiliations, the methods used, the theoretical content, the references and citations, and the degree that the multiple disciplines were integrated.

The first theme that emerges from the full text is the quality of team science that characterizes the stage T1 and T2 translational research. These clinical trials are conducted by large groups of researchers, always including a variety of disciplines such as Oncology, Virology, Pathology, Immunology, Microbiology, Molecular Biology, and Public Health. In phase 2 and 3 clinical trials, clinical disciplines such as Obstetrics and Gynecology, Pediatrics, and Medicine also appear in the author lists.

These clinical trials are a clear example of what is called Contextual Multidisciplinarity in Klein's taxonomy (Klein 2010b). This type of interdisciplinary research occurs when multiple disciplines work on separate parts of a larger problem, each within their own domain, and the results are combined at the end to solve the problem. This type of instrumental interdisciplinary, more strictly classified as composite multidisciplinarity, is evidenced in all of the clinical trials. Indeed, in one article, the authors make explicit this type of work flow:

> Main investigators and co-investigators in the HPV Vaccine Study group obtained data for the study and cared for the patients. GlaxoSmithKline Biologicals did all HPV serological testing, Quest Diagnostics processed all cytology and histology specimens, and Delft Diagnostic Laboratory undertook PCR for HPV types. To ensure study blinding, all statistical analyses were done by external independent statisticians (Harper et al. 2006)

It illustrates just how isolated each discipline is in the effort, with little interaction between the teams as they work. Furthermore, the same disciplines are in each clinical trial. It would not be surprising if similar sets of disciplines would be found in any similar pharmacological clinical trial, as the tasks needed, particularly the clinical management and biostatistics components, would be common across trials.

In the T3 articles, there was a trend towards a small number of authors. One study had only one author, but this study was highly interdisciplinary. Indeed, the author's institution was listed as an interdisciplinary institute. This study was also one of the only studies to exhibit signs of integration across disciplines, through the blending of multiple theories, in this case culture-centric communication theory with vaccine intervention strategy (Hopfer 2011). This is the type of research that would be categorized as theoretical interdisciplinarity, where the theoretical backgrounds of multiple fields are combined, interact, and come out changed in the end.

The other article that demonstrated true interdisciplinarity, defined by not just the presence of multiple disciplines, but the interaction between them, was the first clinical guideline in the dataset (Saslow et al. 2007). This clinical guideline, just like the clinical trials, had a full range of disciplines in the large author team, but the content was clearly the product of a blending and unification of these disciplines. The medical aspects of the vaccine were juxtaposed with the public health issues of the population, and likewise with the economic and policy aspects. The guideline, published in a clinical journal, had sections dealing with vaccine

immunobiology, public education programs, cost effectiveness analysis, social acceptability, and international challenges. This is an example of how medicine may be considered, in Klein's taxonomy, a transdisciplinary field. It serves to unify a number of disciplines to solve a particular problem (Klein 2010a).

The role of industry is apparent in the author lists, as well as the conflict of interest sections of many papers. The impact on interdisciplinarity is difficult to measure, as industry authors lack the department information that academic authors have.

One of the early studies on vaccine acceptance shows signs of interdisciplinarity of a different type. This is a study on physician attitudes towards the vaccine in males, and the cited references show a large number of psychology references (Kahn et al. 2005). However, there is little evidence in the text of integration of the disciplines, and this fits the general trend of contextual multidisciplinarity. This is the most common type of interdisciplinarity seen in the HPV case, which consists of one discipline using its own tools in the context of the problem of another discipline. This is seen many times in the dataset, where public health researchers, economists, psychologists, and other disciplines apply their tools to the problems presented by the HPV vaccine.

The timeline of the HPV vaccine innovation is shown in Figure 4.18. The preclinical work on the basic science supporting the vaccine was outside of the scope of the dataset, and occurred prior to 2000. The clinical trials of the early 2000s were largely successful and highly cited. FDA approval followed by 2006, making the path from trial to market quite rapid. Incorporation into clinical guidelines swiftly followed in 2007, making it the standard of care to use the vaccine. However, widespread compliance in the population has taken much longer, and even in 2011 the rate of vaccine usage was considered disappointingly low in the literature, at 34.8% (Holman DM et al. 2014). It is clear that there is still work to be done on the translation of the HPV vaccine before it is fully realized for improving health.

4.2.2 Back to Sleep Case

The full texts of 22 Back to Sleep related studies were examined for interdisciplinary research. The questions asked during the analysis were whether interdisciplinarity was seen in the author affiliations, the methods used, the theoretical content, the references and citations, and the degree that the multiple disciplines are integrated.

Author collaborations did not exhibit the large teams of multiple disciplines seen in HPV research, but did show signs of multidisciplinary collaboration between small groups of researchers from the public health and clinical medical fields in the T2 research, and between respiratory therapists or physiologists and clinical medicine in the T1 research. A substantial number were published by groups within single departments of medicine, however.

The references and citing articles also followed a similar pattern of drawing on the disciplines of clinical medicine, public health, and physiology, depending on the phase of translational research as discussed above. This was mostly seen in the T1 phase research, which had concurrently high integration scores as well. Other translational articles had low degrees of integration in their cited references.

Methodologically, most of the translational work was not interdisciplinary, but fell firmly within the purview of clinical medicine. Two of the studies on the physiology and neuroscience of SIDS made clear use of a combination of neuroscience and medical methods (Machaalani and Waters 2008; Wong et al. 2011). Several of the studies made attempts at theoretical interdisciplinarity by creating new models of SIDS prevention using the combination of public health and medical theories (Task Force on Sudden Infant Death Syndrome 2005; Trachtenberg et al. 2012). These works tended to be T2 or T4 research, and often showed high degrees of citing and cited diversity as well as high citedness. T3 research was monodisciplinary in authorship and references, consisting of implementation studies on programs to promote Back to Sleep.

The timeline of the Back to Sleep innovation shown in Figure 4.20 shows the high overlap of the dataset with the important events of the translational process. As part of an international effort, within ten years of major findings relating sleep position to SIDS incidence, an intervention was made and implemented, and outcomes were determined. By 2012, the

literature has reached a consensus that the Back to Sleep campaign was a successful translation, causing a 77% decrease in SIDS incidence after implementation (Chang et al. 2008).

4.2.3 Transcutaneous Bilirubinometry Case

The full text of 31 articles from the transcutaneous bilirubinometry literature were analyzed for indicators of interdisciplinary research. The questions asked during the analysis were whether interdisciplinarity was seen in the author affiliations, the methods used, the theoretical content, the references and citations, and the degree that the multiple disciplines were integrated.

The TcB literature exhibited a high degree of disciplinarity in its authorship. Most of the articles were published by small groups of authors from single academic departments, most often Pediatrics. Most followed the form of testing a commercially available device on the correlation between readings and standard medical tests. The few collaborations between disciplines were between Pediatrics and fields related to biomedical engineering.

The cited references and citing references of most of the TcB dataset were from one or two clinical medical disciplines, most often pediatrics. There were isolated instances where other fields were found, but these were exceptions to the general pattern. The lack of basic science publications may be related to industry practices, where evidence of effectiveness is held closely as trade secrets rather than published. This may be a barrier to translation that is rarely explored.

There was only a single study that could be classified as T3 research on implementation or dissemination (Dani et al. 2011). While there was T4 research on cost effectiveness, there were none on outcomes measures following implementation.

The timeline of the transcutaneous bilirubinometer innovation is shown in Figure 4.21. The first publication of an instantiation of the device was in 1980 in Japan, however, this was not covered in Web of Science with an abstract, and hence was not included in the dataset. Following this, it is 14 years before the device is incorporated into clinical guidelines, while other devices are developed at the same time. In 2014, the use of the transcutaneous

bilirubinometer as a screening tool is still not widespread, being used in only 63% of surveyed hospitals, and only as a screening tool, and still after 30 years the utility of the device is quoted as one of the "most important topics for investigation" for newborn research (Taylor et al. 2015). Translation of this device still is ongoing, as Bosschaart et al. point out about the inexplicably “limited clinical value” of the device currently, and suggest a multidisciplinary approach to improve it:

> we suggest that 2 approaches can result in a better clinical value for transcutaneous bilirubinometry: (1) a medical approach, requiring an extensive risk analysis for the predictive value of the TcB for the occurrence of kernicterus and (2) a technological approach, where the measurement volume of the transcutaneous bilirubinometer is confined to the intravascular space, enabling a 1 to 1 comparison with the TSB. (Bosschaart et al. 2012)

Figure 4.19. Timeline of HPV Innovation

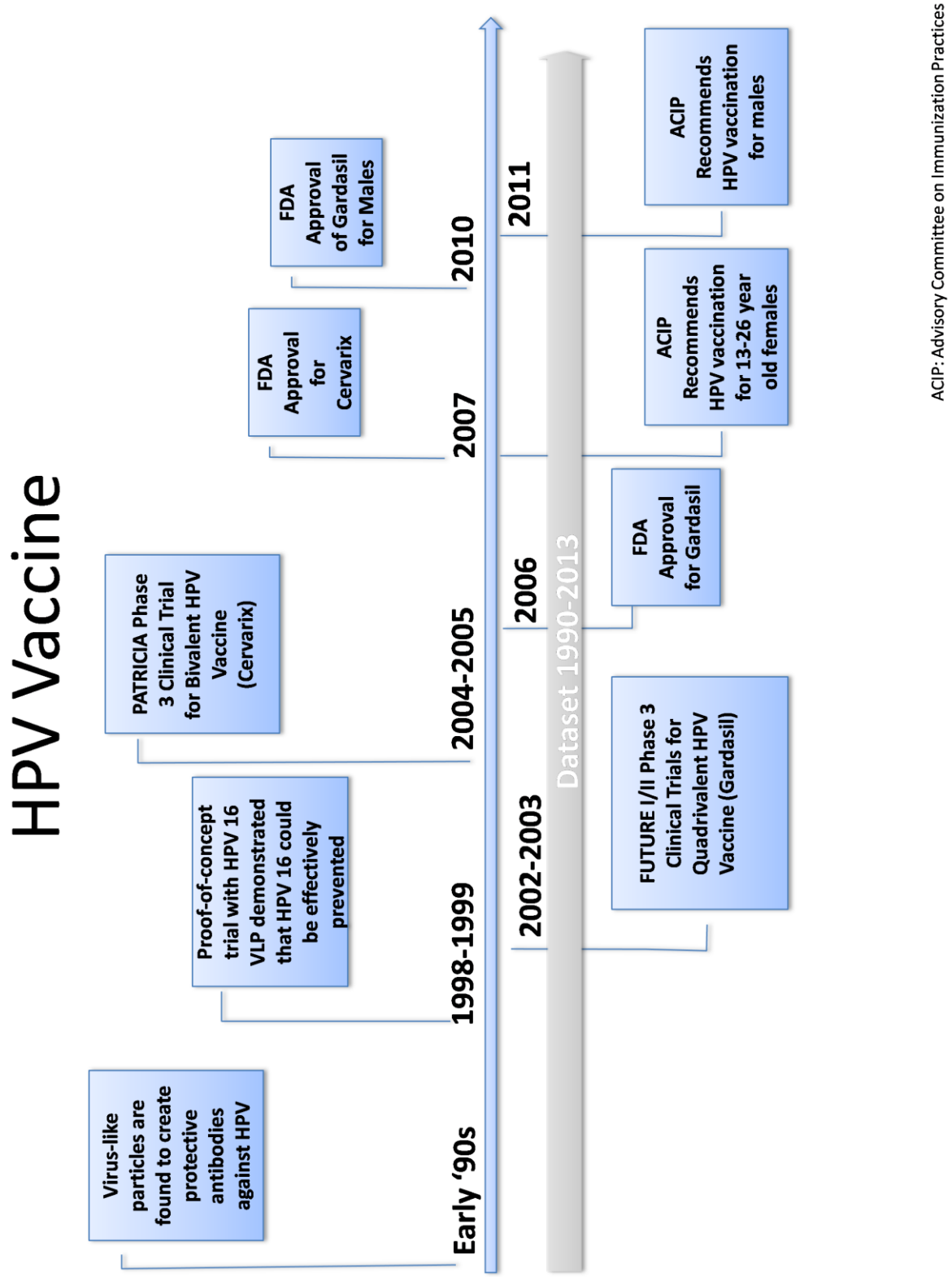


Figure 4.20. Timeline of Back to Sleep Innovation

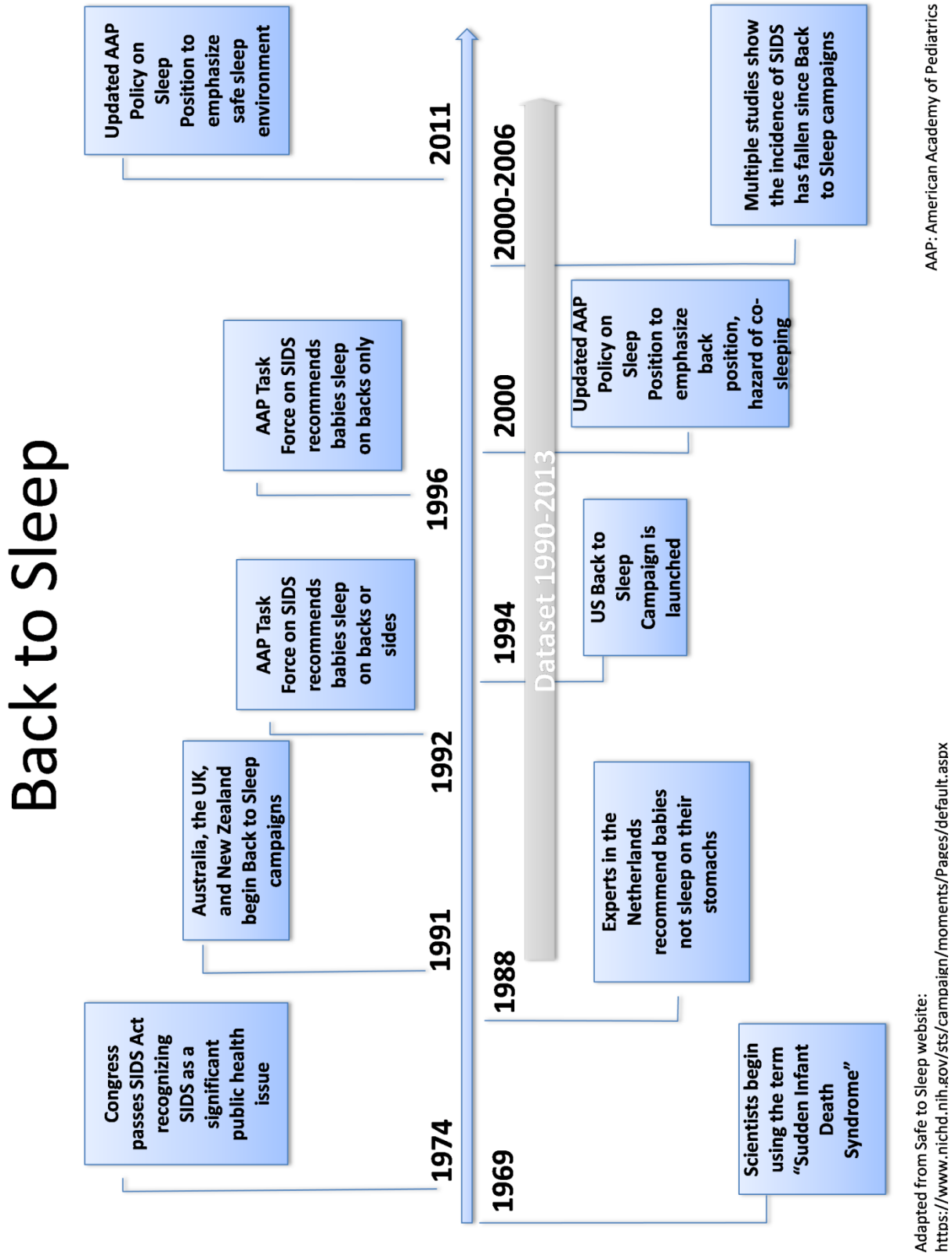
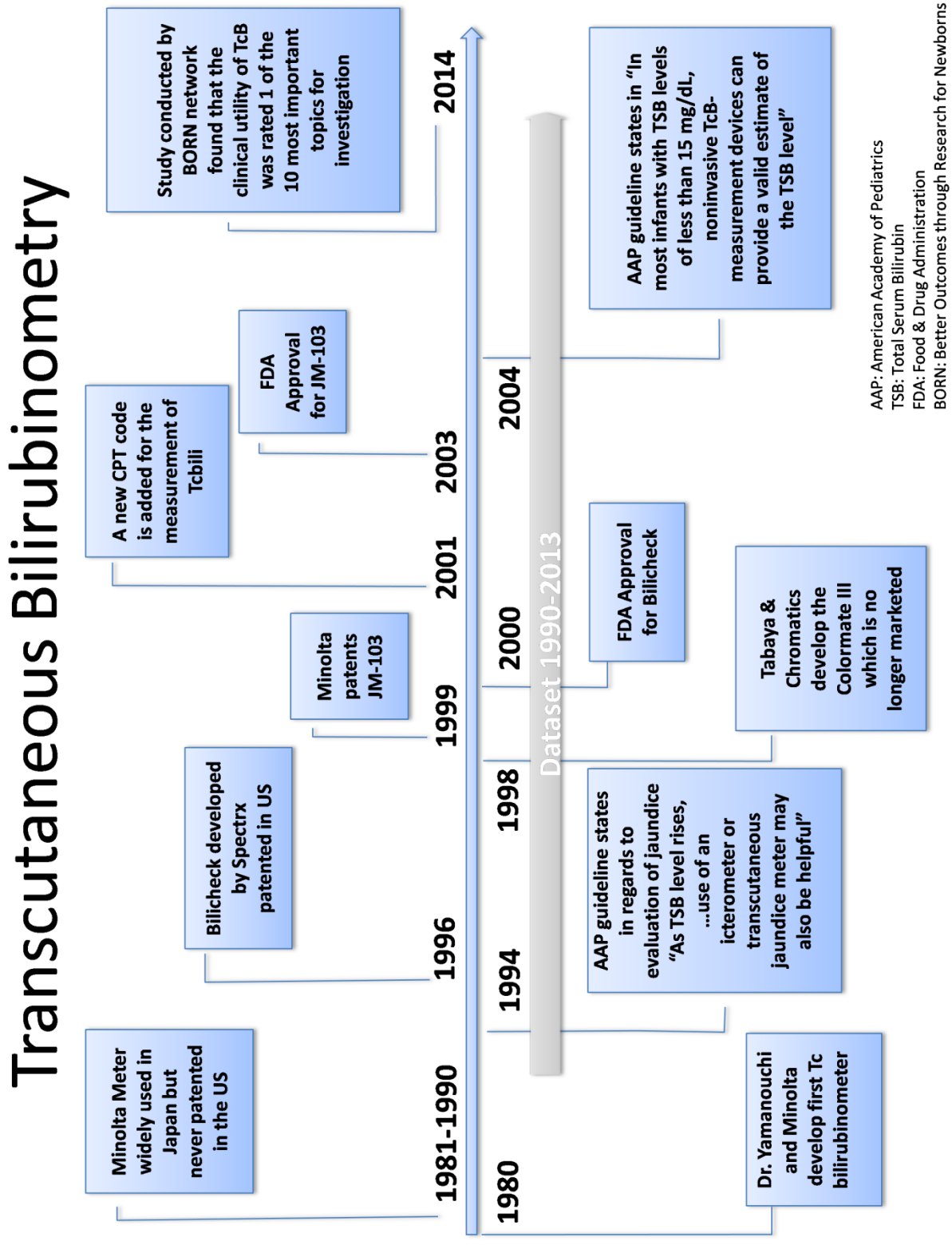


