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Translational Research: Ethical Considerations

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Introduction

No agreed upon definition of translational research (TR) exists currently. However, TR encompasses activities from basic laboratory science to the application of knowledge gained from the lab in clinical settings to improve population health. The term first appeared in the 1990s in relation to the discovery of cancer related genes. While their discoveries were expected to produce quick clinical applications and a decrease in the burden of cancer, in reality they did not. The development of TR as a specific realm of research derives from the perception that the large public investment in biomedical research was not producing enough new therapeutics (Butler, 2008; Goering, Holland, & Edwards, 2011b; van der Laan & Boenink, 2012). The process of translation is perceived to be slow and inefficient. Indeed, one study found that "it takes an average of 17 years for research evidence to reach clinical practice" (Morris, Wooding, & Grant, 2011, p. 510) and another found that "only 5% of 'highly promising' basic science is translated to applications for clinical use" (Goering et al. 20011b, p.3). Proponents of TR argue it aims to bridge the gap between basic science and clinical research in order to apply a greater amount of basic science knowledge to ultimately achieve population level health improvements. This has placed an emphasis on the speed and efficiency at which basic science is turned into clinical applications for population health improvement. This is reflected in policies such as those of the National Institute of Health (NIH), a major driver of national research agenda, and 1990s legislation. In 2003, the NIH published the "Roadmap for Medical Research" that established the research goals of the NIH and was centered on promoting efficient translational research. The NIH laid out specific steps and encouraged interdisciplinary collaboration, collaboration with industry, and infrastructural changes to facilitate greater information exchange

and the practice of translational research. However, the emphasis on speed and the collaboration with industry set forth by the NIH and other national policies provides challenges in maintaining the integrity of scientific research, especially when there is no definition of TR and standard by which to evaluate the progress of translational efforts against. I contend that the success of TR should be evaluated based on the standards of the bioethical principles of beneficence and distributive justice. They should be used for informing the values of TR and generating a consensus on a new definition of TR that prioritizes justice and improvement of public health.

History of the Term

While there is no agreed upon definition of translational research yet, various ideas of what activities it encompasses exist. The term represents a new public interest in the speed and efficiency of biomedical research. A look at the history provides insight into why no clear definition exists. The land of science represented by the term "translational research" is not new within the biomedical sciences. While we have come to accept the distinction between applied and basic/pure sciences, Graeme Gooday, Professor of History of Science and Technology at the University of Leeds, argues the distinction was an ideological invention by T.H. Huxley and followers who sought to protect academic laboratory science and experimental knowledge from occlusion by the commercial industrial machinery of the 1800s. "Applied science" had been occurring within the realm of science since the beginning and was separated out from pure science to be considered "an area of industrial endeavor and artifact production that did not draw much from institutionalized science" (2012, p. 549). It was thought to be self-funding due to the profitability of commercial utilization of its products. In comparison, "pure science" was being promoted as the exclusive endeavor of universities and for the "discovery of the great principles

of nature" (2012, p. 548) for knowledge sake without expectation of producing benefits for others. Proponents of pure science, T.H. Huxley and followers, argued that "pure science" provides the foundation for "applied science" and "applied science" is a subordinate process to that of "pure science." The translational model in a sense is the new form that "applied science" is taking and emphasizes the efficiency and speed at which applications arise. There is a conscious effort to ensure applications arise more frequently and quickly. It also rejects the formulation that "pure science" is separate from "applied science." While basic sciences are indeed the building blocks for producing therapeutics, it is seen as the first steps of the applied pathway rather than a separate enterprise all together.

Declan Butler, a senior reporter for *Nature*, argues that barriers to the existing process of using basic science in developing medical therapeutics arose after the 1970s when molecular biology became more advanced. There was increasing specialization due to increased complexity of molecular biology and the separation of bench research from clinical research as physician-researchers became a rarity. A single person was no longer able to see the research all the way through. With the separation, challenges in communicating information and cooperation throughout the process arose. Additionally, within the culture of sciences, the quantity of publications is valued in considerations for promotions and grants over the contributions a researcher makes to advance clinical medicine (Butler, 2008). Another contributing factor is the lack of interest in publications showing negative or null results (Ioannidis et al., 2014; van der Laan & Boenink, 2012; Wilholt, 2009). The latter phenomenon is specifically acknowledged by the NIH Director and attributed to a peer review process that is conservative and values likelihood of success over impact (Zerhouni, 2003). These factors push researchers to work

towards publications and positive data without necessarily keeping in mind the needs of clinical sciences or communicating negative ends to colleagues.

