Scientific Support for Genetically-Targeted Therapies: Investigating the Hypothesis of Technological Hype

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EXTENDED ABSTRACT:
"Economic Dimensions of Personalized and Precision Medicine"

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"If you read them now, the claims made for genomics in the 1990s sound a bit like predictions made in the 1950s for flying cars and anti-gravity device." Jack Scannell, 2014.[1]

1 Introduction

The beginning of the 21st century brought a big promise for the future of medicine. It was announced on the 26th of June of 2000, when President Bill Clinton welcomed Francis Collins and Craig Venter into the East Room of the White House to present the completion of first draft of the Human Genome Project (HGP). Francis Collins had lead a decade-long publicly-funded effort to sequence all the genes in human DNA, coordinating the effort of scientists from the US, the UK, Japan, Germany, France, and China. Backed by powerful new gene-sequencing technology, Craig Venter initiated in 1998 a parallel private initiative. The resulting compendium—a characterization of the most basic elements responsible for variation in human trait expression—has been considered a major achievement for science, compared by some to the moon-landing or Copernicus' heliocentric theory. Recognizing the magnitude of the contribution, Venter stated that day that "the basic knowledge that we're providing the world will have a profound impact on the human condition and the treatments for disease and our view on our place in the biological continuum."[2] After 13 years of sequencing and a $3 billion investment, the final draft was unveiled in 2003.

Many scientists immediately predicted a revolution in the prevention, diagnosis, and treatment of diseases. For example, Randy Scott of Incyte Genomics stated that "in 10 years, we will understand the molecular basis for most human diseases." Lander et al. (2001) concluded that "The scientific work will have profound long-term consequences for medicine, leading to the elucidation of the underlying molecular mechanisms of disease and thereby facilitating the design in many cases of rational diagnostics and therapeutics targeted at those mechanisms." The genome map would allow scientists to link genetic mutations

[1] "Why Are So Few Blockbuster Drugs Invented Today?"
[2] http://transcripts.cnn.com/TRANSCRIPTS/0006/26/bn.01.html

to the manifestation of diseases, and once these were identified, targeted therapies could be designed to replace genes, manipulate their expression, counteract protein imbalances, among others.

But in 2016, there is still not a full understanding of the biology of most human diseases—particularly for the most burdensome ones—and therapies providing fully effective cures are few and far between. The leading causes of death remain the similar to those in the 2000's and new therapies have not substantially increased life expectancy.[3] Voices of skepticism have gradually started to rise, with some people claiming that the project has not delivered as promised and that the industry should move past genetically targeted approaches.

Intuitively, when there are large rewards from being the first to solve a problem, a new method promising the possibility of solving the problem is an attractive bet. However, when there is not a clear reason for why this new method would be a good approach to solve the problem, it may be efficient to wait to better understand the underlying mechanism rather than invest in the new method. Despite the fact that it is efficient to wait for the technology to mature to reveal the underlying mechanism, the rent-seeking incentive of competing firms pushes them to invest too early relative to the efficient time. This, in turn, generates negative signals about the value of the new method, which diminishes the value of the new method potentially forfeiting the discovery of the underlying mechanism.

In this project we develop a systematic evaluation of the translation of basic genetic research into the discovery of new therapies for human disease. We focus on a first generation of gene-disease research, the genome-wide association studies (GWAS), the first of which was published in 2005, shortly after the completion of the HGP. Our empirical strategy exploits rich disease-level temporal variation in the stocks and flows of new such studies to explain patterns of drug discovery. Our results indicate a quick industry adoption of new genetic insights during the 2006-2010; firms pipelines reveal an increase in

[3] "Where Are All The Miracle Drugs?"

