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Productivity and Aligning Prices with
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**Restraining High and Rising Cancer Drug Prices: Need for Accelerating R&D
Productivity and Aligning Prices with Value**

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Disclaimer: The opinions expressed in this article are solely of those of the author and do not reflect the view of the organization.

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ABSTRACT

The high price of cancer drugs has become a world-wide phenomenon. In recent decades, studies have produced ample evidence of rising research and clinical testing costs underlying pharmaceutical innovations. There is a general concurrence that the current model of drug development needs a thorough streamlining. It is also alleged that the prices of new anticancer agents seem to be decided by pharmaceutical companies, according to what the market will bear, in a producer-dominated market. Studies have noted with concern that there is a little correlation between the actual efficacy of a new drug (in terms of prolonging a patient's life in years, or quality-adjusted life-years (QALYs) and its price. The present study is an attempt to address some major challenges which are: (i) how to increase the overall pace of innovation (R&D productivity); (ii) how to control the costs and prices of new innovative drugs; (iii) how to direct more innovation to areas where social returns are highest; and (iv) how to improve patients' timely access to innovative medicines while balancing 'safety' concerns.

Primary proposals suggested in recent literature to deal with the above challenges include, among others, (a) modernization of the drug development process through 'open models' of strategic partnerships (between government, academia, and industry), (b) adoption of a value-based pricing system, (c) promotion of 'Personalized/targeted Medicine', (d) introduction of evidence-based decision making by stakeholders based upon 'comparative effectiveness research'(CER) analysis, and (e) implantation of regulatory reforms in drugs' evaluation and approval practices. The present study makes an attempt to shed light on the above challenges and proposals.

1. Introduction: Cancer Drugs Prices

The high price of cancer drugs has become a world-wide issue. The average cost per month of branded oncology drug treatment in the U.S. is now about \$10,000, up from an average of \$5,000 a decade ago (IMS 2014, Oncology Trend Report). As per the report of the Canadian Cancer Society (2009), the price tag of the average cost per course of treatment with newer cancer drugs is reported to be CAD \$65,000. What is more disconcerting to note is that with each advance in treatment, the magnitude of the increase in the cost of treatment exceeded the magnitude of improvement in efficacy, thus making each treatment advance less cost-effective than the one that preceded it (Bach 2009). Rising costs are not only an issue of affordability in terms of direct payment, but there is the added danger of out-of-pocket expenses which often cripple individuals in their quest for good treatment. High prices raise questions of crowd-out of other services in payer budgets, affordability of copayments to patients, and concern whether the health benefits gained warrant the high cost. These concerns reflect the broader challenge of assuring value for money in health care (Danzon & Taylor 2010).

The problems posed by high and rising prices have led researchers to examine in more details the underlying causes. There is now a general consensus that the current model of drug development (right from basic research, discovery of the medicine, preclinical development tests, clinical trials with humans, and to regulatory approval stage), and current market environment, including pricing behavior of firms, needs thorough streamlining. The inefficiency of the current model is manifested in many ways. First, high attrition rates during all phases of clinical trials result in high cost of new drugs with the consequences that some people are being denied access. Since the past few years, steadily declining R&D efficiency (measured in terms of the number of new drugs brought to market by the global bio-technology and pharmaceutical industries per billion US dollars of R&D spending) has had critical implications of productivity growth for the entire biomedical research enterprise, especially for the ability of this "enterprise" to provide a steady flow of life-saving/life-enhancing new medicines for a whole host of diseases (unmet medical needs like cancer and Alzheimer's disease) and at affordable costs/prices.

Second, several concerns have been expressed in press and academic journals in regard to the competition-restricted market environment in the drugs industry. Kelly et al (2014) argue that profiteering (the practice of making profit by unethical methods, such as raising prices after natural disasters) could be applied to this recent trend, where a life-threatening disease is the natural disaster. In addition, collusive practices of pay-for-delay deals tend to reduce

competitive pressures from generic drugs makers. The prices of new anti-cancer agents seem to be decided by pharmaceutical companies, in a producer-dominated market, according to what the market will bear (Kantarjian et al., 2013). If drug price reflects the value, then it should be proportional to the benefit to patients in objective measures, such as survival prolongation, degree of tumor shrinkage, or improved quality of life. Studies have noted little correlation between the actual efficacy of a new drug (in terms of prolongation of patient's life in years, or quality-adjusted life-years, QALYs) and its price.