The term "translational research" first appeared in the early 1990s in the context of the discovery of BRCA1 and other cancer related genes. These genes were expected to lead to immediate applications to the treatment and prevention of cancer (Butler, 2008). Genes and other biomarkers were seen as presenting great promise for achieving TR through the linkage between molecular markers and identification of cancer, prevention, personalization, and treatment. However, as the rapid improvements in cancer treatment and prevention were not realized, basic science was thought to not be "effectively applied to reduce the burden of cancer" (Callard, Rose, & Wykes, 2012; van der Laan & Boenink, 2012).

The rise in usage of the term "translational research" provided direction to scientists and funders for what types of research should be prioritized. While the NIH budget doubled from 1998 to 2003 when it was $27 billion (Butler, 2008), "only 5% of 'highly promising' basic science is translated to applications for clinical use" (Goering et al., 2011b, p. 3). Translational efforts were initially driven by the desire to see treatments for disease, however, more recently it is driven by the large disparity in speed of health improvements gained by society and the speed of life science discoveries. In the early stages of translational efforts results were assumed to be within close reach, but with the progression of time and the lack of results seen, efficiency became important. The Human Genome project is a prime example of where the results fell short of expectations. Despite the huge public funding and the relative rapid sequencing of the entire human genome, application of the knowledge and gain in public health have been slow (van der Laan & Boenink, 2012). The goal of TR is now reflected in the NIH's mission "to seek fundamental knowledge about the nature and behavior of living systems and the application of

that knowledge to enhance health, lengthen life, and reduce illness and disability" ("Mission and Goals," 2014). It no longer is sufficient to merely do applied science and assume producing scientific knowledge will lead to application and efficient application based discovery has become a public priority. With translational science, the goal of the older conception of "applied science" gained an emphasis on speed. Most clearly this can be seen through the NIH Roadmap.

NIH Roadmap

Translational research became a funding priority and the term proliferated in the lexicon of scientists and policy makers in the 2000s with the publication of the NIH "Roadmap for Medical Research" in 2003 written by the NIH director Elias Zerhouni (Butler, 2008; van der Laan & Boenink, 2012). The Roadmap was an effort to address public concerns about the progress of science and set forth three new themes in its ongoing priorities: 1) new pathways to discovery, 2) research teams of the future, and 3) reengineering the clinical research enterprise (Zerhouni, 2003). New pathways to discovery entails improving knowledge about the complexities of biological systems and improving tools to utilize this basic knowledge, such as the development of "-omics" databases essential for biomarker discovery and imaging techniques. Research teams of the future were created to combine the skills and disciplines of the physical and biological sciences. Central to these interdisciplinary collaborative efforts are partnerships between the public and private research sectors. Additionally, there are greater efforts to promote high-risk, creative, groundbreaking research. Zerhouni argued clinical research has become more difficult and that the most important challenge will be to increase efficiency and better inform the efforts of basic sciences for applied aims. This requires

integrated infrastructure to connect academic research institutions, community patient organizations, and community based physicians and reduce redundancies in research efforts.

One such infrastructure is the Clinical and Translational Science Award (CTSA) programs established by the NIH around the country in 2006 (Butler, 2008; Goering et al., 2011b). Its mission is "to develop innovative solutions that will improve the efficiency, quality and impact of the process for turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public" ("Clinical and Translational Science Awards (CTSA) Program," 2015). As a major funding source, policies set forth by the NIH drive research direction and priorities for US researchers. The NIH's effort to promote the practice of translational research centers on increasing interdisciplinary collaboration, increasing collaboration with industry, and establishing infrastructure that would enable these collaboratory efforts and increase data sharing.

Defining TR

It should be kept in mind that throughout the development process of the term translational research, no specific definition of the term has been adopted. There remain diverse conceptions of the translational gap and ambiguity as to what activities constitute TR, similar to the debate between applied and pure science. No singular definition exists and authors discuss it as a process that can be divided into phases. There is consensus that the process starts with the work to gain knowledge about molecular and basic science of diseases through cell cultures and animal models done by lab scientists preceding clinical trials and the involvement of human subjects. However, there are diverse conceptions about how far to translate the knowledge within different contexts. Variations include translation of basic scientific knowledge to 1) knowledge

of the human body functioning and bodies, 2) new approaches to therapeutics, 3) medical applications, 4) clinical practices, 5) individual patient benefit, and 6) population level benefits (van der Laan & Boenink, 2012). These variations fall into two categories: TR that aims to produce new therapeutics and TR that aims to implement therapeutics to improve health. The first type can be thought of as the research and development stages seen in drug development and focuses on the production of a new technology or product, while the second broader type leads to aims of affecting clinical practices. The broader conception acknowledges that technologies are not always used once produced and the value of new knowledge lies in its effects on health (van der Laan & Boenink, 2012). The broader conception is of most use as it aims to produce real changes through the application of basic science to produce new therapeutics and clinical practices that are then applied in clinical practice in order to improve population health.