Figure 4.21. Timeline of TcB Innovation



4.3 Bibliometric Indicators of Interdisciplinarity in Translation

4.3.1 Integration: Interdisciplinarity of Reference Sets

The integration scores of records across all cases were calculated for each translational stage and compared to non-translational records.

This seems to show a clear pattern where early stage translation (T1, T2), has low Integration, while late stage (T3, T4) has high Integration. However, this is an artifact of the inappropriate pooling of data across heterogeneous populations. When separated by case, this pattern is seen to be caused by the difference in average Integration Score across cases combined with varying population sizes, and not by a general pattern. Given that this pooling of data is also discouraged by case study methodology, further analysis was done on a case by case basis.

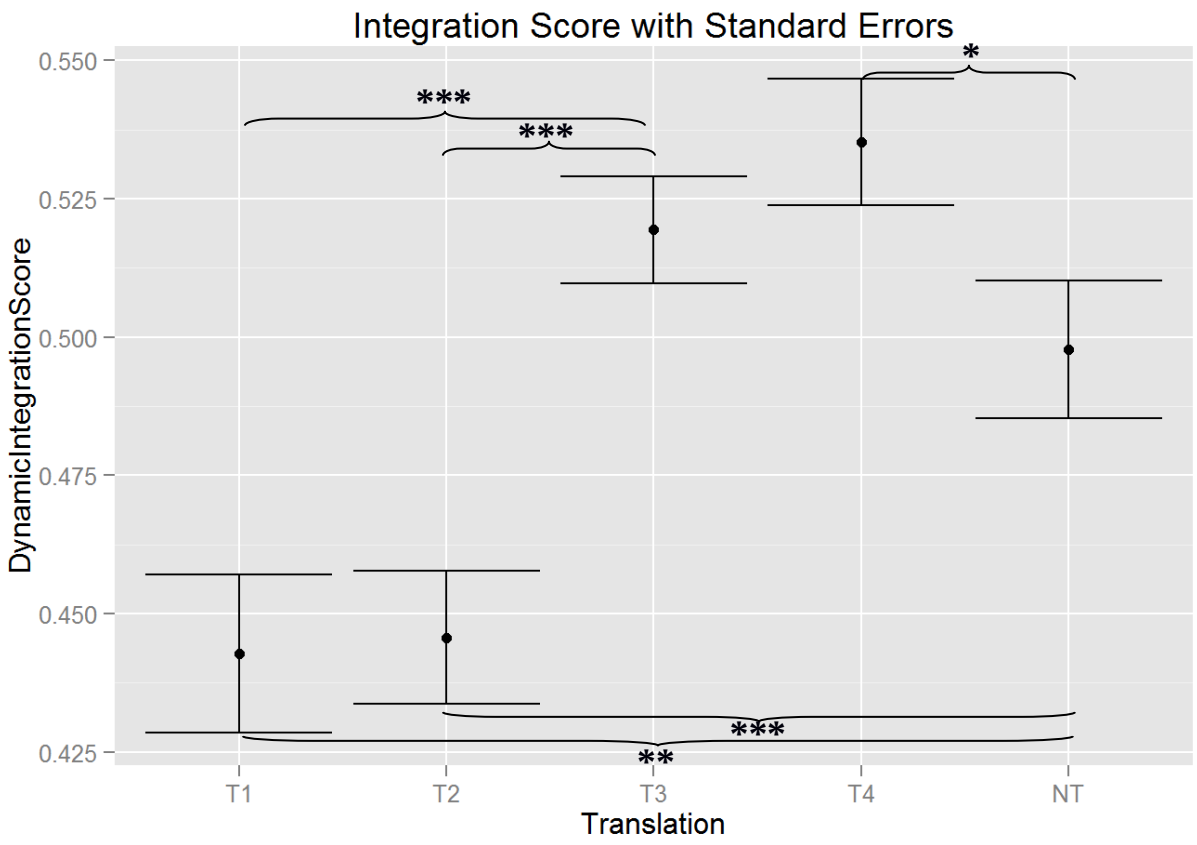
The relationships that remain between Integration Score and translational stage are that in BtS research, T1 research has a higher Integration Score, while T3 and T4 research have lower Integration. In HPV research, T2 research has a lower Integration Score than the other translational stages. In TcB research, T4 research has a lower Integration Score than the other translational stages. HPV research has very high average Integration Scores across all stages as well as non-translational work. TcB research has very low average Integration Scores across all stages as well as non-translational work.

The integration score is a measure of interdisciplinarity in that it increases as *knowledge sources* in the reference set of an article increase in intellectual distance.

It was hypothesized at the outset of this study that translational research should have high integration scores due to the need to cite knowledge from a large number of fields to bridge the gap between basic science and clinical practice.

This is not seen in this dataset for translational research as a whole. There are clearly certain types of translational research that do show evidence for increased integration in their reference sets compared to similar research, such as the clinical trials in the HPV case and T1 research in BtS.

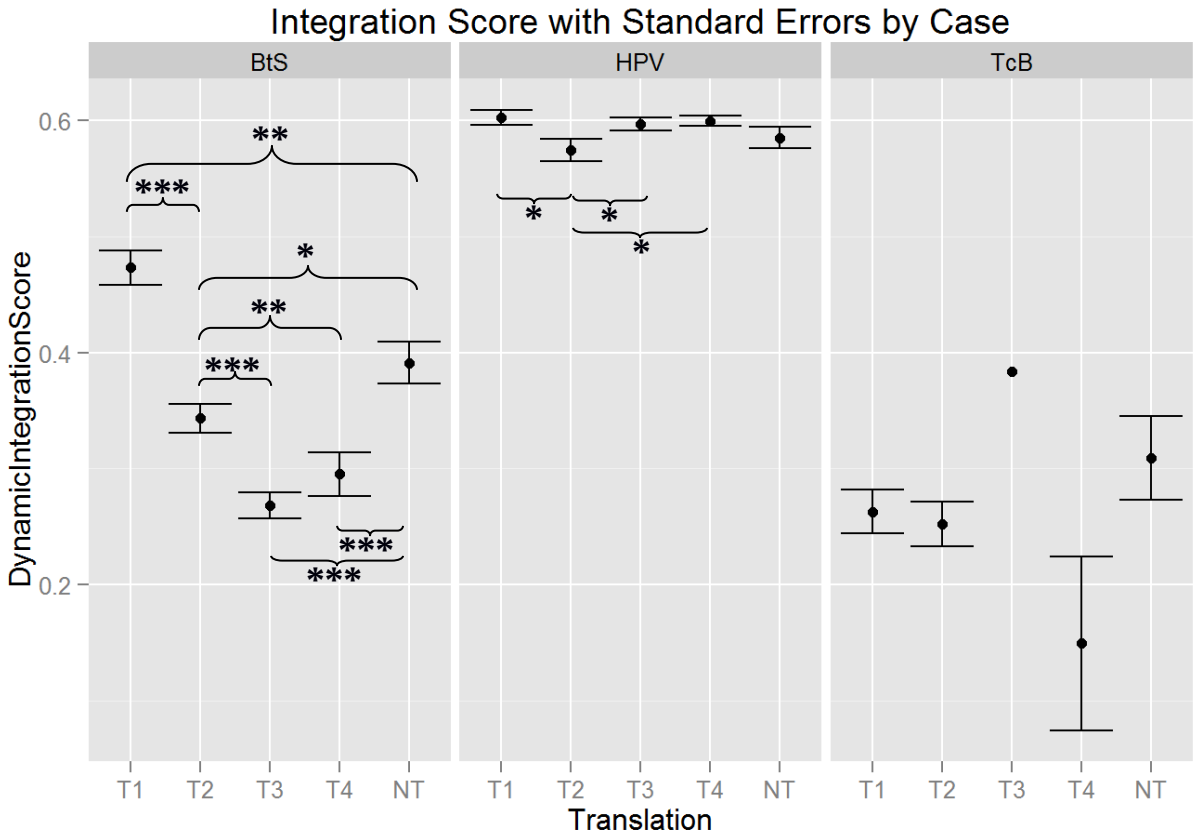
Figure 4.22. Average Integration Score of Translational Stages of Pooled Data



The mean values of the Integration Score across all cases, grouped by the translational stage assigned during coding. Standard error of the mean is shown with error bars. Statistical significance between pairs of variables is shown with asterisks:

* designates $p<0.05$; ** designates $p < 0.01$; *** designates $p<0.001$.

Figure 4.23. Average Integration Score of Translational Stages by Case



The mean values of the Integration Score within each case, grouped by the translational stage assigned during coding. Standard error of the mean is shown with error bars. Statistical significance between pairs of variables is shown with asterisks:

* designates $p<0.05$; ** designates $p < 0.01$; *** designates $p<0.001$.

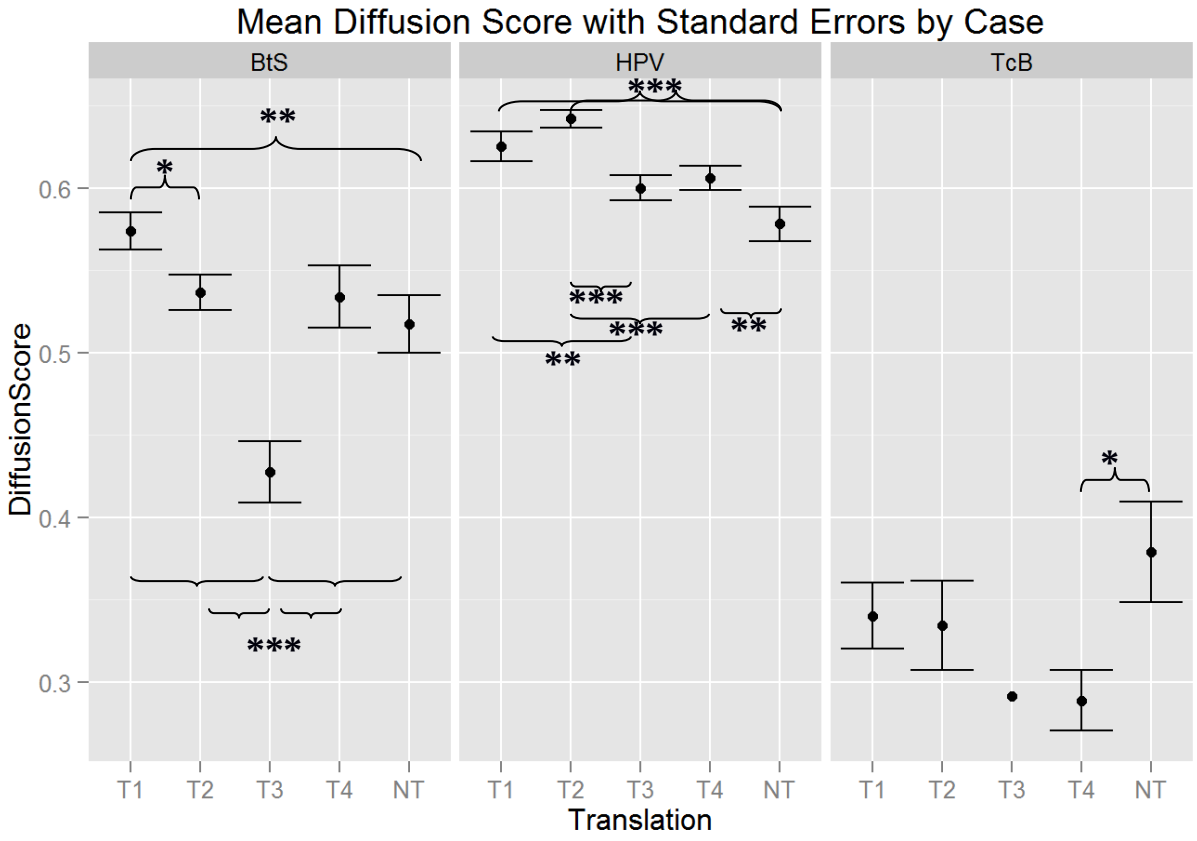
4.3.2 Diffusion: Multidisciplinarity of Citing Sets

The mean Diffusion Score of each translational stage of the cases are shown in Figure 4.24. These results show that T3 BtS research has lower Diffusion Score than the rest of the records in the case. T1 and T2 HPV research has higher Diffusion than the rest of the case, and all of the translational records have higher diffusion than non-translational work. T1 and T2 TcB research has higher Diffusion than T4 research, but not non-translational.

The diffusion score measures the diversity of the citing article set for a particular record and is therefore an indicator of the interdisciplinary impact of that record. It is found that the diffusion scores vary on a case by case basis, presumably due to the reach of each case into other disciplines. TcB has universally low diffusion scores as expected from its highly monodisciplinary presence in the single field of pediatrics. In both the HPV and BtS cases, T1 research has higher diffusion scores on average than other research which may be explained by this discovery type research serving as the intellectual foundation for many other translational studies. The TcB innovation, on the other hand, should be expected to have low diffusion scores, since it is a device used only in a small subfield of Pediatrics.