Bio-similars cannot be considered 'generic' equivalents of innovator products as they are not necessarily clinically interchangeable and in some cases they may exhibit different therapeutic effects. Thus, biological drugs, after the expiry of their patents, pose special problems in regard to promoting competition in market. Unlike small-molecule, chemically synthesized drugs and biologic cancer therapies have often faced no competition, even after their patent expires, because historically there was no path for the development of generic biologics.

Biopharmaceuticals ("biologics")¹ constitute a growing segment of the medicines market. In the USA, the Biologics Price Competition and Innovation Act of 2009, (which was part of the Patient Protection and Affordable Care Act of 2010), set in motion a regulatory process for approval of "generic" biologic medications (biosimilars). In order to gain FDA approval, the manufacturer must demonstrate that the biosimilar product is highly similar to the approved biologic (Duetzina et al., 2014). These therapies, however, may pose special challenges because of the complexity of both the products themselves and of the manufacturing processes.

Scope and Plan of the Study

It is true that while dealing with grave and complex ailments like cancer, consideration should be given to the entire spectrum of interventions, including prevention and screening strategies as well as diagnosis, treatment, and hospital care. The present paper, however, limits its focus to issues relating to cancer drugs interventions only.

With regards to drugs development, some significant challenges need to be delineated. These include: (i) how to increase the overall pace of innovation (R&D productivity), (ii) how to control the costs and prices of new innovative drugs, (iii) how to direct more innovation into areas

¹ Biosimilars have also been referred to in other terms: follow-on-biologics (the usual name in the US), subsequent entry biologics (Canada), similar biotherapeutic products (WHO), biogenerics, biocomparables, follow-on proteins, etc.

where social returns are highest, and (iv) how to improve patients' timely access to innovative medicines while balancing the 'safety' concerns. One of the formidable tasks to tackle these challenges lies in rationalizing the entire drug development cycle --from discovery to final approval--in a way that successfully incorporates the new scientific advances, and promotes innovative effective therapies at an accelerated pace. Primary proposals suggested in recent literature include, among others, (a) modernization of the drug development process through 'open models' of strategic partnerships (between government, academia, and industry), (b) a value-based pricing system, (c) promotion of "Personalized/targeted Medicine", (d) evidence-based decision making by stakeholders based upon 'comparative effectiveness research' (CER) analysis, and (e) regulatory reforms in the drugs evaluation and approval practices. Figure 1 provides a pictorial view of suggested measures for restraining the costs of cancer drugs through improving productivity and regulatory reforms.

With a view to shedding light on the above issues, the paper is divided into four sections, including the 'Introduction' section above. The second section, using the 'Pharmaceutical Value Equation' (Paul et al., 2010), describes an R&D model that analyzes productivity in terms of its two major constituents - R&D efficiency and effectiveness of drugs. R&D efficiency, which refers to the number of new drugs approved per billion US dollars spent on R&D, has been declining for the past few years. The problem of declining R&D efficiency, as suggested by researchers, emanates from the current level of high attrition rates, particularly in phase II and phase III of the drugs development path. In this part of section 2, the paper reviews some major studies that examine the underlying problems of declining efficiency and suggests proposals for accelerating R&D efficiency. The next subsection of section 2 deals with the drug effectiveness component of R&D productivity. To improve the effectiveness of drugs, two key measures that merit special attention include the value-based pricing principle and the emerging challenge of promoting "personalized medicines". Under value-based pricing agreements, payers and pharma companies agree to link payment for a medicine to value achieved (*e.g.*, outcome or performance variables of interest like quality of life), rather than volume (Neumann et al 2011). 'Personalized' cancer treatment - that identifies discrete genes, proteins, or other indicators that can differentiate one type of cancer from another, and thus enables the use of highly tailored therapies--offers tremendous potential for improved outcomes and lower treatment costs.