While policy (like the NIH roadmap) reflects the broad conception, most researchers aim to address the narrow gap of producing therapeutics in their labs and use the broad gap of affecting population health as the rationale for their research and funding. The activities needed to bridge the narrow gap are typically within lab researchers' areas of expertise and present more achievable goals for a single lab that will lead to publishable data. However, within grant proposals, researchers are required to identify a broad issue that their research aims to solve in order to broaden their chances of receiving funding. In addition, while lab researchers may utilize the broad gap as the rational, many of them are unaware of patient's clinical needs (Butler, 2008). This is in part due to the disconnect between basic science and clinical science that arose in the 1970s. Whilst mission statements of national funding institutes subscribe to the broad concept, the basic scientists who generate the initial knowledge needed for translation are not necessarily focused on the end goal of population health improvements. Without awareness

of patient needs that are critical to achieving the true ends of TR – improving health – lab researchers cannot be expected to produce basic knowledge with clinical application in mind.

Sources of the Gap

In addition to varying conceptions of the gap that TR is aiming to bridge, there are also varied views of the cause of the gap. Some view the issue to be deriving from scientific methods, such as the inadequacy of animal models and cell culture experiments in evaluating the complexity of human diseases and clinical trials that produces results not applicable to general populations. Within this view, solutions are centered on improving the way science is done through the incorporation of bioinformatics and interdisciplinary collaboration. Others point to causes external to the methodology of the sciences such as the social, political, economic, and moral context in which science occurs. Lack of funding, communication barriers between scientists and experts of different fields, strict regulations, and lag in creation of clinical guidelines are often cited as factors limiting science from effectively creating clinical applications in the translational science setting. From this view, proposals for addressing the gap involve providing extra support to science to enable their findings to have a greater impact, such as removing regulatory obstacles, changing methods of recruiting research subjects, new ways of recruiting and training researchers, stimulating collaboration between academia and industry, stimulating communication between parties involved throughout the translational process, and encouraging publication of preliminary research data in journals (van der Laan & Boenink, 2012). Not only is there little consensus regarding the scope of TR and the gap it should bridge, there are differing conceptions of why the gap is present. These variations lead to ambiguity

within the discussion of TR, since there is not a commonly agreed upon meaning of the term, it becomes difficult to evaluate the success of TR and achievement of goals.

Bioethical Considerations

In light of a missing agreed upon definition of TR and standard of evaluation, bioethics is proposed as a metric by which to evaluate translational efforts and aid the development of a consensus definition. Bioethics can be used to inform the TR values and practices by analyzing TR's priorities and values to ensure they are consistent with those of biomedical ethics. Critics of TR have raised concerns on issues of justice and collective health care rights, such as population representation, sampling bias, conflicts of interest in collaboration with industry that prioritize the production of products and profit, and the difficulty for marginalized groups to benefit from publically funded research. One central ethical theory in bioethics is principlism. Beauchamp and Childress present four *prima facie* binding principles: respect for autonomy, nonmaleficence, beneficence, and justice which together provide "an analytical framework of general norms derived from the common morality that form a suitable starting point for biomedical ethics" (Beauchamp & Childress, 2013, p. 13). These principles are accepted by a majority of classic ethical theories and provide the bases for medical codes. No single principle has greater value than another. They are each said to be *prima facie* obligations, meaning at first glance they are all obligatory but upon further investigation of a particular situation must be balanced and justified against other conflicting principles.

Autonomy can be defined as the ability to self-determine actions based on own desires and plans. An autonomous choice is intentional made with understanding, and is without external

or internal controlling factors. Respecting autonomy "involves acknowledging the value and decision-making rights of autonomous persons and enabling them to act autonomously" (Beauchamp & Childress, 2013, p. 107). Nonmaleficence obligates us to intentionally "abstain from causing harm to others" (Beauchamp & Childress, 2013, p. 150) with harm understood to be adverse effects on another's interests not necessitating a violation of individual rights. Beneficence promotes taking positive actions for the benefit of others and a sub-principle of utility obligates us to "balance benefits, risks, and costs to produce the best overall results" (Beauchamp & Childress, 2013, p. 202). Justice entails "fair, equitable, and appropriate treatment in light of what is due or owed to persons" (Beauchamp & Childress, 2013, p. 250). More relevantly, distributive justice entails "fair, equitable, and appropriate distribution of benefits and burdens determined by norms that structure the terms of social cooperation" (Beauchamp & Childress, 2013, p. 250). Just distribution will depend on the morally relevant characteristics considered based on balancing of subsequent material principles such as those emphasizing maximizing social utility, fulfilling needs, or free-market exchanges.

