Research Proposal:

Characterizing The Drug Development Pipeline for Precision Therapies

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Background

In early 2015, the White House announced a "bold new research effort to revolutionize how we improve health and treat disease," and President Barack Obama's Precision Medicine Initiative was launched with a $215 million investment in 2016.[i] Other major research institutions have also introduced multi-million dollar programs to advance precision medicine.[ii] [iii] [iv] These efforts lag industry innovation: almost 150 FDA approved drugs already include pharmacogenomic information in their label.[v]

Precision medicine, and in particular therapies that rely on genetic, epigenetic, and protein biomarkers, can help patients by using identifiable genetic mutations to define disease subtypes. Different treatments may work differently in patients who vary in these subtypes. For example, among patients with non-small cell lung cancer, those with the ALK (anaplastic lymphoma kinase) gene mutation will benefit more from therapies like Alecensa (alectinib) than patients without this mutation. The CFTR modulator, Kalydeco (ivacaftor) has been approved for people with cystic fibrosis (CF) who have at least one of ten CF mutations—out of 1800 mutations in the gene that causes the disease. Other common precision medicines that are already marketed include Harvoni (ledipasvir and sofosbuvir) and Viekira Pak (ombitasvir, paritaprevir, dasabuvir and ritonavir) to treat patients with genotype 1 of chronic hepatitis C infection.

Innovation and the drug development pipeline

The first challenge to personalized medicines is therapeutic innovation. As we improve our understanding of the genetic and cellular basis of disease, it will be possible to use genetic and protein biomarkers to classify patients into increasingly more specific subtypes where medicines

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are more effective. Thus, many diseases may become "rare," even as their broader prevalence in the general population remains unchanged. The rarity of a disease reduces the incentives to research and develop medicines for it. [vi] [vii]

Our project will describe the early drug development pipeline for precision therapies, by characterizing the set of new drugs that have entered phase II clinical trials over the past two decades.

We have recently secured a license for Cortellis Competitive Intelligence Data (Thompson Reuters) and will be using this database to identify the full set of drugs (with their respective indications) that have entered phase II clinical trials each year. The database includes detailed information on the type of biomarker, if any, associated with each drug. These include physiological, proteomic, genomic, biochemical, anthropomorphic, structural (imaging), and cellular biomarkers.

Using biomarker and drug target information, we will first characterize the number and type of drugs with potential precision applications by therapeutic area, over time. Since cancers represent a set of diseases in which precision therapies are already successfully used, and since cancer applications of precision medicine are expected to grow in coming years, we will separately characterize the cancer applications of pipeline precision therapies in detail.

Second, we will track both broad trends in the types and fractions of therapies with potential precision applications in the drug development pipeline over time and will also consider the development pipeline in light of a number of specific economic incentives, such as the introduction of the FDA's Breakthrough Therapy (BT) Designation in 2012. Using already-assembled data on the set of all pipeline drugs – both approved and not yet approved – that have been granted BT status, we will consider the prevalence of precision therapies among both BT and non-BT products at the time of New Drug Application and FDA approval.

Third, we hope to be able to trace the role of National Institutes of Health (NIH) in supporting the existing pipeline of precision medicines, by asking what share of these medicines rely on

early stage research supported by NIH grants. Related, we will ask whether precision therapies are more likely to be brought to FDA regulatory approval by larger pharmaceutical companies, indicating that they reflect riskier ventures.

We expect that the output of this project to be largely descriptive in nature, but will serve as a basis for understanding the empirical trends in the development of precision therapies over recent years.

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[i] https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative

[ii] http://www.hbs.edu/news/releases/Pages/kraft-family-foundation-establishes-endowment.aspx

[iii] https://www.ucsf.edu/news/2015/08/131341/new-center-will-advance-life-saving-genome-based-diagnostic-tools

[iv] https://uanews.arizona.edu/story/2-couples-make-major-donations-to-precision-health

[v] http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_personalized_medicine_by_the_numbers.pdf

[vi] Acemoglu, Daron, and Joshua Linn. "Market Size in Innovation: Theory and Evidence From the Pharmaceutical Industry." *The Quarterly Journal of Economics* 119.3 (2004): 1049-090.

[vii] Dubois, Pierre, Olivier De Mouzon, Fiona Scott-Morton, and Paul Seabright. "Market Size and Pharmaceutical Innovation." The RAND Journal of Economics 46.4 (2015): 844-71.