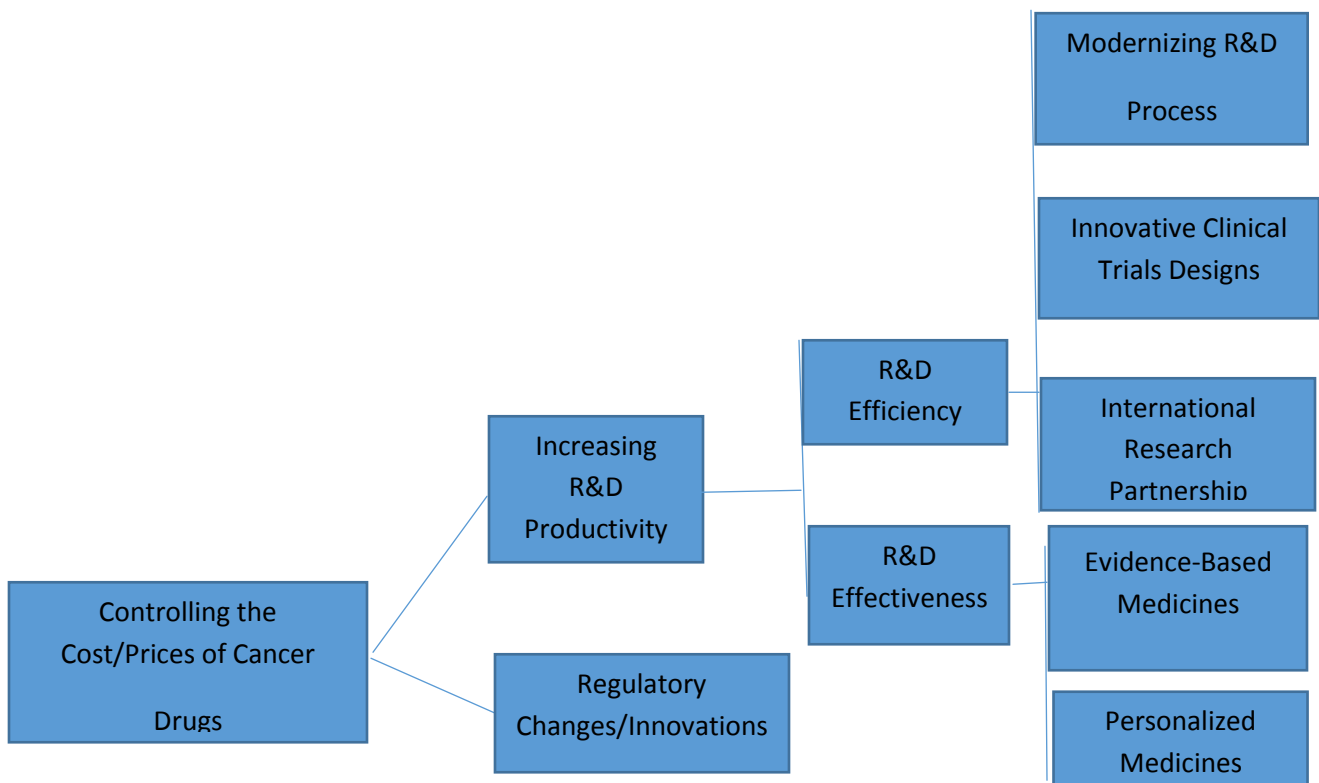
The development of new and innovative drugs necessitates addressing additional policy initiatives, involving improved decision making by all stakeholders (patients, physicians, drug

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makers, payers, and regulators) as well as policies that balance the need for faster and timely access to new medicines by patients and ‘safety’ concerns arising from risks and uncertainties associated with the novel therapies. Stakeholders have emphasized a vivid need to shift the center of gravity of pharmaceutical R&D. This will help them design drugs around patients when the morbidity of the disease is significant or when the disease is potentially life-threatening. In other words, this will lead to a redesigning of the drug development pathway that will make valuable (innovative) medicines available to the needy patients in a timely manner.