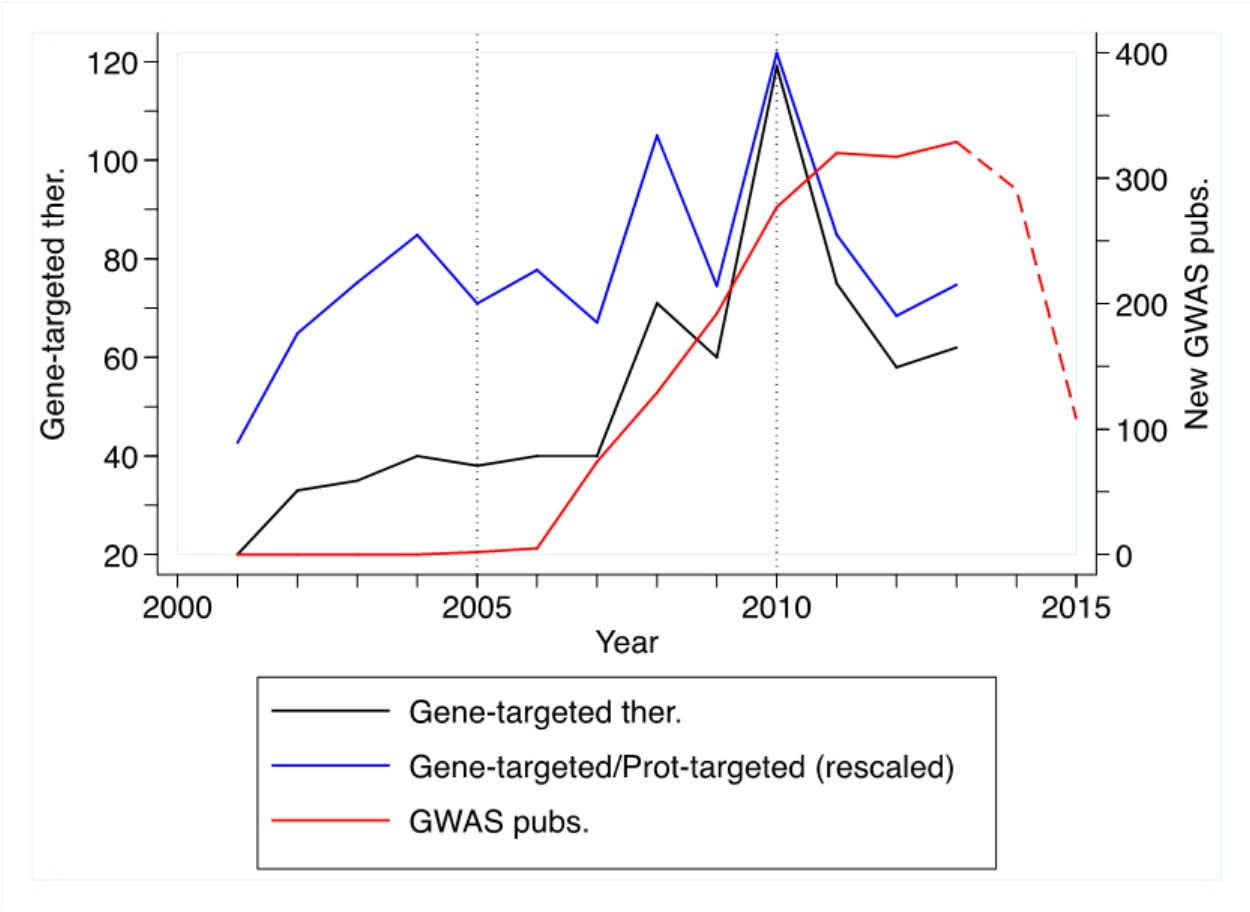

Figure 1: Number of therapies over time and number of GWAS publications.

the number of therapies that enter the discovery stage for diseases associated to genes by scientific publications, relative to diseases not associated to genes. However, clinical trial results did not support the alleged therapeutic superiority of genetically-based targets, gradually eroding the level of enthusiasm, and with it, the pace of translation. Indeed, after 2010, our results show that the new arrival of genetic insights did not translate into additional drug discovery attempts. Figure 1 shows the number of genetic therapies over time and the number of GWAS publications.

Our findings are in line with a "hype" hypothesis, i.e., the pharmaceutical industry reacted promptly to the initial belief about the superior therapeutic potential of genetically targeted medicines. However, the these investments did not prove to be a dominant alternative over time and the industry became less responsive to novel academic publications.