One finding that must be explained is the particularly low diffusion scores of BtS T3 delivery research. This cannot be explained by this research occurring later and therefore not accruing enough citations as in the BtS case, T3 research occurs from the beginning of the dataset. Therefore, one must draw from this the interpretation that T3 research will naturally have lower diffusion scores due to the limited cross-disciplinary interest in this type of practical research. As T3 research generally consists of implementation studies on the details of how clinicians incorporate an innovation into practice, it is understandable why only these clinical disciplines would cite these studies. The other two cases, while not showing this difference to the point of being statistically significant compared to non-translational research, do show a trend towards decreased diffusion scores in T3 research.

Figure 4.24. Average Diffusion Score of Translational Stages by Case



The mean values of the Diffusion Score within each case, grouped by the translational stage assigned during coding. Standard error of the mean is shown with error bars. Statistical significance between pairs of variables is shown with asterisks:

* designates p<0.05; ** designates p < 0.01; *** designates p<0.001.

4.3.3 Citations: Impact of Translation

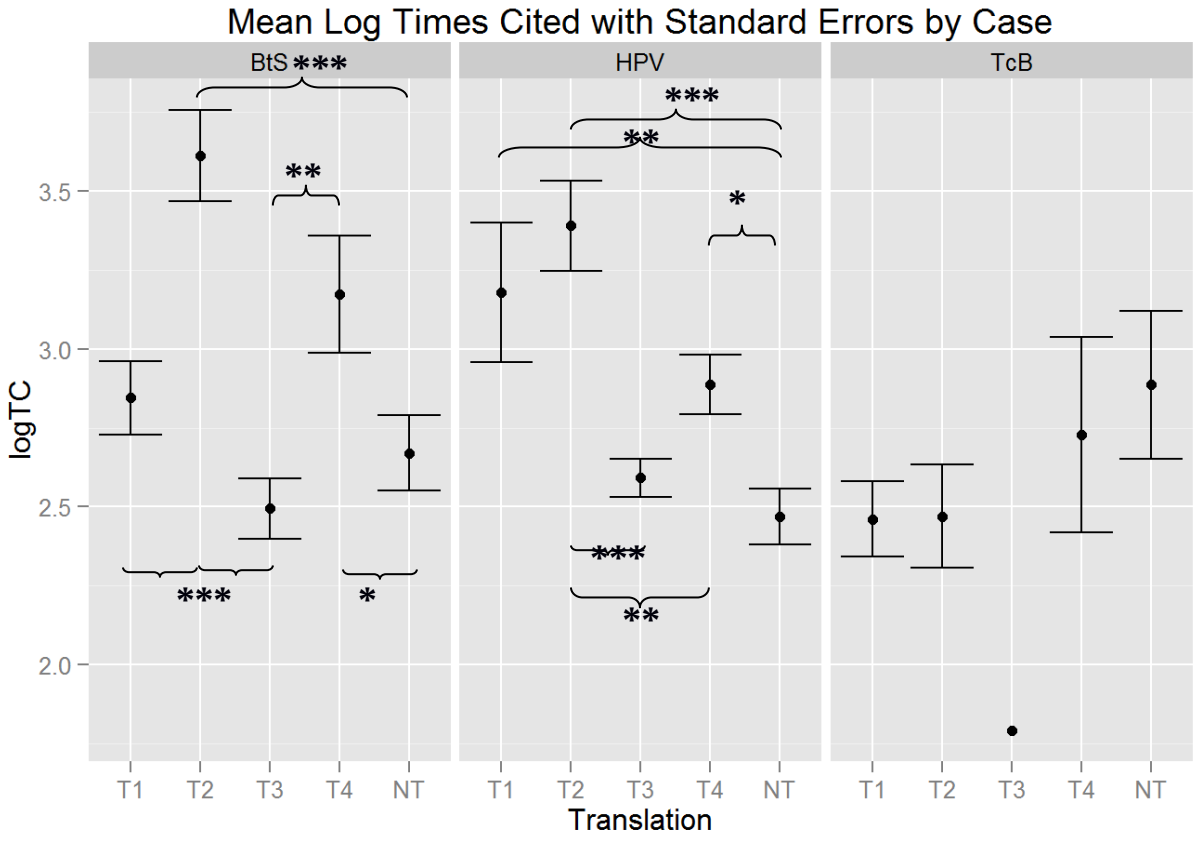
The number of citations were examined to see the relative impact of various translational stages. As citations are a highly skewed variable, the logarithm was used to approach a more normal distribution. Some observations are that in BtS research, T2 and T4 translational work have higher average citedness. In HPV research, T1 and T2 translational work have higher average citedness. In TcB research, no translational stages have higher citedness than non-translational work.

With patterns of citations, one expects to see that the highest cited works have made the most impact on later research. While citations can be made for a multitude of reasons, not all of which correlate with scholarly impact, it has been shown that the overall trend still promotes this. There is also a well-known correlation of publication time with citation, as older works have more time to gather citations than newer works.

With the linear model of translation, one would expect these two factors to combine to create a trend where earlier translational stages, T1 and T2, would have higher citation rates than later stages due to those being the foundation of the field, and being published earlier. One would expect many later translational works to cite the key early discoveries that allowed the innovation to progress.

This pattern is indeed seen in the case of HPV research. The early clinical trials that showed the efficacy and effectiveness of the vaccine are very highly cited. In BtS research the same is true for the T2 retrospective studies that showed the correlation between sleep position and SIDS, but not for the T1 research that investigated the physiological mechanisms for this. Also, in BtS research, the T4 research that studied the outcome of the Back to Sleep intervention campaign is heavily cited, while this is not the case for HPV. There is no evidence that any stage of TcB research is more heavily cited than average, which may be an indication that there has been no 'breakout' translational work that has convinced the field of its impact.

Figure 4.25. Average Times Cited of Translational Stages by Case



The mean values of the Times Cited, with the logarithm applied to make the highly skewed values more normal, within each case, grouped by the translational stage assigned during coding. Standard error of the mean is shown with error bars. Statistical significance between pairs of variables is shown with asterisks:

* designates p<0.05; ** designates p < 0.01; *** designates p<0.001.

4.3.4 Authorship Counts: Team Science

The average number of authors within each translational stage are shown for each case in Figure 4.26. This is a measure of the amount of collaboration. There are no significant differences in either the BtS or TcB cases, however, in the HPV case translational stages T1 and T2 show significantly higher number of authors compared to both T3 and T4 as well as non-translational records.

There is a substantial and unmistakable pattern of large numbers of authors publishing research in HPV research in stages T1 and T2. These are generally the clinical trial type of research that involves large multidisciplinary teams. This pattern is not observed in BtS or TcB although it is unclear whether this is optimal or due to lack of funding or differences in disciplinary culture. The clinical trial methodology is well established and accepted in pharmaceuticals research but has no equivalent in device or policy research. As noted in the BtS literature, "there have been no randomized controlled trials with regards to SIDs and other sleep-related deaths; instead, case-control studies are the standard." (Task Force on Sudden Infant Death Syndrome and Moon 2011)

4.3.5 Bibliographic Coupling Betweenness

The average values of the bibliographic coupling betweenness of each translational stage for each case is shown in Figure 4.27. There are no statistically significant differences between the translational stages for this variable. If there are only a handful of records with high betweenness for each stage, this would lead to this type of non-difference between the stages, as they would be functionally identical at the population level.

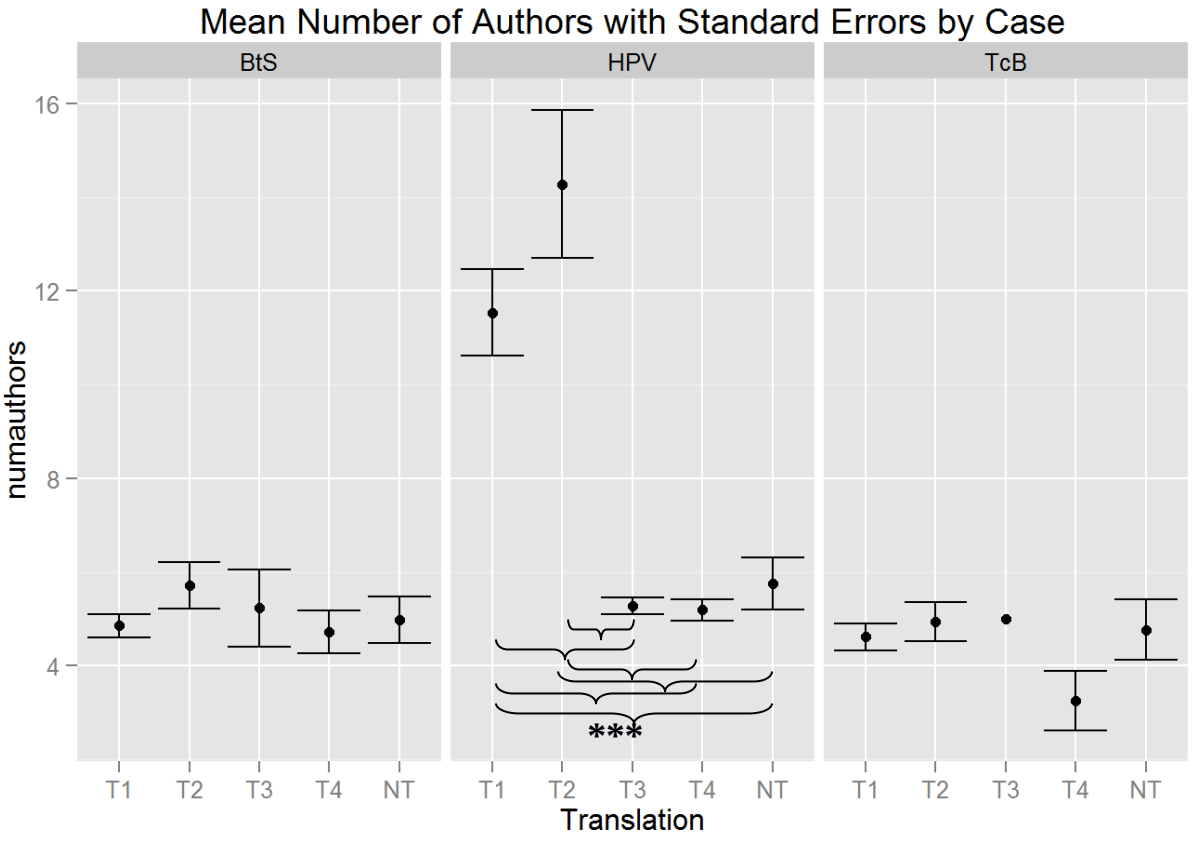
4.3.6 Co-citation Betweenness

The average values of co-citation betweenness for each translational stage for each case is shown in Figure 4.28. No statistically significant differences are seen between any two stages.

When used as a population level metric, these betweenness indicators do not show any significant differences between translational stages or between translational and non-translational

records. This may be a limitation of the metrics in a situation where the majority of the network consists of the variable of interest. In these networks, a majority of records are translational and therefore it is difficult for these betweenness measures which are sensitive to nodes with unusual positions within the network to detect translation. This may indicate a need for refinement of the definition of translational research which will be discussed below.

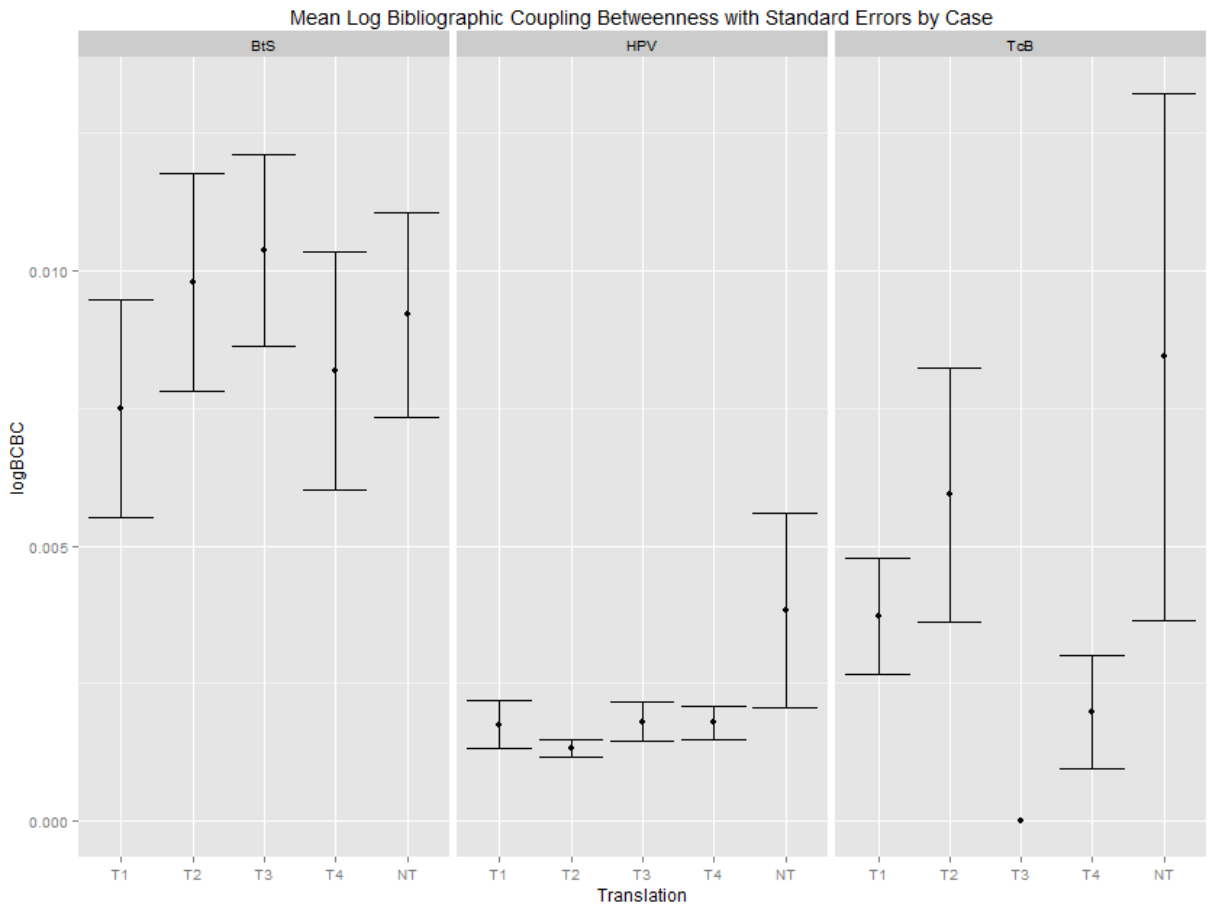
Figure 4.26. Average Author Number of Translational Stages by Case



The mean values of the Number of Authors within each case, grouped by the translational stage assigned during coding. Standard error of the mean is shown with error bars. Statistical significance between pairs of variables is shown with asterisks:

* designates p<0.05; ** designates p < 0.01; *** designates p<0.001.