Movements in Addressing the Translational Gap and Ethical Critics

As these principles provide bases for medical codes, they also provide relevant bases for research and in particular translational research as it intersects with the clinical field. Within the context of TR, the principles of beneficence and justice are the most relevant. The ultimate goal of TR in the broadest conception entails achieving population health improvements. Thus, TR should balance the risks and benefits of research and aim to promote just distribution of produced health resources as reflected in the actions taken by researchers and policy makers. However, current actions aimed at achieving health improvements over emphasizing speed and

collaboration with industry. This creates conflicts of interests (to be discussed in later sections) and challenges to maintaining values that are consistent with its benevolent aims. Central issues when designing translational efforts should be whether positive steps are being taken to prevent harm, promote good, and promote the just distribution of benefits and burdens of research. Peterini argues that biomedical, clinical, and public health research must follow the same set of ethical principles in order to protect the participants of research and individual patients (2010). He provides the important reminder that participants of research are at the same time the patients of the researchers. Since TR includes biomedical, clinical, and public health research, the primary priority should be safety in clinical trials and translation and greater caution should be taken due to the accelerated nature of TR.

Secondly, TR should also promote just health care. Goering, Holland, and Edwards (2011b) suggest a framework of responsive justice that incorporates distributive justice with recognition of the needs of the systematically disadvantaged and obligation of those with more power to ensure fair distribution in guiding the scientific practices in TR. In practice responsive justice entails interdependent elements of distribution, recognition, and responsibility (Goering, Holland, & Fryer-Edwards, 2008). Distribution is concerned with "allocating material goods – benefits and burdens – among the members of a society" (Goering et al., 2008, p. 45), meaning the therapeutic products developed through translational efforts. Researchers must ensure the inclusion of marginalized populations in their studies, if desired by the group, so that their perspectives are included in the development process and they are thus able to meaningfully benefit from the results of the studies. Recognition is achieved through true understanding of minoritized perspectives and subsequent actions to remedy conflicts that may require major reorganization of research structures and protocols. The final element is that majority and

dominant groups to take responsibility of their duties to the needs of other more marginalized groups and practice distribution and recognition to ensure that those groups are able to benefit from societal efforts.

Currently within the common practices of TR, emphasis is placed on speed and collaboration without specific attention paid to elements that would contribute to a just distribution of health care benefits derived from knowledge and technology gained through TR. The priorities and values of TR must be continuously evaluated with the responsive justice framework and the principle of beneficence in mind. The practice of science has transformed in recent years and changes have been made to the underlying infrastructure of research that prevents effective translational research. Two trends that present challenges to maintaining justice and beneficence in translation research are the emphasis on speed and the collaboration with industry.

Biomarkers

The investment in infrastructure and utilization of biomarkers epitomizes the great emphasis placed on efficiency of translating basic knowledge to application in the NIH roadmap. There is increasing preference for biomarkers within clinical practice following trends in basic sciences and biomarkers are seen to be a highly promising translational opportunity for fast applications. Biomarkers are defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definition Working Group as cited in Strimbu & Tavel, 2010, p. 1–2). They are used in the basic sciences to elucidate the complexity of biological pathways and disease states and to evaluate the efficacy of treatments. As such they

are seen to be a core instrument of TR and are being investigated for their uses in personalized treatment and disease prevention. There are high hopes that biomarkers will increase the speed of development of pharmaceutical interventions (Callard et al., 2012). Investment in small-molecule libraries, bioinformatics, and "–omics" sciences like genomics and proteomics is promoted for example by Zerhouni in the NIH Roadmap and these technologies allow for high volume analysis of standardized quality data and generation of predictions and models. Omic fields, such as genomics , transcriptomics, and proteomics, aim to understand biological systems as a whole in normal and disease states. This is accomplished through investigation of the entire set of genes, mRNA, or protein present in a sample and correlating certain genes, mRNA, or protein to functions. Omics are used to generate hypotheses, discover biomarkers, in the selection of drug targets, and in drug development. As such, these approaches also generate enormous amounts of data that requires the help of statisticians and bioinformaticians (Horgan & Kenny, 2011).

However, omics data are not without flaws. The preference for biomarkers signals a shift from clinical judgment to objective standards for diagnostics. It creates more objective standards for successes in medical practice but brings the draw back of diminishing patient's individual experiences with their disease and the practical measures that are important to them. Suzanne Fleischman argues "disease are ultimately constructs – of medical diagnostics in the first instance and ultimately of language" (1999, p. 5). The language and the medical diagnosis of the disease confine the individual patient's experiences into one large general category. An individual suffering from a disease may not experience all of the signs and symptoms associated with it and they may not experience it the same as another person with the same disease. Arthur W. Frank, in writing about the illness experience states that someone who enters the role of a

sick individual "accepts having the particularity of his individual suffering reduced to medicine's general view" (Frank 1995/2012, p. 210). Medicine itself reduces individuals with illnesses to their diagnosis and disease and often times leaves out how a person's identity is affected by the disease and how the person experiences the disease. This effect is increased by the use of biomarkers that completely objectifies a person to a set of measurements, leaving no account of their illness experience and aspects that they may consider important.