Abundant anecdotal evidence supports an industry reaction driven by technological "hype" fueled by the media and the scientific enthusiasm that followed the completion of the project. For instance, Derek Lowe, former Bayer employee, claimed: "The whole industry went crazy with it. Bayer committed half a billion dollars into human genome research, and they got nothing for it. Nothing at all" .[4] The director of National Human Genome Research Institute, Eric Green, addressed this sentiment directly in 2011: "I feel bad if our enthusiasm and euphoria over completing the genome project was misinterpreted to mean that we would have cures 10 years later."[5] Others haven gone further, overtly faulting the media for inflating expectations beyond justification: "Journalists wrote about how we were going to have drugs for all these diseases in the next decade. Somebody was smoking something. This was just nuts."[6] Further evidence of this "hype" is discussed in Alpert and Chen (2012) and in Evans et al. (2011).

We complement this anecdotal evidence by performing a sentiment analysis over the abstract of news articles that are related with the effect of genetics on the development. Figure 2 shows that the number of articles with a postive or extremely positive view on the impact of genetics on the development of human diseases started at a peak in the year 2000 declines until 2010. Only after 2010, the positive perception starts to recover.

In hindsight, the failure to meet the initial expectations seems to have been caused from under-estimating the complexity of the problem. We now know that genetic variants are rarely mapped one-to-one into the most burdensome diseases (e.g., cancer, Alzheimer's, diabetes). Thus, even when targets are identified (i.e., a genetic variation has a statistically significant association with a disease), it is hard to develop a therapy that safely and effectively "hits" the target.[7] Furthermore, the genome has revealed new layers of

[4] "Why Are So Few Blockbuster Drugs Invented Today?"

[5] The Future of the Human Genome.

[6] http://blogs.nature.com/boston/2011/02/23/nnb-report-ten-years-later-harvard-assesses-the-genome-map

[7] This problem does not exist for "Mendelian" diseases (e.g., Huntington's Disease,Cystic Fibrosis), characterized by a one-to-one mapping between gene mutations and diseases expression, so reliable genetic tests and powerful predictive tools are available in those cases. Regrettably, most high-burden (and profitable) diseases are caused by the mutation and interaction of more than one single gene (as well as