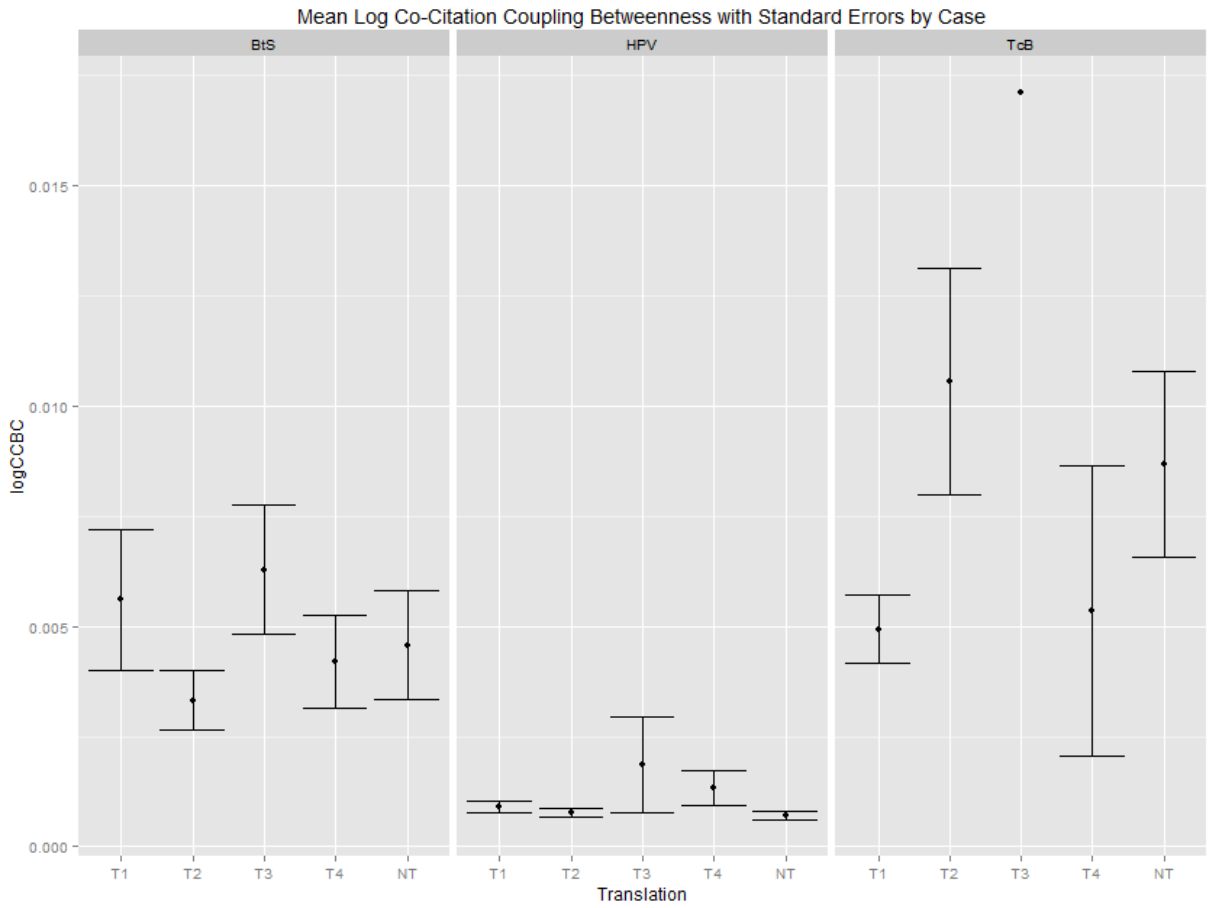
Figure 4.27. Average Bibliographic Coupling Betweenness of Translational Stages by Case



The mean values of the logarithm of bibliographic coupling betweenness within each case, grouped by the translational stage assigned during coding. Standard error of the mean is shown with error bars. Statistical significance between pairs of variables is shown with asterisks:

* designates $p<0.05$; ** designates $p < 0.01$; *** designates $p<0.001$.

Figure 4.28. Average Co-Citation Betweenness of Translational Stages by Case



The mean values of the logarithm of co-citation betweenness within each case, grouped by the translational stage assigned during coding. Standard error of the mean is shown with error bars. Statistical significance between pairs of variables is shown with asterisks:

* designates $p<0.05$; ** designates $p < 0.01$; *** designates $p<0.001$.

4.4 Bibliometric Evaluation of Translation: Prediction

Random forest decision trees were used to determine the usefulness of the bibliometric indicators in predicting whether a record is translational and which translational stage it is. The motivation of this analysis is to determine: which bibliometric indicators are relevant to identifying translational research, and also to quantify the degree to which they are useful in this determination.

4.4.1 Predicting Translation

The full dataset was used to determine if translational records could be identified from non-translational records. This entailed combining the case records, which has been shown above to lead to problematic results due to the differences between the cases, but is shown here as a baseline analysis and a naïve approach to the problem, but one that could be commonly used in real world situations.

The random forest prediction shown in Figure 4.29 was able to distinguish translational from non-translational test records with near 70% accuracy (68.77%). This is above the 50% expected accuracy for a random predictor.

The most important variables in this predictive model based on the mean decrease in accuracy were Integration Score, Diffusion Score, Co-citation Betweenness and Times Cited per Year.

The relative position of each record in the classification space of the random forest is shown in Figure 4.30 as a two-dimensional scatter plot for ease of visualization. This plot shows points close together if they are classified similarly by the random forest. There is little clustering or differentiation between non-translational and translational records.

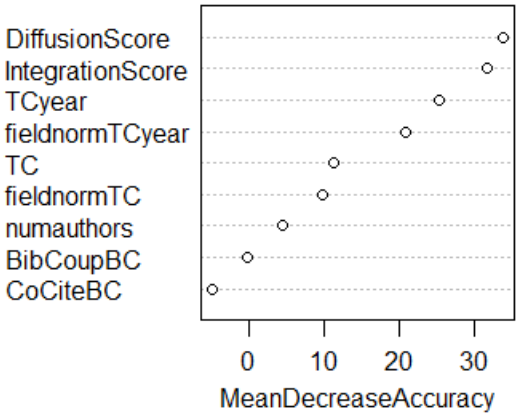
Figure 4.29. Random Forest Prediction of Translational vs Non-translational Records

A

		OOB Error Rate	36.81%
	NT	T	Error
NT	55	46	0.46
T	215	393	0.35

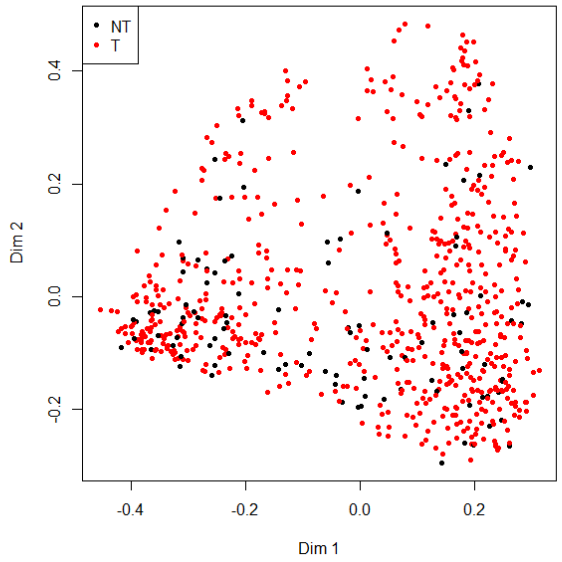
		Test Set Error Rate	35.39%
	NT	T	Error
NT	14	21	0.6
T	42	101	0.29

B



Results of random forest prediction method is shown in panel A. Confusion matrices are shown for Out of Bag results - misclassifications on training set at top, as well as errors on the test set at bottom. Rows indicate true values, columns indicate predicted value. NT - Not translational T - translational. Panel B shows the decrease in accuracy that occurs when each variable in turn is randomized.

Figure 4.30. Relative Position of Translational and Non-translational Records in Random Forest Classification



Multidimensional scaling plot showing the relative positions of the data when collapsed to 2 dimensions. Black - Not translational; Red - Translational.

4.4.2 Predicting Translational Stage

The random forest prediction shown in Figure 4.31 was able to distinguish between translational stages with 45% accuracy (44.7%). This is above the 20% expected accuracy for a random predictor. T2 and T3 research were most accurately classified.

The most important variables in this predictive model based on the mean decrease in accuracy were Diffusion Score, Number of Authors and Times Cited per Year.

The relative position of each record in the classification space of the random forest is shown in Figure 4.32 as a two-dimensional scatter plot for ease of visualization. This plot shows points close together if they are classified similarly by the random forest. There is some amount of clustering that makes T1/T2 and T3 research separable. T2 and T3 records move far from the main cluster in what can be described as two arms, whereas the other categories are intermixed in the center. This is visual indication of how the classifier does a better job at identifying T2 and T3 research than the other categories, with error rates as low as 0.3, much better compared to the random chance error rate of 0.8. The classifier uses times cited per year and the number of authors as its first two major classification factors, with the Integration Score coming third in importance. Based on other results, this likely means that T2 research is distinguished by its high number of authors and high citation rate per year, while T3 is identified through high Integration scores.

4.4.3 Predicting Case Identity

The random forest prediction shown in Figure 4.33 was able to distinguish between case identities with 92% accuracy (91.9%). This is above the 33% expected accuracy for a random predictor. Back to Sleep and TcB had the largest number of misclassifications for each other.

The most important variables in this predictive model based on the mean decrease in accuracy were Integration Score, Bibliographic Coupling Betweenness, and Times Cited per Year.

The relative position of each record in the classification space of the random forest is shown in Figure 4.34 as a two-dimensional scatter plot for ease of visualization. This plot shows

points close together if they are classified similarly by the random forest. HPV records appear far from the records of the other two cases which are more mixed but still somewhat separable.

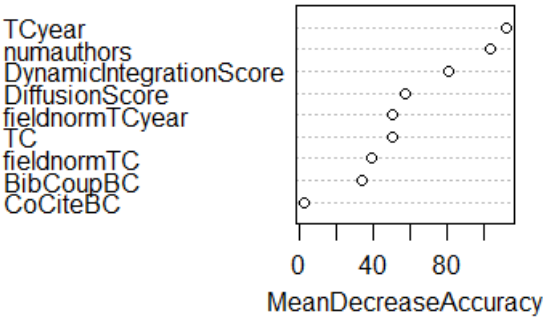
Figure 4.31. Random Forest Prediction of Translational Stage of Records

A

					OOB Error Rate	57.40%
	NT	T1	T2	T3	T4	Error
NT	17	17	21	40	6	0.83
T1	15	32	33	18	7	0.7
T2	11	26	76	30	9	0.5
T3	14	8	25	149	26	0.33
T4	11	5	16	69	28	0.78

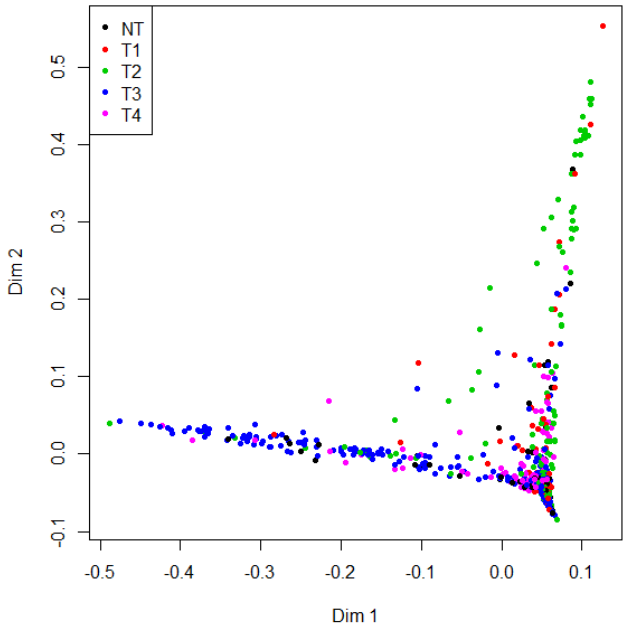
					Test Set Error Rate	59.55%
	NT	T1	T2	T3	T4	Error
NT	6	4	7	15	3	0.83
T1	2	9	5	5	3	0.63
T2	2	3	17	11	4	0.54
T3	0	3	7	34	6	0.32
T4	4	0	3	19	6	0.81

B



Results of random forest prediction method are shown in panel A. Confusion matrices are shown for Out of Bag results - misclassifications on training set at top, as well as errors on the test set at bottom. Rows indicate true values, columns indicate predicted value. NT - Not translational T1-T4 translational stages. Panel B shows the decrease in accuracy that occurs when each variable in turn is randomized.

Figure 4.32. Relative Position of Translational Stage Records in Random Forest Classification



Multidimensional scaling plot showing the relative positions of the data when collapsed to 2 dimensions. Colors indicate translational stages.

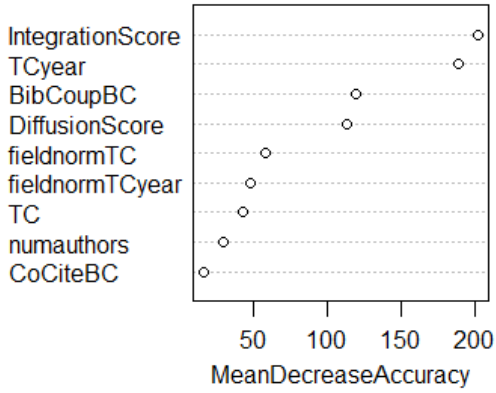
Figure 4.33. Random Forest Prediction of Case Identify

A

			OOB Error Rate	7.48%
	BtS	HPV	TcB	Error
BtS	166	11	9	0.11
HPV	8	435	2	0.02
TcB	20	3	55	0.29

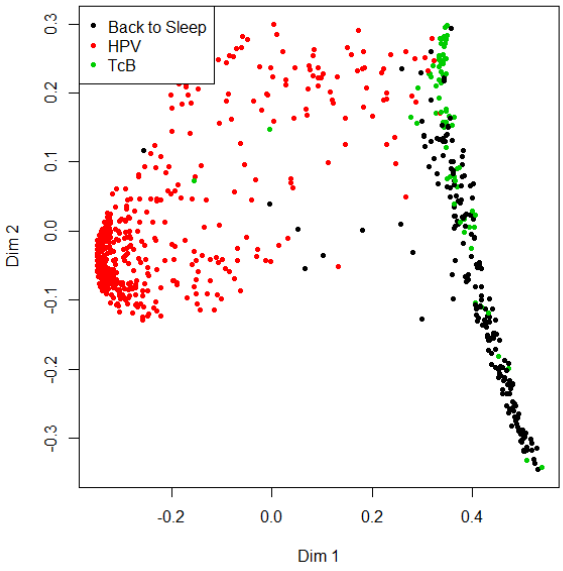
			Test Set Error Rate	8.99%
	BtS	HPV	TcB	Error
BtS	42	2	3	0.11
HPV	2	109	2	0.04
TcB	5	2	11	0.39

B



Results of random forest prediction method are shown in panel A. Confusion matrices are shown for Out of Bag results - misclassifications on training set at top, as well as errors on the test set at bottom. Rows indicate true values, columns indicate predicted value. NT - Not translational T1-T4 translational stages. Panel B shows the decrease in accuracy that occurs when each variable in turn is randomized.

Figure 4.34. Relative Position of Case Identify in Random Forest Classification



Multidimensional scaling plot showing the relative positions of the data when collapsed to 2 dimensions. Colors indicate Case identity.

4.4.4 Case Specific Prediction

4.4.4.1 HPV Vaccine Case

The random forest prediction shown in Figure 4.35 was able to distinguish between translational stages in the HPV case with 52% accuracy (51.8%). This is above the 20% expected accuracy for a random predictor. T1 and T2 records were often misclassified as well as translational versus non-translational.

The most important variables in this predictive model based on the mean decrease in accuracy were Number of Authors and Diffusion Score.

The relative position of each record in the classification space of the random forest is shown in Figure 4.36 as a two-dimensional scatter plot for ease of visualization. This plot shows points close together if they are classified similarly by the random forest. There is some amount of clustering that makes T1/T2 and T3 research separable.

4.4.4.2 Back to Sleep Case

The random forest prediction shown in Figure 4.37 was able to distinguish between translational stages in the BtS case with 41% accuracy (40.9%). This is above the 20% expected accuracy for a random predictor. The classifier did poorly in detecting translational from non-translational records and made most other errors misclassifying stages in adjacent classes.

The most important variables in this predictive model based on the mean decrease in accuracy were Integration Score and Times Cited.

The relative position of each record in the classification space of the random forest is shown in Figure 4.38 as a two-dimensional scatter plot for ease of visualization. This plot shows points close together if they are classified similarly by the random forest. While some T1 records are clustered, there are many that are intermixed with T2 and T3 research compared to the HPV case.