Additionally, Fullerton (2011) points out that there are biases in population sampling due to variation in participation rates across racial and ethnic groups in genomic studies. European genomes are commonly overrepresented, making up 76%-96% of data collected. This is in part due to deficiencies in recruitment practices as well as barriers for retention that are seen in other areas of studies, but these sampling biases results in the failure of some groups to benefit from publicly funded translational genomic research. The biases in the population samples can lead to overlooking gene variations that are prominent in groups other than Europeans, discovering variations without knowing the significance, and inaccurate characterization of genetic variation risks. Despite the large amount of data and the ability to more or less quickly identify important genes, study design and the lack of attention paid to later implications limit the usability of the knowledge. Understanding of the complexities of genetics needs to encompass understanding of various population variations, not only those of European decent. From the responsive justice framework, scientists should use their place of power to ensure population samples are representative so that those of non-European decent may also benefit from the results of genomic studies. Biomarkers are overly relied upon and expected to produce quick results, leading to inadequacies like improper population sampling. A balance between speed of translation and the

rigor of scientific studies must be found so that omics data has a more equitable distribution of ethnic groups tested and more individuals may benefit from the findings.

Collaboration with Industry

Another key aspect of the NIH translational roadmap is collaboration with industry. Zerhouni (2003) stated the private sector should play an essential role in the new translational paradigm of acceleration and interdisciplinary collaboration. Collaboration with industry is seen to be a key to accomplishing the interdisciplinary collaboration and translational efforts. Studies have found that the "the strongest predictor of moving to randomized experimentation was industry involvement in the original basic science publication" (Ioannidis, 2004, p. 2). Randomized experimentation represents the first steps towards clinical trials that evaluate the efficacy of a new therapeutic in humans and receiving clinical approval. However this collaboration provides challenges to maintaining the integrity of science and the independence of results from outside forces.

The current system of collaboration with industry favors commercialism and the development of products. Morin argues the actions outlined by the NIH roadmap are too focused on drug and device production and not giving enough attention to services and prevention (2008). Device production represents only the early stages of the TR process and does not aim to implement innovations. Additionally, the US has a history of legal precedence in place that focuses on technology transfer, translation, patents, protection of knowledge, and profitability, favoring the commercial interests of industry. In 1980 two acts were passed to facilitate the movement of federally developed knowledge to commercial products. The Stevenson-Wydler Technology Act sought to encourage the development of scientific innovations and increase

utilization of technology created from federal funding while the Bayh-Dole Act allowed universities and non-profit organizations to retain ownership of knowledge discovered using federal funds and private organizations to license the development rights of products from research conducted in federal labs (Kuszler, 2011). These acts marked a shift in government agency policy about ownership of knowledge produced by public funds. The Federal Technology Transfer Act of 1986 strengthened the relationship between government and industry. This act allowed for pooling of government personnel, facilities, and equipment with industry funding and other resources and industry to have first licensing options. The Hatch-Waxman Act was passed in 1984 and had the ultimate result of lengthening the patent life of brand name drugs (Angell, 2004). Combined these acts encouraged translation and allowed private companies industries to carry basic knowledge on to produce applied therapeutics. However, it has also lead to the privatization of knowledge that should be available for public use due to their public funding. Researchers are increasingly moving to patent their research as broadly and as early as possible in order to protect the future commercial potential of the subsequent products and their profitability (Kuszler, 2011). This system emphasizes the product of drug and devices without a specific consideration of the uses and practical applications (Kelley et al., 2012). While collaboration with industry may appear to be the fastest way for a basic knowledge to be translated into clinical products, it can undermine collaboration and detracts from the ultimate goal of translational research, which is to produce health improvements.