These issues call for adopting policies that effect (a) improved decision making, using synthesis of systematic research comparing different interventions (like Comparative effectiveness research), (b) regulatory changes that would facilitate new innovative medicine available to the marketplace, and (c) changes in the role of HTA bodies/payers, who are responsible for assessing and/or paying the costs of the medicines. In facilitating timely and faster access to innovative medicines by patients, researches are calling for developing a new regulatory model of drugs approval, containing a series of approval stages with iterative phases of evidence gathering and regulatory evaluation. Such a prospectively planned ‘adaptive approval’ (or staggered approval) approach, it is claimed, can easily be aligned more closely with patients’ needs for timely access to new medical technologies (See details in Eichler et al. 2012). These proposals about CER and ‘adaptive’ licensing are covered in section 3. The study is concluded in section 4.

Figure 1: Model of Efficient and Effective Drugs Development Process



2. Declining R&D Productivity: The Economic Challenge

R&D productivity² has gained increased attention since the late 1990s due to an exponential growth of the pharmaceutical R&D expenses, and a decrease in NMEs output.³ From 1998 to 2008, the number of NMEs approved per year declined (although it has been roughly constant since 2005), whereas attrition rates, development times, and R&D expenditures have all increased. Scannell et al. (2012) have shown that the number of new drugs approved per billion US dollars spent on R&D has halved every nine years since 1950, falling around 80-fold in inflation-adjusted terms. Indeed, some observers have described the situation as a ‘productivity crisis’ (Pammolli, et al 2011). Drug attrition rates for cancer are much higher than in other therapeutic areas (Hutchinson & Kirk, 2011, and Table 1). In oncology, the success rate for new drugs from Phase I trial to FDA approval was around 6.7% in the period 2003 to 2011, a figure that is about half the rate for non-oncological drugs (Hay, et al). As a result of declining productivity, more resources have been needed to produce a constant level of new drugs. High costs of developing drugs, long timelines, and high attrition rates are creating pressures for biopharmaceutical companies towards achieving a better return on investment in order to be able continue with R&D programs for other potential drug candidates. High costs and time delays also tend to have inimical effects on patients who may have benefited from pharmacotherapy earlier (Quintiles, White paper 2013).

	Failure By Therapeutical Area
Oncology	30%
Central Nervious System	14%
Musulokeletal	8.50%
Infectious Diseases	29.50%
Cardiovascular	8.50%
Other	9.50%

Source: J Arrowsmith and P Miller (2013)

Paul et al., (2010) have analyzed R&D productivity based on data from a recent industry-wide benchmarking study of 13 top pharmaceutical companies. According to Paul et al.,(2010) the

² Typically, R&D productivity is measured as the ratio of R&D output to inputs.

³ New Chemical Entities (NCEs) are the compounds that emerge from the process of drug discovery.

probability of products from a group of major companies making it to market from initiation of Phase I trials fell steadily from 10% in 2002–2004 to 5% in 2006–2008, the most recent period for which sufficient data were available. To provide a perspective on the challenges involved in conducting efficient cancer clinical trials, DiMasi (2013) showed that Clinical development times for cancer drugs between 2006 and 2011 were 8.2 years on average, vs. 7.6 between 2000 and 2005. In addition, only 13 percent of anticancer compounds that enter the clinical testing pipeline actually get approved.

Measuring R&D productivity⁴ is a difficult task since the input builds comprise of heterogeneous and multiple sources of knowledge. The output contains knowledge spill-overs that might last for several years, and the available data may not take into account the quality of the NME. The ‘pharmaceutical value ‘equation’ can be expressed as follows (see equation 1 in Paul et al., 2010):

$$P \propto \frac{WIP \times p(TS) \times V}{CT \times C} \quad (1)$$

Where,

WIP: the work in process;

P : R&D productivity ;

p(TS) : the probability of technical success;

V: Value.