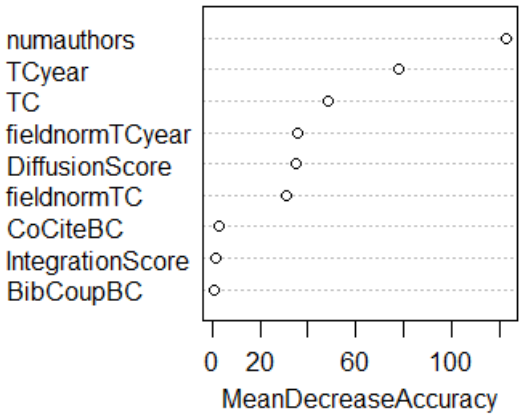
Figure 4.35. Random Forest Prediction of HPV Translational Stage Identify

A

						OOB Error Rate	50.45%
	NT	T1	T2	T3	T4	Error	
NT	10	5	5	41	9	0.86	
T1	4	7	10	5	4	0.77	
T2	5	3	39	21	8	0.49	
T3	8	1	8	132	21	0.22	
T4	10	2	3	52	33	0.67	

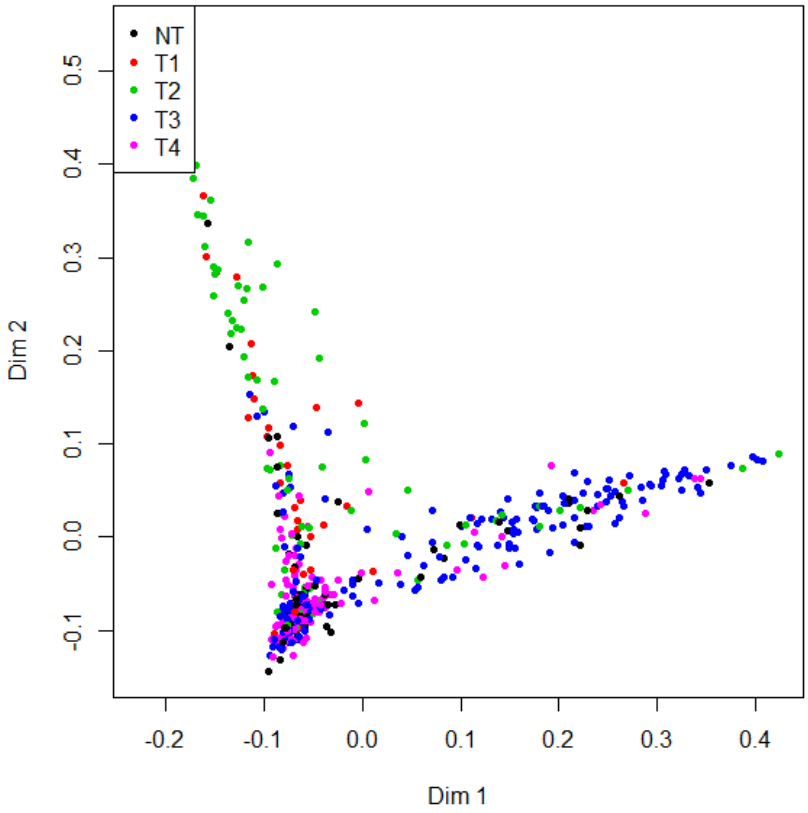
						Test Set Error Rate	56.25%
	NT	T1	T2	T3	T4	Error	
NT	2	0	0	7	3	0.83	
T1	3	0	3	2	1	1	
T2	2	3	11	5	1	0.5	
T3	2	1	1	32	3	0.18	
T4	4	0	0	22	4	0.87	

B



Results of random forest prediction method are shown in panel A. Confusion matrices are shown for Out of Bag results - misclassifications on training set at top, as well as errors on the test set at bottom. Rows indicate true values, columns indicate predicted value. NT - Not translational T1-T4 translational stages. Panel B shows the decrease in accuracy that occurs when each variable in turn is randomized.

Figure 4.36. Relative Position of HPV Translational Stage Records in Random Forest Classification



Multidimensional scaling plot showing the relative positions of the data when collapsed to 2 dimensions. Colors indicate translational stage.

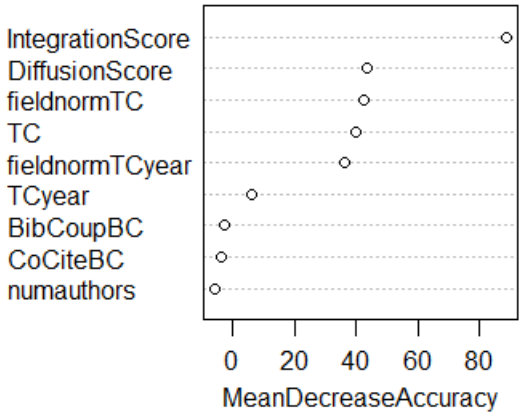
Figure 4.37. Random Forest Prediction of BtS Translational Stage Identify

A

					OOB Error Rate	55.91%
	NT	T1	T2	T3	T4	Error
NT	3	13	6	9	0	0.9
T1	4	23	7	6	0	0.43
T2	3	9	18	8	2	0.55
T3	4	5	6	38	1	0.3
T4	0	5	5	11	0	1

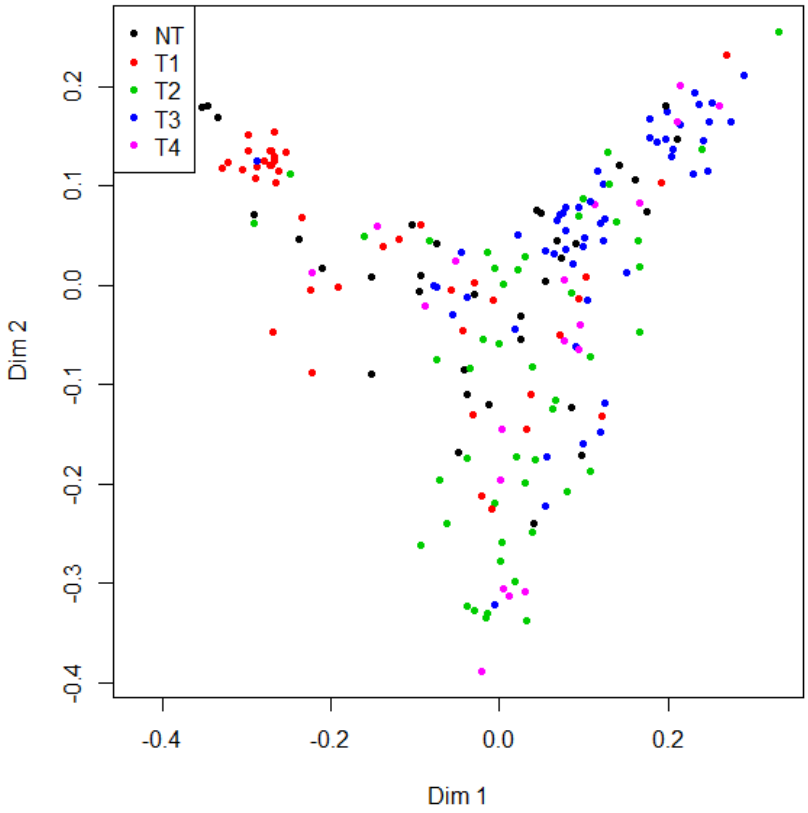
					Test Set Error Rate	55.32%
	NT	T1	T2	T3	T4	Error
NT	1	5	0	3	1	0.9
T1	0	4	3	0	0	0.43
T2	1	2	9	3	0	0.4
T3	1	0	0	7	0	0.13
T4	0	1	4	2	0	1

B



Results of random forest prediction method are shown in panel A. Confusion matrices are shown for Out of Bag results - misclassifications on training set at top, as well as errors on the test set at bottom. Rows indicate true values, columns indicate predicted value. NT - Not translational T1-T4 translational stages. Panel B shows the decrease inaccuracy that occurs when each variable in turn is randomized.

Figure 4.38. Relative Position of BtS Translational Stage Records in Random Forest Classification



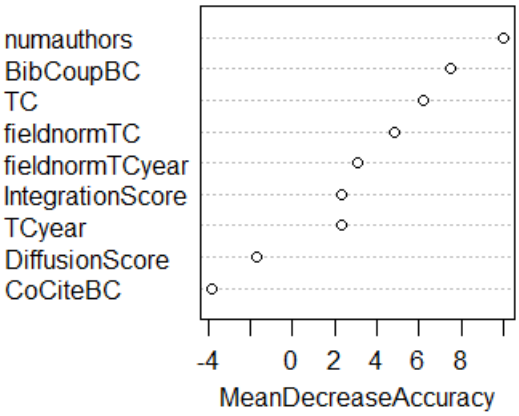
Multidimensional scaling plot showing the relative positions of the data when collapsed to 2 dimensions. Colors indicate translational stage.

Figure 4.39. Random Forest Prediction of TcB Translational Stage Identify

A

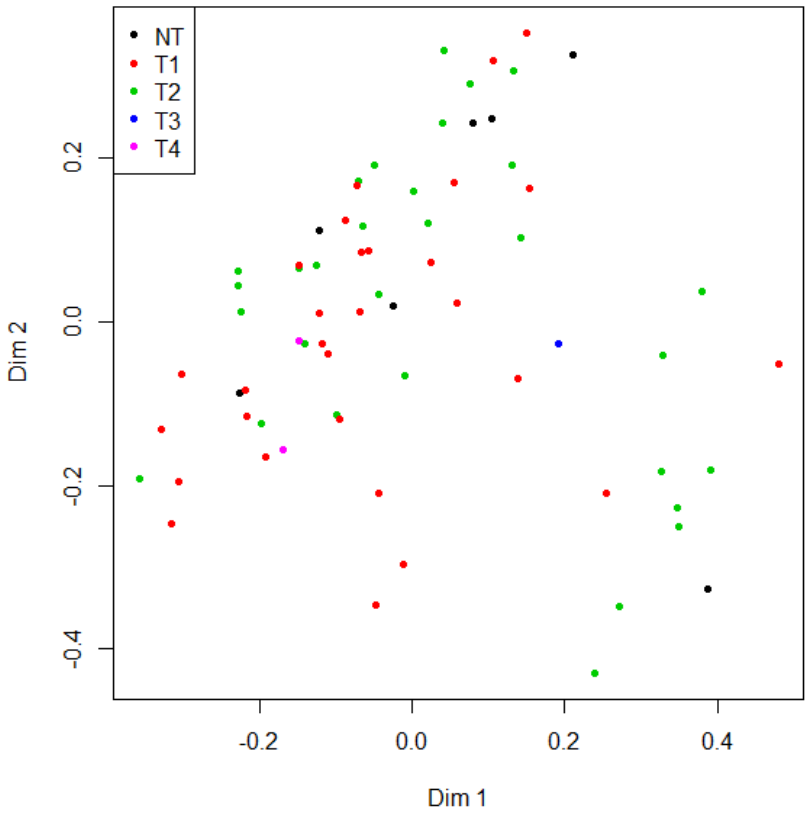
						OOB Error Rate 57.89%
	NT	T1	T2	T3	T4	Error
NT	0	8	3	0	0	1
T1	3	26	8	0	0	0.3
T2	1	18	6	0	0	0.76
T3	0	1	0	0	0	1
T4	0	1	1	0	0	1

B



Results of random forest prediction method are shown in panel A. Confusion matrices are shown for Out of Bag results - misclassifications on training set, there were not enough T3 records in the TcB case to supply a test set. Rows indicate true values, columns indicate predicted value. NT - Not translational T1-T4 translational stages. Panel B shows the decrease in accuracy that occurs when each variable in turn is randomized.

Figure 4.40. Relative Position of TcB Translational Stage Records in Random Forest Classification



Multidimensional scaling plot showing the relative positions of the data when collapsed to 2 dimensions. Colors indicate translational stage.

4.4.4.3 Trancutaneous Bilirubinometry Case

The random forest prediction shown in Figure 4.39 was able to distinguish between translational stages in the TcB case with 46% accuracy (46.3%). This is above the 20% expected accuracy for a random predictor. The small size of the TcB dataset made it impractical to generate a test set.

The most important variables in this predictive model based on the mean decrease in accuracy were Times Cited per Year, although values are very small.

The relative position of each record in the classification space of the random forest is shown in Figure 4.40 as a two-dimensional scatter plot for ease of visualization. This plot shows points close together if they are classified similarly by the random forest. There are no clear separable clusters in the TcB records.

4.4.5 Overall Results of Prediction

If the bibliometric indicators of interdisciplinarity are information bearing with regards to translational research, it should be possible to use these indicators to predict which records are translational and which are not. If they contain information regarding where in the process of translation the record is, they should be able to be used to predict this as well.

The random forest machine learning method was used to determine the ability of bibliometric indicators to predict translation, translational stage, and case. This method provides the advantage of being able to easily determine the relative importance of variables in the prediction strength.

Predicting the stage of translation, or the type, also showed better than chance performance, and the key variables were Diffusion Score and the number of authors. This is a quantitative confirmation of the trend of early stage, type 1, Stage 1/2 translational research to operate in a team science, high number of co-authors mode. The case specific predictions, while losing some power based on their smaller sizes, show that each case is unique in the correlations between bibliometric indicators of interdisciplinarity and translational stage. HPV research is distinguished heavily by the team science aspect of Type 1 translational research, but this is not

useful in the other two cases. In Back to Sleep research, it is the Integration Score, presumably the very high scores seen in the integrative work of the T1 physiology research on SIDS and sleep position that distinguishes the stages. The transcutaneous literature exhibits very little importance for interdisciplinary indicators, and times cited and times cited per year are more important for distinguishing the higher cited T4 stage from the T1/T2 research.

The results show a weak, but real importance of some interdisciplinary indicators in predicting translational research. This is a result that would be expected if there is a correlation between interdisciplinary work and translation. The most important indicator is Integration Score, followed by Diffusion Score. This indicates that the diversity of both the communities that are drawn upon as a knowledge source, as well as the diversity of the communities that cite the work, are correlated with whether a work is translational. However, given that this information can only provide around a 70% success rate in predicting translation, there are clearly examples of translational records that do not have high integration or diffusion scores, as supported by the qualitative analysis here. Indeed, it is important to keep in mind that the importance of a variable in predicting the translational stage of a record does not at all imply that a high value of that variable is important, it could equally be that a low value of that variable is the distinguishing feature.

CHAPTER 5. CONCLUSIONS

5.0 Summary of Conclusions

5.0.1 Types of Interdisciplinary Research in Translational Medicine

There were multiple types of interdisciplinary research observed in the data on translational research. The hypothesis that multidisciplinarity in team science would be observed in early stage translation was confirmed for the case of the HPV vaccine, but was not observed in the other cases. Methodological interdisciplinarity was the most commonly observed type of interdisciplinarity, while examples of high levels of integration or transdisciplinarity were rare, but was more associated with later stages of translation than with early stages. This indicates that there may be a reason to promote certain types of interdisciplinarity to achieve different stages of translation.

5.0.2 Interdisciplinary Research is Not Synonymous with Translational Research

The results of the predictive models and the qualitative observations agree on the weak link between interdisciplinarity and translational research as a necessary component. This argues against the claims that supporting translational research requires supporting interdisciplinary research. However, this does not rule out that there may be some positive benefit to translation of having appropriate types of interdisciplinarity. Still, the evidence here suggests that multidisciplinarity, rather than interdisciplinarity, is a promoter of translation.

5.0.3 Translational research is described better by case identity than by translational identity

With regard to the bibliometric identifiers studied here, it is shown that records are described more completely by which case they belong to, rather than by which translational stage or even if they are translational or not. This suggests that translation should not be considered a single common process, but is highly dependent on the particulars of the case. It also should remind investigators of the great importance of taking subject specifics into account when doing bibliometric work, as those factors may dwarf the signals coming from factors like translation.

5.0.4 Translational linear model is not supported by the evidence

The cases shown here raise grave doubts about the applicability of the linear model of translational medicine. Even with a generous reading of expected ratios, there is no consistent path followed by innovations from basic science to clinical science to population science. While each individual record could be classified into the T1 to T4 taxonomy, they did not align temporally into that sequence.

5.0.5 Balanced Model Proposed

The most successful of the cases, Back to Sleep, exhibited a temporal trend of translational stages that can be described as balanced. All four of the stages are present at each time point, rather than appearing in a sequence. In the other cases, at various times different types of translational research were missing. This suggests that there is some benefit to having research that addresses all aspects of translation, rather than waiting for certain research to appear before proceeding. This inspires the balanced model of translation, where all four stages of translation work together, both within disciplines and bridging other disciplines, to advance translation.

5.0.6 Bibliometric Measures Have Limited Ability to Predict Translational Research

This work shows that there is the potential to identify translational work using bibliometric methods. While the indicators used here do not achieve very high levels of accuracy, this is likely due to the problems identified here which could be overcome with other methods. Combined with the balanced model proposed here, this suggests a valuable tool for translational policy makers to use in improving the efficiency of translation by identifying and enhancing appropriate types of translation.