Conflicts of interests and the issues with maintaining integrity arise when collaborating with industry. Not only is collaboration with industry needed to move research into the clinical trial stage, 70% of clinical trials are funded by industry (Mello as cited in Marks, 2008). Marks argues that collaboration with industry undermines the research process and public health

interests (Marks, 2008). Preferential bias, the increased likelihood of the preferred outcome within the results of a study, exists. It can occur in subtle ways like how a hypothesis is formulated or in more obvious ways where the interests of the industry funder sway the interpretation of results (Wilholt, 2009). Due to this preferential bias, Marks suggests the creation of independent ethics consulting services to provide external advise on the direction of research and results interpretation for researchers (Marks, 2008). Angell rightly warns that collaboration with industry is "entrusting the development of medicines to an industry that is entirely accountable to investors, and not the public" (Angell, 2004, p. 48). Industry is interested foremost in the profitability of the technologies they produce. This means production of products that will have a reliable and large customer base. Within this setting and the lack of adequate incentives for industry to produce drugs for the poor and underserved and less visible diseases (Kuszler, 2011), the values driving translational research must be carefully evaluated. "Conflicts of interest, demise of scientific independence, and the subordination of scientific quality to profit seeking" are issues that need to be balanced against the benefits of collaboration between government, academia and industry (Ioannidis, 2004, p. 5). Collaboration with industry does not need to end; it must however proceed with continuous reflection about the values and priorities that should drive the research questions and directions.

Critics of Values Reflected in Translation Research

Translational research is not used in the sciences merely as a categorization of research methodology, but is a broad ranging term with strong rhetoric and moral force on the direction of research (van der Laan & Boenink, 2012). Driven by public dissatisfaction about the return of

their investment, translation is now considered to be unquestionably desirable with science that leads to results viewed as the best science (Maienschein, Sunderland, Ankeny, & Robert, 2008). Collectively we have placed great value on speed and these values of translational research are reflected in policies and scientific practices. Solutions proposed by the NIH have thus far directed researchers to increasingly collaborate with industry as they are the ones who have the capacity to manufacture goods for wide usage and increase the speed at which they produce new knowledge. With this collaboration come conflicts of interest between the commercial interests of industry and the public health interests that should ultimately drive translational research. The bioethical principles of beneficence and justice obligate us to ensure a just distribution of benefits from research. Medical research, particularly those that derive from public funding, should aim to promote the health of all people, not only those with the ability to pay. Additionally, the current reward systems and scientific culture rewards quantity and novelty of knowledge over quality and reproducibility (Ioannidis et al., 2014). However, TR instead needs to be a values-based endeavor that prioritizes public health and the collective good. As Morin states, the goals of TR should emphasize collective rights and benefit sharing (2008).

Translational research needs to re-center its driving values on reducing health disparities. Goering, Holland, and Edwards argue that justice is essential to translational research. There needs to be continuous evaluation of who will benefit and how to define benefit. Ionannidis (2004) goes even further and argues that US research efforts should also aim to address global health needs, not only those of the US, and increase health care access for all. While the NIH is the largest global government funder of research, the US only holds about 4% of the global disease burden. From a justice perspective and through a lens of need, the rest of the world is in greater need of the products of US research. As such, efforts should be made towards providing

healthcare and new therapeutics to countries with greater need than the US. Ionannidis (2004) provides a reminder that high tech molecular solutions are not always the most useful even in the most important health dilemmas such as malnutrition and infectious diseases. The innovations shared with other countries need not include the newest technological advances as long as they are effective. Some ways to reducing health disparities are increasing reflection throughout the process, increasing implementation and outcomes research, and allowing more discussion of negative and null results.

Potential Solutions

Translational Process as a Cyclical Process

The translational processes need to be thought of as a set of feedback loops rather than a linear process in order to increase communication between the different phases of translational research as well as to increase reflection on the process itself. Van der Laan and Boenink (2012) suggest a bi-directional research process with "backward translation," which takes the knowledge about needs and values from clinical practice and patient experiences to help innovations be more useable and relevant. While the emphasis on including experiential expertise is an important one, this model should be expanded even further to include integration between all phases. More authors are proposing cycles such as those in Figure 1.