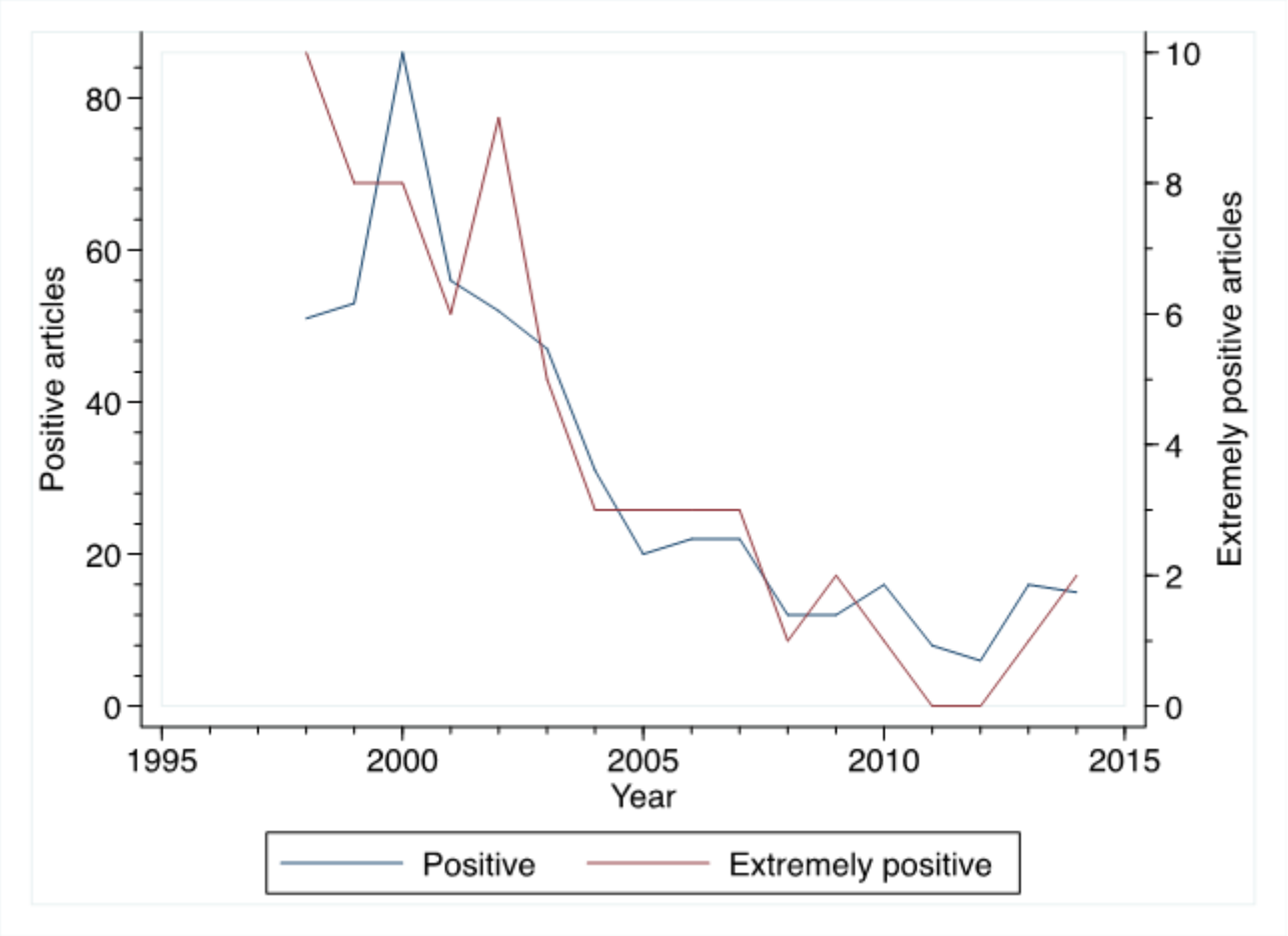

Figure 2: Sentiment analysis on articles related to genetics and human diseases.

biological complexity, delaying advances in applied science as basic science gaps are being filled. This point was eloquently made by the prominent UK researcher Roger Highfield, with an analogy between the genome and a book: if the HGP gave us a book, scientists are now learning how to read it and "...biologists are beginning to face up to the uncomfortable truth that they have only been looking at the nouns... now we are reading the spaces in between—verbs, adverbs, adjectives, pronouns and the rest, and they are complicated indeed."[8]

The slow progress of translating science into successful drugs was anticipated by the more rigorous analysts and it does not negate a scientific revolution. For example, in 2000,

the influence of environmental factors).

[8] "Life just got a lot more complicated."

Francis Collins emphasized that progress would primarily unfold towards the end of a four-decade period.[9] Even in the relatively short span of time since the completion of the HGP, genetics have enabled the new field of personalized medicine, and delivered advances in basic biology that offer strong support to Venter's prognosis of a better understanding of "our place in the biological continuum."[10] Effective genetically-based therapies have reached the market, including treatments for Chronic Myelogenous Leukemia and early-onset breast cancer diagnostic tests.

Accordingly, and due to the relatively short span of time since the completion of the HGP, we view our study as a "Progress Report." Our results do not inform an evaluation of the long-term impacts HDP on the quality and abundance of human therapeutics. However, they do suggest that that the pharmaceutical industry may energetically reacted to discontinuous advancements in the study of gene-disease associations. Such progress may indeed be currently unfolding, as a second-generation of gene-disease association studies ("Next Generation Studies") start to gain traction at the hand of declining computing power costs (Nordhaus et al., 2007).

Our results shed light on how misleading expectation could have an enormous welfare consequence. The initial hype could have distorted the direction of innovation, having firms gradually moving away from a "trial and error" to a "target-based" method to discover new drugs. Our findings can be rationalized by the observation that competitive pressures give incentives to firms to invest too soon, relative to the efficient timing. It may have been more efficient to allow for the basic science to develop further before investing in the novel approach.