5.0.7 Structural IDR Metrics are Useful for Distinguishing Early and Late TR

The use of Web of Science subject categories to analyze the cited and citing references of records shows some promise in identifying translational research. This type of bibliometric

analysis offers the potential of providing a way of identifying gaps in the translational literature without great effort of manual coding.

5.0.8 Structural IDR Metrics Have Unique Problems in TR Due to Clinical Medicine Subjects

One clear issue with the use of the Web of Science subject category for the identification of translational research is the overarching broadness of the clinical medicine fields. As shown in the data here, the subject categories of Pediatrics or General Medicine can span the entirety of the translational process, and therefore using them to detect different stages of translation becomes difficult.

5.0.9 Spatial IDR Metrics are Unhelpful for this Definition of TR

The use of spatial interdisciplinary indicators, such as cocitation and bibliographic coupling betweenness centrality, was surprisingly unhelpful in detecting translational research in this dataset. On reflection, this may be due to the inclusive nature of the definition of translation used in this study, which include studies that may not necessarily be bridging fields to be translational as long as they fit the type of research defined by the NIH as translational. These metrics should be more useful to identify the more rare transformative works that bridge fields in a novel way.

5.0.10 Definition of TR could be Refined

Any study of translational research must first grapple with the problem of defining it, and any conclusions will be based on that definition. In this study, translation was defined in a broad sense, as any study meeting the topical criteria in the NIH definition. However, one of the conclusions of the findings of this study could be that this definition is overly broad compared to what some would consider a useful definition of translation. This would be a definition that looks for the rare, paradigm shifting works that greatly advance innovation, rather than the stepwise research that gradually advances the current state of knowledge. This is worth

discussing, and a combination of the two definitions may be useful to fully understand translation. In addition, there are theoretical frameworks such as Service Dominant Logic that could be used to create a new expansive definition of TR that fits with the results shown here. Yet the most salient point emerging from this study is the wide range of differences in how different innovations undergo translation, and a classification and codification of TR by its different types could be extremely useful in aiding research.

5.0.11 Late Stage TR is Lacking

In two of the cases, the proportion of studies that fall into T3 or T4 translational stages are greatly diminished compared to the earlier stages of translational work. While it is certainly not shown definitively here that a balanced number of articles in each stage is optimal, there is at least supporting evidence in the form of the Back to Sleep case, the most successful of the three cases. This is coincident with a surge in the calls for this type of translation in the literature(Westfall, Mold, and Fagnan 2007). This study suggests further evidence for the necessity of that trend to improve translation, and offers some methods to enable it. Foremost, this should be a call to policymakers and funding agencies to support this type of research.

5.0.12 Role for Information Professionals in TR

With the results of this study showing that there is a real possibility of guiding translational research by using bibliometric indicators, there is an immediate role for information professionals here. Beyond doing the bibliometric analysis that supports this, there is further evidence here that the work of information professionals to serve an "integrationist" role to disseminate and explain diverse information sources could be useful in promoting translational research(Gazan 2004).

5.0.13 Policy Implications

The implications for policy from this study center in the promotion of the balanced framework for translation, and in the potential of bibliometrics to enhance it. These policy

implications include supporting the dissemination of information across disciplines rather than interdisciplinary collaboration, and in the development of systems to promote this type of cross-disciplinary information travel, and increased funding and regulatory support for all stages of translation.

5.0.14 Future of TR

The future of translational research is more important than ever, with the recent advances in technologies that can potentially revolutionize the practice of medicine. If the conclusions drawn here are implemented, then a future which involves the convergence of data and balanced research that leads to enhanced health for all society will be possible.

5.0.15 New Types of Indicators that could be useful

Future research should investigate the possibility that other types of bibliometric indicators could provide more information on translational research. The use of text based indicators, given the increasing availability of full text databases, is a possible way to provide information that goes beyond the coarse information provided by subject categories. Further refinement can be done to citation analysis as well, such as by using natural language processing techniques to look at citations in context to differentially weight them.

5.1 Research Question 1: How do interdisciplinary interactions affect translational research?

The results of this study provide insight into the question of how interdisciplinary research is related to translational research, and surprisingly show that the relationship is less close than the literature has assumed. There are several converging lines of evidence stemming from this research that points towards this result.

The qualitative analysis shows a pattern of a minority of integrative, interdisciplinary research occurring in translation. There is much in the way of multidisciplinary work in the HPV case in stage 1 and stage 2 translation, but this is not matched by equivalent research in the

other two cases. The cited references reveal that it is common for translational research to draw from single disciplines, particularly clinical disciplines, rather than from a diverse reference set, especially in the TcB case.

Therefore, unlike the results that were expected, there is no simple relationship between increased interdisciplinarity and increased translation. Each case exhibits unique patterns of disciplinary and interdisciplinary research. The possible trend across cases is that T1/T2 translation may be associated with increased diversity of disciplinary knowledge, while T3 research may be more disciplinary in nature.

The finding that all translational stages may occur in any order makes the question of efficient progression through a linear translational path meaningless. This is discussed in more detail in regards to the linear model below.

With regard to the taxonomy of interdisciplinarity, the most common types of interdisciplinarity observed in the qualitative analysis were composite and contextual multidisciplinarity. This took the form of either team science type approach where many specialists applied their disciplinary skills to a problem, such as in large clinical HPV trials or guideline writing, or as small teams of disciplinary researchers in other fields that applied their disciplines to the translational problem. Integrative interdisciplinarity was less common, and could not be considered essential for translation.

So in conclusion on this question of what types of IDR are seen in translation, we are left with some associated but not necessary types: multidisciplinarity in T1 and T3 research, theoretical and methodological interdisciplinarity in T4 research. These associations do not seem strong enough to warrant a blanket statement that interdisciplinarity is vitally important for translation. More likely, there are subtypes of translational research, such as clinical trials or guidelines, which could be said to follow these rules. This fits with recent evidence that collaboration, in and of itself, does not lead to higher research impact (Gazni, Larivière, and Didegah 2016).

5.2 Research Question 2: What are appropriate bibliometric indicators of interdisciplinarity in translational research?

The second research question hinged upon the discovery of bibliometric indicators at the article level that would enable researchers and evaluators better access to identifying translational research as it is produced.

The interdisciplinary indicators measuring diversity of references or citing articles show a weak correlation with translation, as shown by the ability of the predictive methods to utilize this information. The most informative variable was Integration Score, but depending on the case, other indicators such as Diffusion or Times Cited were also important. The spatial indicators of bibliographic coupling or co-citation coupling were not highly predictive, which may be due to the high saturation of the dataset with translational records. These indicators excel at identifying unique nodes that serve a structural role in a network. However, when nearly the entire network consists of translational records, as is the case here, those indicators necessarily cannot be high for all of them.

The clearest indicator of translation was authorship and integration score for T1 and T2 translation, especially in the HPV and BtS cases. No indicators were successful in the TcB case, most likely because of the highly disciplinary nature of the case, which may be related to its long translational process. Diffusion score was seen to be high in many of the key translational works in the qualitative study. It was very low in the BtS T3 research which may be due to the nature of delivery research as it includes implementation studies which are necessarily highly disciplinary. There may be a difference in diffusion score if dissemination studies, which also fall into T3 delivery research, are examined separately (see coding handbook in Appendix for definition of study types). This type of research may require more interdisciplinarity and more study would be needed to examine this hypothesis. Preliminary investigation in this dataset suggests that this may be the case: as seen in the qualitative coding of IDR types in the various cases, the appearance of integrative interdisciplinary work, both methodological and theoretical, is associated with T3 and T4 research rather than T1 or T2, which is characterized by multiple author multidisciplinarity.

5.3 Interdisciplinary Indicators in Translational Research

The results of this study cast doubt on the assumption that interdisciplinary research is fundamentally important in translational research. There was little difference on average in the Integration or Diffusion scores of translational research compared to research as a whole. The first level of conclusion would be that there is no core, fundamental connection between translational research and interdisciplinary research. The two are overlapping, but neither is a subset of the other. Certainly, it is demonstrated in this research that translational research can and does occur without the work being interdisciplinary or even multidisciplinary.

However, this does not preclude that there is not a more complex and subtle relationship between interdisciplinarity and translational research. The trend of higher diffusion scores being associated with major translational works shows that there is a multidisciplinary audience for translational research. In two of the three cases, interdisciplinary indicators were of high importance in the predictive models that could identify translational stages from each other and from non-translational works.

Practically, this level of association may not be high enough to support efforts in the field to use the methodology applied here to evaluation or policy decisions. But there is possibly a different combination of indicators that could yield higher accuracy.

5.4 Translation as a Bibliometric Concept

One goal of this research was to explore the possibility that translation could be identified by a bibliometric measure, one that could be used by future evaluators or policymakers to determine where and when good translational research was occurring. The premise of this work was that interdisciplinarity might be that measure, if interdisciplinarity and translation are linked.

As discussed above, given that this premise has been shown to be largely untrue, this means that any universal bibliometric sign of translation will not likely be found. The analysis done here shows that the case studies have far more coherence bibliometrically within themselves than the translational research does across cases. This brings up the important caveat to any bibliometric study of translational research, that it be aware of the difficulty of

aggregating works of different fields which may not behave according to the same patterns of citing or publication.

5.5 Issues in the Bibliometric Study of Translational Research

Several major concerns were identified in the course of this study on the bibliometrics of translational medicine that may be the topic of future studies. If these can be resolved, then more fruitful measures of translation might be possible.

First, the use of Web of Science subject categories in the study of translational medicine is problematic due to the expansive nature of the medicine categories. Even still, they continue to be used in bibliometric research due to the convenience and accessibility of using them. While this may be appropriate for some types of analysis of science as a whole, it breaks down in this case of studying translational research. As shown in the cases, all translational stages are observed within the same medicine or pediatrics subject categories. No correlation was observed between subject categories and translational stages.

This means that metrics, such as the Integration or Diffusion Scores, which rely on these *a priori* categorizations, may be ill-suited for this type of work. At the very least, a narrower and more specific, medically oriented categorization might be necessary, such as that provided by the National Library of Medicine's Medical Subject Headings (MeSH).

However, spatial methods, such as network measures, are also difficult to use, as shown here, due to the need to specify the boundaries of the network to obtain meaningful results. As the results will change depending on the members of the network, it is very difficult to compare metrics across cases in a way that would be most useful to evaluators and policymakers.

5.6 Translational Linear Model

This study was in part a test of the translational stage model that is predominantly referenced in the translational research literature. If the model is correct, we would expect to see the translational stages mostly occur in order, from T1 to T4. This was not borne out, as a whole, in the case studies. As Huxley famously quoted in defense of the theory of evolution, he

would find it disproven if there was found one example of a "rabbit in the Precambrian." Similarly, if we find many examples of T3 or T4 research early on in translation, this means the linear translation model is not well supported.

One case, that of the HPV vaccine, does fit this model relatively well. This case is what could be considered a 'classic' translational problem: how to develop, test, and bring a pharmaceutical drug into use. The major variation from the linear model is that T4 research, particularly on cost-effectiveness modeling, does occur early in the process. This suggests that a circular model, which has been proposed by Kelley et al., might be valid, where the Outcomes research can drive future Efficacy research (Kelley et al. 2012).

The other two cases, however, do not fit this linear T1-T4 pattern. The case of the Back to Sleep campaign presents with T2 research occurring initially, which then later drives the emergence of T1 research to investigate the basic science behind the *clinical* discovery of the correlation between sleep position and SIDS. This supports a theory that due to the transdisciplinary nature of clinical medicine all four of these aspects of translation are important to enable physicians to provide quality health care. One can imagine that without all of these foundations, practicing physicians or their patients may find the evidence for a new innovation lacking. This can be seen in these cases both in the lack of Delivery evidence in HPV and the lack of Discovery evidence in TcB.

5.7 Beyond the Circular Model: Balanced Model

Given that the linear model does not fit the data in this study well, what might be a more appropriate model for translation? If we take a look at the circular model of Kelley et al., it is apparent that it can be seen to fit the data more closely than the linear model (Kelley et al. 2012).

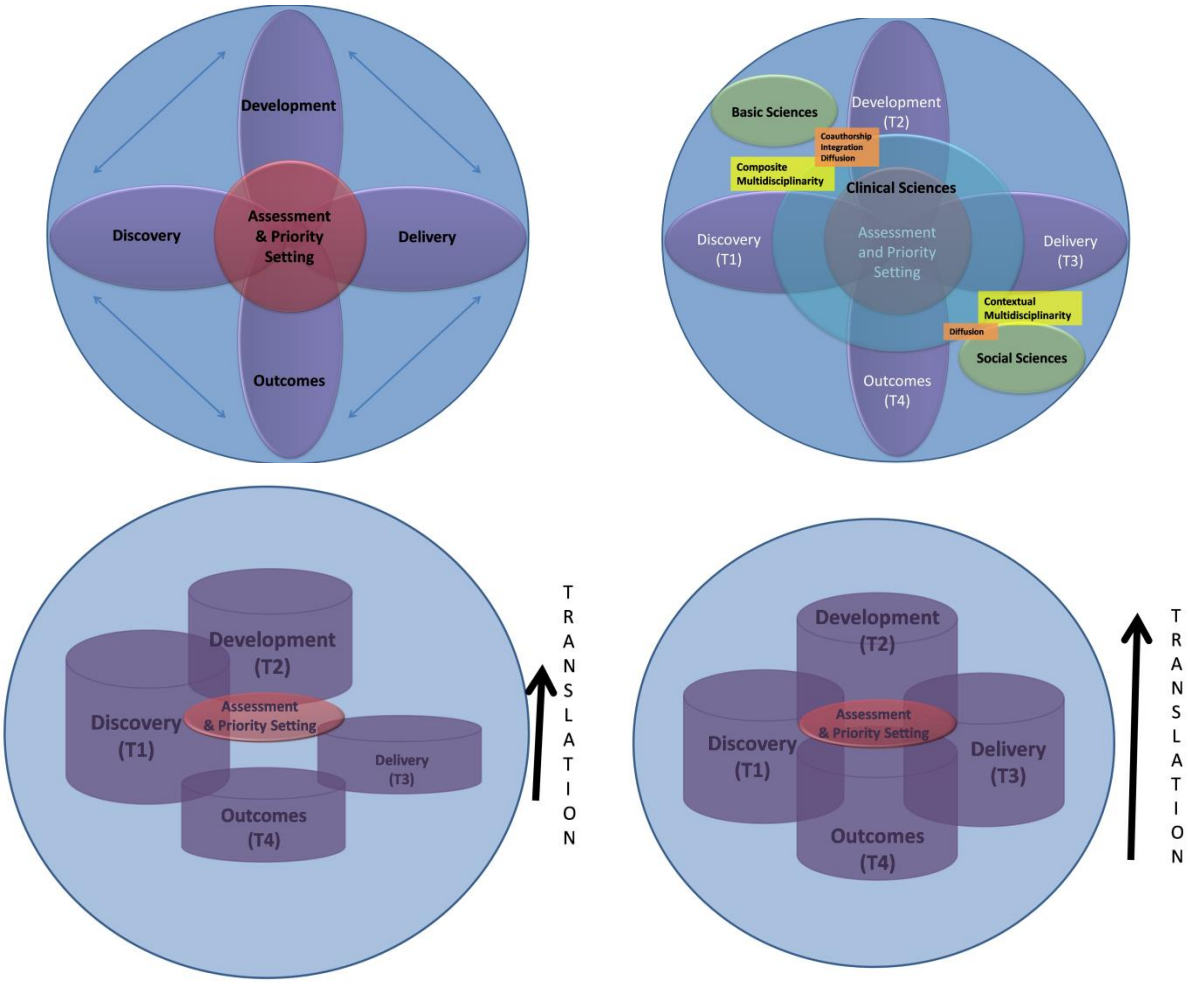
In this model, there is no particular sequence of events that occurs during translation. The appearance of cost effectiveness research in the HPV case, concurrent with the T1 and T2 clinical trials, supports the circular model, while conflicting with the linear model. Similarly, the late appearance in the Back to Sleep case of T1 research to investigate the physiologic basis of the clinical results developed with the Back to Sleep campaign is also not a problem for the circular model.