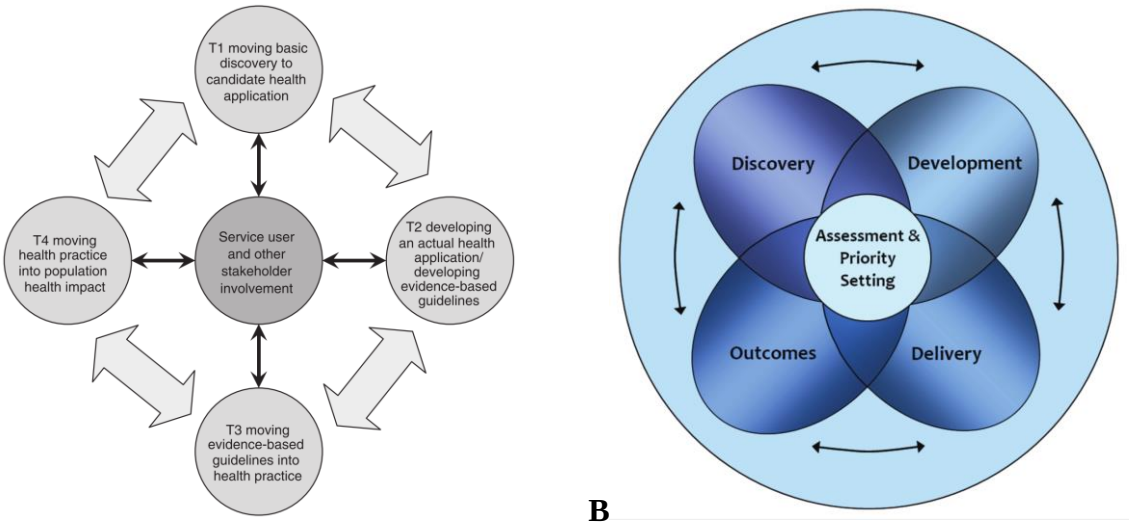

Figure 1. Translational cycles. A) Proposed in Callard, Rose, and Wykes (2012). Emphasis is place on the involvement of stakeholders and service users in all phases. B) Proposed in Goering, Holland, and Edwards (2011b). Includes a new explicit phase of assessment and priority setting.

The model proposed by Callard, Rose, and Wykes (2012) separates the translational process into T1-T4 phase. T1 is the basic science knowledge generation phase while T2 applies to knowledge to produce a therapeutic or clinical guideline. T3 involves the implementation of therapeutics and guidelines. Finally T4 encompasses the final goal of population health impact. Key aspects to this model are the interconnections between the various steps of translation and the central step of involving the public in the translational process. The participation of the public in the conversation is central because it allows those with personal experiences to inform the decisions that scientists and researchers make in the early stages of therapeutic development (more on its importance will be discussed shortly).

More importantly, Goering, Holland, and Edwards (2011b) recommend a model that explicitly includes a reflective step at the center of the cyclic process, which they call assessment and priority setting. Not only should the process be cyclical and involve the public, researchers

should stop and evaluate their work for effectiveness and potential impacts within an ethical, social, cultural, and economic context. They state "as a society with a predilection for technology, we tend to surge forward, eager to have more knowledge, without necessarily taking the time to assess the relative merits of that information" (Goering et al., 2011b, p. 4). The assessment and priority setting step within the translational process that emphasizes speed will be crucial to ensuring the products meet the needs of the public and promote therapeutics that will improve population health. In a related article, Kelley et al. (2012) provides questions to be asked through the process. They argue that by making the questions and answers explicit, translational research will lead to better ends and results. Indeed, what these newer models of TR rightly emphasize is the need for TR to be increasingly reflective so as to better achieve population health improvements. There needs to be greater connection and communication between TR steps and integration of knowledge. Some processes that can aid priority setting are multidisciplinary collaboration, implementation research, and outcomes research.

Multidisciplinary Collaboration and Implementation Research

One of the key elements to the NIH translational roadmap is the development of interdisciplinary collaboration efforts accomplished by training scientists specializing in translational research and by establishing the infrastructure to facilitate the communication of scientists, clinicians, bioinformatics, statisticians, engineers, industry experts, social scientist and ethicists. This collaboration aims to enable scientists to better utilize the knowledge that has already been generated in the past or by other research groups, navigate regulations and patent laws, and to produce knowledge that is more clinically relevant. The Clinical and Translational Science Award (CTSA) Consortium is one such multidisciplinary effort. It promotes

multidisciplinary, inter and intra-institutional collaboration throughout the country as well as the training of scientists in translational research (Kon, 2008). It embodies the translational push for more efficient movement of knowledge to clinical applications. However, the program has been criticized for the emphasis on basic knowledge production. Studies have shown that the funding at CTSA sites going towards T1-T2 is far greater than the funding going towards T3-T4 (Solomon, 2010). Additionally, social scientists who do not focus on basic social and psychological processes of health were unlikely to receive funding (Perlstadt, 2009). The discrepancy of funding between the basic discovery phase and the implementation stage contributes to the issue of not giving the knowledge that we already have enough attention. Interdisciplinary collaboration should continue and be improved by the addition of more implementation and outcomes research to make better use of existing information.

Implementation is the last step in the translational pathway. Achieving this step reflects the bridging of the broadest translational gap between basic science and population health improvement. Solomon states implementation research "aims to translate new biomedical and public health knowledge into changes in the behavior of health care professionals, patients or the general public" (2010, p. 31). It involves the uptake of new therapeutics and technology produced into clinical practice and public use. Without this step, the potential impacts of translation are unrealized. It was found the implementation stage only receives 1.5% of biomedical research funds (Moses as cited in Woolf, 2008). Woolf (2008) presents the situation as an opportunity to better utilize and deliver the basic science knowledge that we already have and make it more useful, rather than focusing largely on producing new knowledge and technologies.