[9] "Reading the Book of Life: The Doctor's World; Genomic Chief Has High Hopes, and Great Fears, for Genetic Testing."

[10] For example, the genome has lead to the surprising discovery that the number of genes is not related in an obvious way to the complexity of the organism. Humans have only about 21,000 genes, while a fruit fly –a much simpler organism– has around 17,000. A mouse has around 23,000.

2 Related Literature

An idea that dates back at least to Nelson (1959) and Arrow (1962) is that the creation of knowledge will be under-provided by markets due to its public-good nature. Even more, profit maximizing firms will under-provide the creation of or knowledge that does not have an immediate application (basic science). Bryan and Lemus (2016) explain that the public good nature of knowledge in combination with the difficulty of making new discoveries will not only change the amount of investment, but also the direction of research. Even more, Furman et al. (2012) shows that different patterns of funding can have significant impact on the choice of research of scientists.

Knowledge needs to be created, but also preserved and diffused. Institutions play a major role in all of these aspects. For instance, the human genome project would have not been possible without the financial support and oversee of several institutions. Furman and Stern (2011) present an empirical setting to estimate the role of institutions in the creation, maintenance, certification and accumulation of knowledge. Pisano (2006) discusses whether private companies, specifically biotech companies, can profit from the creation of basic knowledge.

Our project closely relates to the literature that explores how private and publicly-funded research is captured by firms in the industry. Cockburn and Henderson (1998), focusing on the biotech industry, highlights the role played by the network of scientific connections of a firm on the absorption of basic research. We focus on the events that followed the completion of the Human Genome Project, specifically on genome-wide association studies. Our project does not focus on patenting—for example, Jensen and Murray (2005) studies the gene patenting and Hawkins (2011) studies the impact of patents on the development of genetic tests—but rather on how academic publications is translated into the developing of new therapies. In a future version, we will link GWAS patents and papers as in Murray (2002).

We focus on GWAS since it is arguably the most innovative method to identify drug targets. Drews (2000) examines the history of drug discovery and explains that drugs used to be developed using chemistry, but over time biology and genetics became the main tools to guide the discovery of new drugs. In fact, the completion of the human genome project was followed by a significant economic impact, which is analyzed in Tripp and Grueber (2011). New techniques have allowed scientists to identified mutations for more than 2,900 protein-coding genes in humans (Chong et al., 2015; Brinkman et al., 2006). Visscher et al. (2012) evaluates the impact of GWAS from a broader perspective and concludes that it has had a positive impact on new discoveries about genes and new biological insights. Sanseau et al. (2012) discusses the use of GWAS for drug repositioning, and Nelson et al. (2015) studies the use of GWAS as evidence to obtain FDA approval for new therapies. However, despite all the progress and new technology, Scannell et al. (2012) have pointed out that pharmaceutical R&D efficiency—measured as the number of new drugs brought to market by the global biotechnology and pharmaceutical industries per billion US dollars of R&D spending—has steadily declined. Agarwal et al. (2013) explores the competition in the development of novel drug targets, finding that about half of them are pursued by just one company.

Finally, in our database we distinguish whether research is privately funded, since conflict of interest in reporting has been an issue in this industry. An academic institution offers different incentives to a scientists compared to an industry job. Scientists self-select into one or the other given their individual preferences, which can be heterogeneous in their taste for having control and freedom of research (Aghion et al., 2008) or in their ability and their preference for non-pecuniary returns (Agarwal and Ohyama, 2013). In terms of publications, Fugh-Berman (2013) points out the pervasive involvement of the pharmaceutical industry in basic research and emphasizes the consequences of under-reporting of negative results and misrepresenting reported results. Similarly, Bennett et al. (2010) studies the association between pharmaceutical industry funding and basic science research for a specific therapy (erythropoiesis-stimulating agents). The authors

find that when the pharmaceutical industry supports an study, researchers are more less likely to find potentially harmful effects of the therapy.

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