WIP (Work in Process) is the number of molecules in the drug discovery pipeline needed at each stage of development to achieve one new molecular entity (NME) launch. According to industry benchmarks on project success rates, there need to be about 53 projects in various stages in the pipeline in order to have one successful launch. The probability of success per stage (*p*(TS) can be used to define the attrition rate as (1- *p*(TS)). Attrition is considered as the likelihood of a project failing to advance to the next stage in the pipeline. It is estimated that about 11% of the molecules that enter pre-clinical development stage actually reach the market. (*CT*), cycle time is the total time from the initial target to selection to commercial launch. For any given level of R&D investment, substantially reducing *CT* or lowering *C* (such as unit costs)

⁴ The following model is reproduced from Paul et al., 2010).

would increase P (*productivity*). V , value in health care has been defined as health outcomes achieved per dollar spent (Porter, 2009). Many organization across Europe measure value as societal gains, which involve estimating the duration of additional life with a new medicine, compared with that offered by standard therapy combined with an assessment of the quality of the life gained (Sullivan et al., 2011).

Following the literature, we can interpret the above equation in terms of two integral components in the productivity equation: R&D efficiency and R&D effectiveness, expressed as follows:

R&D productivity = R&D efficiency x R&D effectiveness

= (New products / R&D costs) x (Value / New products)

R&D efficiency = New products / R&D costs; and R&D effectiveness = Value / New products

The goal of a highly productive R&D system is to efficiently translate inputs into the most desired and valuable outputs (Paul et al., 2010). As seen from above, efficiency is defined as the inverses of ratio of inputs (ideas, investments, time and money) to outputs (number of projects in pipeline, products launched), whereas effectiveness is the ability of the R&D system to produce outputs with certain intended and desired qualities (for example, this can include medical value to patients, physicians and payers, and substantial commercial value).

2.1 Proposals for Accelerating Productivity

Proposals for reversing the downturn trends in R&D productivity can serve as effective offset against cost escalations. As outlined in the productivity equation, R&D productivity is a combination of R&D efficiency and effectiveness. To improve R&D productivity, it is crucial to understand the interdependencies between inputs (such as R&D investments), output (such as new molecular entity launches) and outcomes (such as valued outcomes for patients) (See Figure 1 in Paul et al., 2010). R& D efficiency means more affordable drugs via less costly R&D. R&D effectiveness means more value for patients via innovative drugs, Thus, the goal of a highly productive R&D system is to efficiently translate inputs into the most desired and valuable outputs (Paul et al., 2010). The following sub-sections deal with these two aspects of R&D productivity.

2.1.1 Accelerating R&D Efficiency

Cost-inefficiency in clinical trials is considered to be one of the leading causes of slowing productivity, since clinical trials represent nearly 40 percent of the R&D budget of major companies. According to Pammolli et al (2011), there has been a dramatic increase in attrition rates — the proportion of failures out of the total number of projects entering any given stage of R&D — across all phases, especially in Phase II and Phase III of clinical trials. Also to be noted is that the average development time — from patenting to product commercialization — has increased for more recent products. As evident from Table 1 above, oncology is the leading therapeutic area for late-stage failures. High failure rate of oncology drugs after entering phase III contributes to higher average development costs. The investigation by DiMasi et al (2007) reveals that while the clinical approval success rates were similar for oncology and other drugs proportionately more oncology failures reached expensive late-stage clinical testing before being abandoned. Thomas (2012), found that from 2004 to 2011, the overall rate of transitioning from phase I to FDA approval was 6.7% for oncology, while it was 12.1% for all other therapeutic areas. As little as 45% of oncology therapeutics progress from phase III to NDA/BLA⁵ versus 64% for all other areas.

Studies show that drug candidates failed in clinical trials for lack of efficacy, (often because the underlying clinical hypothesis about how to treat the disease was incorrect), safety issues (that had not been predicted earlier in development), and greater proportion of drugs with novel mechanisms of action entering clinical trials without adequate proof-of-concept studies in humans (See *report*, President's Council of Advisors on Science and Technology, PCAST report 2012).