Participatory Research

It is important to consider how priority setting occurs and who is involved in the conversation. While implementation and outcomes research examines how innovations are taken up into practice and the implications of therapeutics for patients, inclusion of the public within the conversation at all stages is also important. Callard et al. (2012) propose a model where the public (service users and stakeholders) are involved in all phases. Typically the public is thought to be useful only at the end of the process and is merely the recipient of TR innovations. However, they should be involved as to aid in the selection of research agenda, drug targets, and design by adding knowledge from their lived experience. It is thought that this involvement may lead to increased clinical trial participation and adaptation of new therapeutics into clinical practice and daily use (Callard et al., 2012).

One method for achieving greater public involvement is through participatory research. Participatory research emphasizes the inclusion of the target audience of therapeutics in the research process and collaboration with the audience to inform research and lead to more effective therapeutics. The strength is the merging of the expertise of the researchers and the laypeople. Participatory research is especially needed within the context of TR as it considers the social and cultural aspects of therapeutic implementation. The methodologies of participatory research encompass values for translating knowledge into action, social and environmental justice, and self-determination (Cargo & Mercer, 2008). One method for realistically achieving incorporation of the public may be for researchers to collaborate with colleagues in other academic areas who already have connections to underserved populations (Goering, Holland, & Edwards, 2011a).

Null Results

One prominent issue within science is the bias against the publication of negative results that was described in the introduction. While this bias is not exclusive to the process of translational research, it exacerbates difficulties in the translational process and limits the amount of total knowledge communicated in the field. Ioannidis argues "Research effort should be respected on the basis of the rigorousness of its design, hypotheses, and execution, and not on the basis of its results" (Ioannidis, 2004, p. 5). The result of the research does not determine the validity and its contribution to furthering scientific knowledge. While negative results do not provide new avenues for researchers to pursue, they still offer information that advances scientific knowledge and are important components of the scientific process. Well-designed research that produces negative results should be made known to the scientific community. Additionally, there needs to be greater discussion about the limitations of studies. Ioannidis is a 2007 article states "knowledge and discussion of limitations are essential for genuine scientific progress: they are useful for understanding a research finding, translating the importance of the potential errors involved, placing the current work in context, and ascribing a credibility level to it" (2007, p. 324). Authors preferentially use terminology like error, bias, and false in acknowledging study set backs. However, typically this is not followed by a discussion of the implications of the errors and biases for the results and how they may be addressed in the future. In the case of genomic studies with population biases, the limitations about population sampling are not usually addressed as the bias is seen as so commonplace. Additionally, due the greater variation in the genomes of non-European descendants correlations are more difficult to find and the results usually are inconclusive (Fullerton, 2011). New electronic journals have been established to address the issue of the lack of publication of negative results and as an example

can begin to address the issues of population sampling bias in genomic studies. Many have an open access policy and publish both negative and positive results (van der Laan & Boenink, 2012), increasing dissemination and cutting down cost barriers. The prominence of electronic journals can also allow authors more space to discuss limitations. Science needs to move past a culture where positive results are prioritized over negative results and limitations. This prioritization limits effective translation of knowledge as only positive results are passed on while negative results, which could have unforeseen uses, are lost.

Conclusion

Translational research represents greater public interest in publically funded research that quickly results in applications and perceivable population health improvements. Policy efforts have focused greatly on increasing the speed at which translation occurs and encouraged collaboration with industry. The speed at which basic scientific knowledge is produced has been accelerated with new technologies that allow for high through-put data generation and -omic fields that identify biomarkers. However despite the high interest in TR, no agreed upon definition of the term exists and this adds to difficulties in evaluating its successes. Currently standards of success have focused on the generation of products and the speed at which those are produced, reflecting the prioritizing of speed and industry involvement in the process. These priorities, which have been promoted by legal policies and NIH policies, have created difficulties in achieving real population health improvement. The collaboration with industry has created conflicts of interest between the commercial interests of industry and well-being of patients who relying on therapeutics produced.

A more adequate standard should be the principles of biomedical ethics. At all steps of the process, participants of TR should explicitly evaluate if their translational efforts also meet then standards emphasized by the principles of beneficence and responsive justice. These principles should be used as the guiding forces for what TR prioritizes and can create greater accountability within the translational process of scientists, policy makers, and industry to the interest of patients. Translational research moving forward needs to place greater emphasis on values of beneficence and responsive justice and prioritize minimizing health disparities, a more specific form of improving population health. Through explicit priority setting and reflection throughout the cyclic process, implementation research, and communication of negative results in addition to positive results, translational research can better accomplish its goal to produce just population health improvements. Additionally, from consensus about the values and priorities that should drive translational research, a unifying definition of translational research can be found and allow for greater ease of evaluation of the successes of translational research moving forward.

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