Therefore, with this model in mind, the prediction would be that types of translational research could happen in any order, but that the appearance of all would be necessary for "successful" translation. As this study did not operationalize success, it cannot address whether this occurred in these cases, but it does appear that in the Back to Sleep case, there is more balance in the publication of articles in each translational stage, whereas this is certainly violated for the TcB case, and HPV only has seen a rise in T3 research in recent years.

From the full text analysis, it was seen that while T4 cost-effectiveness research can easily occur before the T1 clinical research, it is not necessarily interdisciplinary. This further supports the circular model, where none of the stages are prerequisites for the others, but all must be developed to support translation. This model does not predict that interdisciplinary research is necessary, as each of the areas can develop independently. The only type of interdisciplinarity necessary in this case is that of information dissemination, both out from the clinical sciences in the form of problems and back to them in the form of evidence.

This study suggests that a refinement of the circular model should be made to address the role of interdisciplinarity in translation. While the model as proposed only allows for the different translational activities to happen in any order, the results of these case studies hints that the balanced appearance of all of these activities is the driver of successful translation. Further, the different activities are most properly investigated in different fields of study. And while clinical medicine appears in the center and can overlap with all the areas, harnessing the other disciplines outside of clinical medicine should improve translation.

Figure 5.1. Updated Translational Model



Original circular model adapted from Kelley et al. (A) and updated model based on interdisciplinarity and bibliometric results of this study (B). Clinical sciences encompass all areas of translation and can support translation without other disciplines. Basic sciences can assist T1/T2 translation through composite multidisciplinary research, which is detectable with co-authorship, integration and diffusion measures. Social sciences can assist T3/T4 translation through contextual multidisciplinary research, which in our dataset is characterized by low diffusion score. Translation occurs not with lateral movement through disciplines, but with vertical movement across all areas. Panels C and D demonstrate the theory of balanced translation, proposing that translation occurs most effectively when all aspects of the process are being equally researched (D), compared to situations where some areas of research are undeveloped (C)

The refined model of translation therefore is not a bridge, traveling from basic science to clinical science in a defined sequence, but is rather like a canal lock, that as a whole lifts up to allow the progress of translation.

However, it does not seem that highly integrative interdisciplinarity is at all necessary for translational work. It is sufficient that composite or contextual multidisciplinarity occur, which is driven by the exporting of problems from medicine to other disciplines. This leads directly to the major implications for policy that emerge from this research.

5.8 Definitional Considerations

What is the most useful definition of translational research? That is a question that this study did not set out to address, but it bears consideration in these conclusions nevertheless. Operationally, researchers choose a definition of translation that is amenable to objective study, whether that is through the NIH definition as in this case, or as other scholars have done by matching keywords in articles or journals, or by identifying research labs that could be called translational. No matter the details, the choice of definition has enormous impact on the results found.

In this study, the definition used ended up being rather broad. Outside of animal models, almost any research that dealt with human subjects tended to fit the NIH definition of translational research. While this fit the letter of the definition, some might take objection that this would diminish the spirit of what translational research means to them. For those, translational research should mean studies that are in some way more paradigm shifting, more about a translational leap over a barrier to improving health, and not merely another study on the topic. That is not the definition used here, and there are defensible reasons for that. Beyond the pragmatic problem of not being able to determine when a study is merely another brick on the wall of research, and when it is revolutionary and creating a new paradigm, these incremental studies are absolutely essential and provide the fuel for advancing science. Meta-analyses and systematic reviews, which are considered one of the pillars of evidence-based medicine and often are the only persuasive arguments that clinicians will consider to change their practices, are built upon the foundation of dozens of these iterative studies that individually may not be

revolutionary, but when combined show the way forward. So this study stands by its choice of definition in this regard.

However, there is a case to be made that there might be some use in also considering the more narrow, restrictive definition of translation and applying these bibliometric approaches to it. This would likely take the form of the spatial-based indicators that did not perform well at all in this study, but would likely be instrumental in identifying the few, revolutionary papers that individually bridge previously unlinked areas. Similarly, records that were coded as fitting multiple stages of translation were omitted from some analyses, and were a small percentage of all records, and their inclusion would not have changed the results. But in this type of definition of translation, it is these rare bridging studies that could be the most important.

Alternatively, there might be room for the field to consider entirely new definitions of translational research which could combine the best of both of these approaches. One that could be considered is theoretically based on a concept coming out of the business literature, which reframes all innovations in terms of the services surrounding them, rather than on their physical manifestations.

The field of business might initially seem to have little relation to the development and spread of new health care innovations. After all, medicine is a discipline that is firmly rooted in the basic sciences, in the study of chemistry and biology, not in the worlds of economics or marketing. However, in fact the business field is very relevant to translational medicine. After all, the spread of a health care innovation is different only in minor ways to the spread of some commercial innovation or idea.

A notable theory that can illuminate the results of this study on translational medicine therefore is the concept of service-dominant logic (SDL). In this theoretical approach, one frames the innovation as a collection of service transactions, rather than the production and distribution of a good (Vargo 2010).

When viewed in the economic light of service-dominant logic, the concept of translational medicine transforms and it becomes more clear. The original conception of translational medicine, with its focus on the T1 translation of research into clinical products, is

essentially using only a goods-dominant logic, where the goal of the system is to produce a good (the drug/vaccine/device).

The foundational principles of SDL offer insights into how to approach translational medicine. Consider one of the principles of SDL, that the customer is always a co-creator of value in SDL. This not only has relevance to the practice of medicine insofar as paralleling the recent surge in interest in patient-centered medical care, rather than the paternalistic practice of traditional medicine, but it also naturally frames translational research into the circular type of model, rather than the linear form. It casts the patients and population as equal partners in developing the new innovation, rather than as the passive recipients of a production line, and this naturally leads to the balanced model of translation proposed here.

Another applicable principle is the idea that all social and economic actors in this framework are resource integrators. It is altogether apt that the name of the indicator this study found is the most relevant to translation is the Integration score. In this framework, information is the key resource, and integration of various sources of information is how economic (translational) value is created.

Future research should look at the models and definitions of translation, and take into account these types of theoretical ideas in advancing a new theory of translation that fits the results shown here.

5.9 Implications for Policy

One of the primary motivations of this project was to test the assumption that interdisciplinarity is a key component of translational research for the purpose of guiding policymakers and funding agencies in healthcare research. The "magic dust" of interdisciplinarity is often cited and tossed about as if it can solve any problem and is the "silver bullet" that is missing from our research system that will enable it to make great leaps forward with little cost. The reality of interdisciplinary research is that it is extremely difficult, and true efforts to make it happen can do more harm than good. Consider that interdisciplinary interaction is often compared to the meeting of speakers of two different languages. While it may be true that doing research with a team of scientists who speak two languages could result in

unusual breakthroughs, there is no doubt that there will be great operational costs associated from that type of working environment as well.

As mentioned above, many of the works studied here were multidisciplinary and not truly interdisciplinary. This includes both the composite multidisciplinarity of the HPV clinical trials, and the contextualizing interdisciplinarity seen in its T3 diffusion studies. This means that what many consider to be "true interdisciplinarity" where researchers work together and their disciplines merge and change in the process, does not seem to be a major part of translation. So policy makers should do well to promote the type of information exchange that would facilitate these kinds of composite and contextualizing relations. One example is the type of translational research center being promoted by the NIH CTSA program where facilitating disciplines can colocate to improve access where needed. But other methods could be multidisciplinary journals, seminars, or programs organized by topics rather than by disciplines, which is often the norm.

The implications of the refined circular model go beyond interdisciplinary research to the entire biomedical research process. Currently, the clinical trials process is well suited for building the support of pharmaceuticals in the T1/T2 areas, or the discovery and development areas. However, one policy implication of this study is that there should be a parallel requirement for building the evidence base of the T3 and T4 areas, in outcomes and delivery, to be simultaneously developed with the T1 and T2 areas. Additionally, there may need to be policy changes to promote the type of discovery and development research in medical devices and practices that already exists for pharmaceuticals.

What might a policy look like that uses the implications of this study for the improvement of translational medicine? We can begin to imagine this by looking at the current NIH grants that are awarded for the purpose of improving translational research, which are the Clinical and Translational Science Award and Collaborative Innovation Award. These both have aims that address interdisciplinary research such as "fostering innovative multi-disciplinary collaborations that bring together new types of teams to solve particular clinical and translational research problems" or help researchers "communicate and collaborate as members of multidisciplinary teams." As explained further in the CTSA award:

> Translational science is a team-based endeavor. CTSA hubs are expected to support active partnerships throughout the translational process. To accelerate discovery, these partnerships should be formed not only between academic collaborators focused on different disciplines in translational science, but also by involving, where and when appropriate, other stakeholders and communities, such as patients, their caregivers and families (local and online communities), non-profit organizations, governmental agencies, community-based clinicians (hospitals, practices, and clinics), health care delivery systems, industry, and other entities. CTSA hubs should develop a methodological framework for discovering, demonstrating and disseminating successful collaboration models (Leshner et al. 2013).

Notice that in these awards, a high priority is placed upon multidisciplinary collaboration, as discussed earlier in the literature review of this study. However, as the results of this study show, this type of multidisciplinary collaboration is only commonly seen in stage T1 and T2 translational research, and even then is not strictly necessary. This award is focused on the type of multidisciplinarity that was observed in this study to be composite multidisciplinarity. However, missing from these awards is any mention of supporting the other type of interdisciplinarity that was observed in this study to be a part of translation, which is contextual multidisciplinarity. This does not take the form of collaboration, but rather information dissemination to other disciplines. Therefore, this proposal should contain calls for CTSA hubs to focus on the dissemination of information about new innovations to other academic disciplines, community stakeholders etc, not just as research collaborators. Instead of teams being the focus for this type of research, the focus needs to be on communication.

5.10 Implications for Roles

5.10.1 Biomedical Policy Maker / Translational Research Center

For those who are directing the funding and direction of biomedical research, this work has implications mainly through its findings on the theory of translational research. Accepting the refinement of the linear model of translation to the balanced model presented here will change the way agencies approach the stimulation of translational medicine. Currently, the incentives serve to promote the multidisciplinarity teams that are associated with T1 type translation, as this study showed. The CTSA program is an example of that, with its emphasis on

integrating functional teams and providing biostatistics support. The results of this study confirm that this is important work, especially in cases like the HPV vaccine, where clinical trials and the multidisciplinary expertise needed to conduct them remain a real barrier to translation.

However, this study shows that there is a lack of a different type of translational stimulus that could serve to improve the rate of translation. This study is not the first to have noticed the relative dearth of so-called late stage, T3/T4, translational research. And this study showed that this type of research does not consist of the same type of large team, multidisciplinary work that is needed for clinical trials. Furthermore, according to the balanced model, even when this research appears, but is indeed late, there is a slowing of successful translation due to a lack of uptake even when the medical innovation is fully mature. So this calls for a complementary type of translational research stimulus, one that promotes this type of research. This does not require interdisciplinary collaboration, but rather cross-disciplinary information dissemination and the identification of the types of translational work that are lacking. Centers might encourage the filling of identified gaps in the study of various areas, and this might even serve as an alternative classification of research, as opposed to the traditional disciplinary schools. By incentivizing researchers to think beyond their narrow area of interest to the broader clinical or population setting, this can improve the rate of translation of the field as a whole, even without formal research collaborations.

5.10.2 Research Evaluator

Both the theoretical and methodological contributions of this work will be of interest to those researchers and administrators tasked with the evaluation of scientific work in translational medicine. While this study may have started with the intention of exploring the usefulness of bibliometric evaluation for this purpose, it also has implications for the construction of more traditional qualitative evaluations as well. As discussed above, one approach that could come out of this research is to emphasize the type of translational work that researchers are addressing. This information can be gained through qualitative surveys, and asking researchers to explain how they are contributing to translation in these terms can be a valuable tool for evaluators.

However, the bibliometric methods shown here do hold some promise for helping evaluators better identify the most productive research. The use of the Integration and Diffusion metrics here show a high correlation with the types of translational work that are needed, and could be used as a rough estimator of the need for intervention on the macroscale, when searching an entire field of literature. It is less clear if they would be useful for individual evaluation. As known in the field of bibliometric research evaluation, field dependent indicators are highly susceptible to distortions based on relative citation rates or practice, and given the only moderate correlation between any of these indicators and translation, as shown here, it would be problematic to base funding or promotion decisions for individual researchers based on these metrics alone. They would provide useful information however, that could verify or reinforce qualitative information of multidisciplinary knowledge work.

5.10.3 Information Professional

The results of this study suggest a major role for information professionals to serve as facilitators of translational research. In addition to their usual roles as curators of information, the importance of information professionals is clear from the prominence of information diffusion in the balanced model proposed here. Information professionals such as librarians and informationists should expand their roles as promoters of information diffusion, aiming to create serendipitous cross-disciplinary discovery. As experts in information, rather than specific subjects, information professionals are ideal for this role. They can also serve as an integrationist type of facilitator for direct collaborations.

5.11 Limitations of the Study

As a bibliometric study, there are many aspects of translation that remain opaque to this methodology. To a certain extent, this is a type of tunnel vision that can come from using bibliometric methods, or any method, that renders those qualities that are unmeasured by it to be meaningless in the mind of the researcher. Care must be taken to recall that this is not the case.

Translation clearly is influenced by many factors that are outside of the realm of the scientific and medical literature. Even in the cases studied here, there are clearly events outside

of the realm of the literature that bear upon their success in translation. For the HPV vaccine, there are aspects of government regulations, industry lobbying and investment, and especially moral and social concerns regarding use of the vaccine, given its supposed emotionally charged influence. The Back to Sleep campaign demonstrates the intersection of politics and science, as some have noted that there was a considerable degree of evidence in East Germany, prior to unification, that showed the importance of sleep position on SIDS, but it was inaccessible until political changes occurred (Vennemann et al. 2006). The transcutaneous bilirubinometer is faced with overcoming barriers of institutional inertia and hospital budgets.

These are clearly limitations of the method, and there is no illusion here that this study can capture the myriad influences that impact translation. There is only the defense that ultimately, if medicine is to be evidence-based, the support for innovations must at some point appear in the literature. If the communication methods of medicine change, this may be untrue at some point, but currently this is how advances are made, however haltingly.

5.12 Future Research

One major caveat of this study is that while it measures the presence or absence of translation from a definitional or methodological sense, it does not address that aspect of translation which implies the successful movement of an innovation from basic science to clinical practice. As is immediately clear just from the presence of T4 modeling research in the HPV case well before the vaccine was even created, it is not the case that "reaching" T4 implies that translation has been achieved. This study does not attempt to measure or quantify the success of any of these cases in achieving translation, although there is some qualitative sense that transcutaneous bilirubinometry has achieved limited success, the Back to Sleep campaign has achieved good success, and the HPV vaccine still has challenges to translation, especially based on new results of vaccine coverage. Future studies could make a more rigorous attempt to operationalize the success of the translation of an innovation.

How could translational success be operationalized? This study has shown that the measurement of the time spans between translational markers, as proposed by Trochim et al. does not make sense for measuring translation in general because of the lack of linear ordering,

although it might make sense for limited sections of translation (Trochim et al. 2011). Therefore, instead of time, it ideally should be measured in some kind of outcome variable, such as improved health. Given the difficulties of using outcome measures, due to the complexity of the health care system, this might prove to be a difficult study to complete.

The development of full text databases, such as PubMed Central, may make possible additional bibliometric methods utilizing full text analysis that may overcome some of the limitations of predefined subject categories that were demonstrated to be particular issues in studying clinical medicine in this research. Full text opens up the possibility of using a large corpus of natural language information contained within each study to classify the translational status of the work. This bypasses the coarse classification provided by the subject categories, which label every record as the same subject as the journal it is published in. Using this approach, however, may also run into the same issue that was found in this study with regard to the spatially based indicators of betweenness centrality, namely the dependence on the local environment of the dataset for all the values of the metrics. What might be a highly unusual combination of textual indicators in one dataset, may be simply the common way of writing in another.

What of the Integration Score and the Diffusion Score? These could be improved in many ways based on the findings of this study, and offer ideas for future research. One of the key advantages of these metrics is that they use the subject categories assigned by Web of Science across all fields, and therefore are independent of the sample collected, offering some level of comparability across cases. However, as seen here, this use of subject categories is also a drawback. Future research might attempt to mitigate this drawback by including some analysis of textual or network information along with the use of subject categories.

Improving citation analysis will lead to additional metrics, and refinement of the metrics used here. There has already been some preliminary work that shows that citations from clinical trials specifically can be used to predict higher impact than general citations (Thelwall and Kousha 2016). The use of citances and refining citation metrics based on how and where they are used and who they cite can become powerful information in determining the translational position of an article.

5.13 Towards an Automated Method

One of the goals of this research was to advance bibliometric methods into studying translation, and the long-term goal should be to refine it to be completely automated. While a few years ago this might have been impossible, there have been many recent advances in data science and machine learning that provide glimpses of possibilities into such a system.

While there is great interest in purely text based machine learning methods, one of the findings of my study is that there remains great information in the structural classifications assigned to the literature through cataloged metadata. Using this information, including keywords, authors, citations both citing and cited, and journal subjects, we might attempt to expand the methods shown here to do supervised and unsupervised learning methods to identify translational research.

This study was a supervised learning study, and it would be very interesting to see the results if it were redone on a greatly expanded dataset. Machine learning methods often require a great amount of data to become truly effective, and it is not inconceivable that the investment could be made to identify ground truth on whether a large number of records are translational, perhaps by using crowdsourcing methods.

Another approach would be to use unsupervised machine learning techniques on the database to search for clusters and bottlenecks in the landscapes of time and citation space. This approach to identifying translation would be most effective in conjunction with a refinement of the definition, as discussed above, but has the potential to be very effective in finding key, transformative researchers and studies.

5.14 The Future of Translation

The world is now entering a time only perhaps matched by the discovery of antibiotics in the early 20th century in terms of the transformational potential of technology on the health of humanity. With the recent discovery of CRISPR/CAS9 technology, for example, which promises to enable a vast array of genetic interventions in healthcare, there will be an imperative

to safely introduce these disruptive innovations to the medical setting as quickly as possible. These approaches involve an entirely new approach to medical intervention that the field has not seen before, and so will present new challenges to translation, adoption, and evaluation. This is the very reason why in this study, great effort was made to broaden the study of translation beyond the narrow definition of pharmaceutical drugs going through the phases of clinical trials. As seen in the cases here, there is little similarity in the translational process between these different cases. Yet the hints obtained here of an ideal setting for translation can be extrapolated to envision a future of enhanced translation.

Imagine a new innovation is being created in a basic science lab using CRISPR/CAS9 to cure a chronic disease like diabetes. Technically, it would entail the sequencing of the patient's DNA, the generation of a vector to deliver the gene edit, and then delivery. These are the technical, basic scientific issues that must be addressed to create a functional therapy. But there are numerous social issues that also must be confronted, similar to the issue around the HPV vaccine, that would impact uptake. And there are simultaneously numerous practical issues involved in the dissemination and implementation of this type of system in clinical practice. If the conclusions found in this dissertation are put into practice, policy makers, funding agencies, and developers will use the balanced model, supported by bibliometric tools and multidisciplinary knowledge sources and research teams, to address all these aspects at once. Information professionals would aid researchers in accessing diverse knowledge sources to support contextual multidisciplinary works, and also help bring together teams to perform the composite multidisciplinary work necessary to advance translation. The patient population would be brought into the research efforts from the beginning, informing and driving policy changes necessary to enable this type of transformative therapy.

If this comprehensive approach is ignored, it is likely that while we might see therapies developed in a relatively short time span (like the 5 years for the HPV vaccine from first clinical trial to incorporation in clinical guidelines), we would see a much longer time to widely improving health benefits (again, like the 10+ years now passed for the HPV vaccine to achieve only limited uptake). When these therapies mean the difference between life and death, each of these years of needless delay is untenable. Consider one last time, the simple innovation of sleep position in infants:

> Advice to put infants to sleep on the front for nearly a half century was contrary to evidence available from 1970 that this was likely to be harmful. Systematic review of preventable risk factors for SIDS from 1970 would have led to earlier recognition of the risks of sleeping on the front and might have prevented over 10 000 infant deaths in the UK and at least 50 000 in Europe, the USA, and Australasia. (Gilbert et al. 2005)

This is the possible societal impact of this research, and future research along its lines, which aim to improve the future of translational medicine.

CHAPTER 6. APPENDIX

6.1 Search Strategies

(((TS=(human papillomavirus OR HPV OR human papilloma virus) AND TS=(vaccine* OR vaccina* OR immuniz*)) OR (TS = (Gardasil OR Gardisil OR Silgard OR Cervarix)))) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=1980-2013

(((TS=((SIDS OR "sudden infant death syndrome" OR "crib death" OR "cot death") AND ((risk factor* AND sleep* AND environment*) OR (position* OR prone OR supine OR nonprone OR nonsupine OR non-prone OR non-supine))) OR TS=(("back to sleep" OR Back-to-Sleep OR "Safe-to-Sleep"))))) AND LANGUAGE: (English)

Timespan: 1980-2013. Indexes: SCI-EXPANDED, SSCI, A&HCI.

(TS=((hyperbilirubin* OR jaundice*) AND (assessment* OR measurement* OR diagnos*) AND (infant* OR neonat* OR newborn*)) OR TS=(“transcutaneous bilirubin*” OR “transcutaneous jaundice” OR bilichek OR bilimed OR JM-103 OR bilicheck OR MBJ20 OR KJ-8000)) AND LANGUAGE: (English)

Timespan: 1980-2013. Indexes: SCI-EXPANDED, SSCI, A&HCI.

TI=(A* OR B* OR C* OR D* OR E* OR F* OR G* OR H* OR I* OR J* OR K* OR L* OR M* OR N* OR O* OR P* OR Q* OR R* OR S* OR T* OR U* OR V* OR W* OR X* OR Y* OR Z*)

Timespan: 1990. Indexes: SCI-EXPANDED, SSCI, A&HCI.

TI=(A* OR B* OR C* OR D* OR E* OR F* OR G* OR H* OR I* OR J* OR K* OR L* OR M* OR N* OR O* OR P* OR Q* OR R* OR S* OR T* OR U* OR V* OR W* OR X* OR Y* OR Z*)

Timespan: 2000. Indexes: SCI-EXPANDED, SSCI, A&HCI.

TI=(A* OR B* OR C* OR D* OR E* OR F* OR G* OR H* OR I* OR J* OR K* OR L* OR M* OR N* OR O* OR P* OR Q* OR R* OR S* OR T* OR U* OR V* OR W* OR X* OR Y* OR Z*)

Timespan: 2010. Indexes: SCI-EXPANDED, SSCI, A&HCI.

6.2 Coding Handbook

Translational Research	Translational research includes two areas of translation. One is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science.

Translational Stage	**The type of translational research, or the particular translational barrier overcome by the research**		
	Definition	**Study Types**	**Examples**
T0	Preclinical Research - Basic Science to Discovery - (Translation to Application)	Phase 0 Clinical Trial	Is there an association between BRCA mutations and breast cancer in non-human models?
T1	Clinical Efficacy Research - Discovery to Application - (Translation to Humans)	Phase I Clinical Trial; Phase II Clinical Trial	Is there an association between BRCA mutations and breast cancer?
T2	Clinical Effectiveness Research - Application to Guideline - (Translation to Patients)	Phase III Clinical Trial; Systematic Review; Meta-analysis; Clinical Guideline; Comparative Effectiveness Study	What is the positive predictive value of BRCA mutations in at-risk women?
T3	Clinical Delivery Research - Guideline to Practice - (Translation to Practice)	Phase IV Clinical Trial; Dissemination Study; Diffusion Study; Implementation Study; Systematic Review; Meta-analysis	What proportion of women who meet the family history criteria are tested for BRCA and what are the barriers to testing?
T4	Clinical Impact Research - Practice to Impact - (Translation to Population)	Phase IV Clinical Trial; Outcomes Study; Quality and Cost Study; Systematic Review; Meta-analysis	Does BRCA testing in asymptomatic women reduce breast cancer incidence or improve outcomes?

Study Types	
Phase 0 Clinical Trial	Exploratory study involving very limited human exposure to the drug, with no therapeutic or diagnostic goals (for example, screening studies, microdose studies)
Phase I Clinical Trial	Research on a new drug or treatment in a small group of people (20–80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. Studies that are usually conducted with healthy volunteers and that emphasize safety. The goal is to find out what the drug's most frequent and serious adverse events are and, often, how the drug is metabolized and excreted.
Phase II Clinical Trial	The study drug or treatment is given to a larger group of people (100–300) to see whether it is effective and to further evaluate its safety. Studies that gather preliminary data on effectiveness (whether the drug works in people who have a certain disease or condition). For example, participants receiving the drug may be compared with similar participants receiving a different treatment, usually an inactive substance (called a placebo) or a different drug. Safety continues to be evaluated, and short-term adverse events are studied.
Phase III Clinical Trial	The study drug or treatment is given to large groups of people (1000–3000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely. Studies that gather more information about safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs.
Phase IV Clinical Trial	The postmarketing studies delineate additional information, including the drug's risks, benefits, and optimal use. Studies occurring after FDA has approved a drug for marketing. These including postmarket requirement and commitment studies that are required of or agreed to by the sponsor. These studies gather additional information about a drug's safety, efficacy, or optimal use.
Systematic Review	A summary of the medical literature that uses explicit methods to perform a comprehensive literature search and critical appraisal of individual studies and that uses appropriate statistical techniques to combine these valid studies.
Meta-analysis	A systematic review that uses quantitative methods to synthesize and summarize the results.
Clinical Guideline	A systematically developed statement designed to assist clinician and patient decisions about appropriate health care for specific clinical circumstances.
Dissemination Study	Systematic study of how the targeted distribution of information and intervention materials to a specific health audience can be successfully executed so that increased spread of knowledge about the evidence-based interventions achieves greater use and impact of the intervention
Diffusion Study	Systematic study of the factors necessary for successful adoption by stakeholders and the targeted population of an evidence based intervention that results in widespread use and specifically includes the uptake of new practices or the penetration of broadscale recommendations through dissemination and implementation efforts, marketing, laws and regulations, systems-research, and policies
Implementation Study	Systematic study of how a specific set of activities and designed strategies are used to successfully integrate an evidence-based intervention within specific settings (e.g., primary care clinic, community center, school)
Outcomes Study	Research that describes, interprets, and predicts the impact of various influences, especially (but not exclusively) interventions on "final" endpoints that matter to decision makers. Decision makers may include patients, families, individuals at risk, provider, private and public payers, and so forth
Cost Benefit Study	A type of analysis that compares the financial costs with the benefits of two or more health care treatments or programs. Health care interventions that have the same or better benefit at a lower cost are better values than treatments or programs that are more expensive.
Comparative Effectiveness Study	A type of health care research that compares the results of one approach for managing a disease to the results of other approaches. Comparative effectiveness usually compares two or more types of treatment, such as different drugs, for the same disease. Comparative effectiveness also can compare types of surgery or other kinds of medical procedures and tests. The results often are summarized in a systematic review.
Cost Effectiveness Study	A type of analysis that is similar to a cost-benefit analysis but is used when the benefits cannot be measured in financial terms or dollars. It would be hard to put a price-tag on living an extra year of life.

6.3 Similarity Matrix

	Genet	Bioche	Oncol	Immu	Chem	Multic	Bioche	Medic	Cell Bi	Public	Psychi
Genetics & Heredity	1.00	0.80	0.43	0.41	0.14	0.83	0.70	0.67	0.81	0.19	0.19
Biochemistry & Molecular Biolo	0.80	1.00	0.41	0.46	0.21	0.90	0.84	0.75	0.94	0.14	0.13
Oncology	0.43	0.41	1.00	0.31	0.09	0.44	0.39	0.53	0.47	0.29	0.08
Immunology	0.41	0.46	0.31	1.00	0.09	0.56	0.46	0.83	0.49	0.22	0.09
Chemistry, Analytical	0.14	0.21	0.09	0.09	1.00	0.23	0.57	0.15	0.16	0.05	0.03
Multidisciplinary Sciences	0.83	0.90	0.44	0.56	0.23	1.00	0.81	0.81	0.91	0.18	0.20
Biochemical Research Methods	0.70	0.84	0.39	0.46	0.57	0.81	1.00	0.69	0.78	0.16	0.14
Medicine, Research & Experime	0.67	0.75	0.53	0.83	0.15	0.81	0.69	1.00	0.76	0.32	0.19
Cell Biology	0.81	0.94	0.47	0.49	0.16	0.91	0.78	0.76	1.00	0.14	0.13
Public, Environmental & Occupa	0.19	0.14	0.29	0.22	0.05	0.18	0.16	0.32	0.14	1.00	0.28
Psychiatry	0.19	0.13	0.08	0.09	0.03	0.20	0.14	0.19	0.13	0.28	1.00

6.4 Landmark Article List

HPV

2007	NEJM	Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases.
2007	NEJM	Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions
2009	Lancet	Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (
2006	Pediatrics	Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like
2007	Journal of Adolescent Health	Immunization of early adolescent females with human papillomavirus type 16 and 18 L1 virus-like particle vaccine containing AS04 adjuvant.
2007	Pediatrics	Prevention of human papillomavirus infection: provisional recommendations for immunization of girls and women with quadrivalent human papi
2009	Cancer prevention research	A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervica
2004	Lancet	Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randc
2009	Lancet	Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-co
2009	Human Vaccines	Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials
2006	Lancet	Sustained efficacy up to 4· 5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a ran
2007	Lancet	Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenoc
2007	Aust Fam Physician	HPV vaccination.
2006	Obstetrics & Gynecology	Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial
2002	NEJM	A controlled trial of a human papillomavirus type 16 vaccine
2005	Lancet Oncology	Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blin
2006	Vaccine	Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18

BtS

2005	Pediatrics	The changing concept of sudden infant death syndrome: diagnostic coding shifts, controversies regarding the sleeping environment, and new variables to consider in reducing risk
2005	J Forensic Sci	Sudden infant death syndrome risk factors with regards to sleep position, sleep surface, and co-sleeping
2009	BMJ	Hazardous cosleeping environments and risk factors amenable to change: case-control study of SIDS in south-west England
2006	Lancet	Major epidemiological changes in sudden infant death syndrome: a 20-year population-based study
2004	Lancet	Sudden unexplained infant death in 20 regions in Europe: case control study
1994	Biol Neonate	A perspective on neuropathologic findings in victims of the sudden infant death syndrome: the triple-risk model
2003	Am J Epidemiol	Infant sleeping position and the risk of sudden infant death syndrome in California: 1997-2000
2003	Arch Dis Child	Factors relating to the infant's last sleep environment in sudden infant death syndrome in the Republic of Ireland
2011	Pediatrics	SIDS and other sleep-related infant deaths; expansion of recommendations for a safe infant sleeping environment
1997	Pediatrics	Combined effects of sleeping position and prenatal risk factors in sudden infant death syndrome: the Nordic epidemiological SIDS study
1993	NEJM	Factors potentiating the risk of sudden infant death syndrome associated with the prone position
1991	Pediatr Pathol	Defining the sudden infant death syndrome (SIDS): deliberations of an expert panel convened by the National Institute of Child Health and Human Development
2012	Pediatrics	Risk Factor Changes for Sudden Infant Death Syndrome After Initiation of Back-to-Sleep Campaign

TcB

2004 Pediatrics	Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation
2000 Pediatrics	Noninvasive measurement of total serum bilirubin in a multiracial predischarge newborn population to assess the risk of severe hyperbilirubinemia
2008 Arch Dis Child	Attempt to improve transcutaneous bilirubinometry: a double blinded study Medick BiliMed versus Respironics BiliCheck
2002 Acta Paediatr	A new transcutaneous bilirubinometer, bilicheck, used in the neonatal intensive care unit and the maternity ward
2009 Clin Chem	Hyperbilirubinemia and transcutaneous bilirubinometry
2006 Pediatrics	Bilirubin measurement for neonates: comparison of 9 frequently used methods
2004 Pediatrics	An evidence-based review of important issues concerning neonatal hyperbilirubinemia
2004 Pediatrics	Evaluation of a new transcutaneous bilirubinometer
1997 Pediatrics	Transcutaneous bilirubinometry decreases the need for serum bilirubin measurements and saves money
2001 Pediatrics	Transcutaneous bilirubin measurement: a multicenter evaluation of a new device
2002 Pediatrics	Transcutaneous bilirubinometry and diagnostic tests: "the right job for the tool"
2003 J Perinat Med	New transcutaneous jaundice device with two optical paths

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