On the basis of the drug development model used by Paul et al 2010, one can distinguish the following factors that can contribute to enhancing R&D efficiency and NMEs (or New Chemical Entities (NCEs) output: (i) a reduction of attrition rates and overhead costs, (ii) sufficient work in

⁵ New Drug Application (NDA) and Biologic License Application (BLA) approvals.

process (WIP)⁶ and (iii) the transformation of the R&D organization to one that is highly networked, partnered and leveraged (Paul et al., 2010).

Towards implementing the above changes, the following proposals have been suggested: (a) modernizing drug development process through implementing novel research partnership practices that enhance early-stage R&D productivity, (b) reforming the traditional clinical trials design approach by incorporating adaptive designs principles aimed at reducing trials cost; (c) considering alternative approaches to rewarding innovations in place of the current reliance on patents; and (d) restructuring the regulatory evaluation and approval pathways. The subsections below deal with these proposals.

(a) Modernizing Drug Development Process and Incorporating Recent Scientific Advances⁷

The diminishing productivity of the pharmaceutical sector has prompted a re-evaluation of the drug discovery process, with pharmaceutical companies and payers seeking ways to increase the efficiency of the innovation process and to ensure continued emergence of effective new medical products. To improve efficiency, the modernization proposal envisages strategies that encompass measures aimed at (i) preventing attrition rates in late-phase clinical trials, (ii) encouraging new models of collaborative and multidisciplinary research, (iii) reforming of clinical trials methodology and end points, and (iv) promoting informed decision making based upon the evidence obtained from 'Comparative Effectiveness Research'. Each of these is discussed below.

(i) Preventing Attrition Rates in Late-Phase Clinical Trials

One explanation for high drug prices and falling R&D productivity is that too many resources are often applied to late-stage development of drug candidates with relatively low $p(TS)$ and/or post-launch support of marketed products (See Paul et al., 2010). Clinical studies are increasingly expensive because of the rising costs of conducting Phases II and III trials. It is therefore crucial to ensure that these phases of drug development are conducted more efficiently and cost-effectively. Through a sensitivity analysis, the authors (Paul et al., 2010) have shown that reductions of Phase II and Phase III attritions are the two most critical success

⁶ That is, to build a larger pipeline of qualified leads in the preclinical stages.

⁷ The following sections under subheadings (a) and (b) are written with the assistance of Atul Bhardwaj.

factors for improving R&D productivity. Several other studies have also echoed similar concerns (see e.g. Pammolli et al., 2011). The available evidence indicates that oncology has the highest attrition rate for late stage clinical trials. It has been observed that the late-stage attrition rate for oncology drugs is as high as 70% in Phase II and 59% in Phase III trials (Kola and Landis, 2004). In view of the above findings, Kola and Landis (2004) suggest that scientific and technological innovations that affect efficacy and safety (factors that most significantly contribute to attrition in the clinic) will have to be addressed.⁸ One effective strategy suggested is to improve the ability to predict a drug's success or failure in the pre-clinical phase.

Strengthening the Pre-Clinical Phase/Translational Research

Reducing failures early in development is said to be far more important than filling a pipeline with poorly chosen late-stage products likely to fail, and fail expensively. Studies suggest that only those molecular targets which are specifically associated with and relevant to disease need to be selected from preclinical development programs that are truly worthy of advancing to Phase I clinical trials and likely to meet the criteria for success in later-phase trials (Quintiles, White paper 2013).The 'quick win or fail paradigm' (Paul et al., 2010), which means discarding marginally effective drugs quickly, requires information-based (like molecular profiling and molecular markers) early screening for both efficacy and toxicity in order to yield more predictive results. The selection of an inappropriate target at the start of the drug development process causes the spending of hundreds of millions of dollars and the wastage of perhaps a decade of continuous effort as the results reaped at the end of the process are disappointing. (Grundy et al., 2014).

This points to the need for models and approaches that ensure more effective evaluation of novel cancer therapeutics and identification of predictive biomarkers early in drug development. Improved understanding of cancer biology gained through translational research enables scientists to define predictive markers in order to assess the effectiveness of new molecules and better identify the patient sub-groups that are most likely to benefit from them. It has been

⁸ The standard road to drug approval involves demonstrating safety in phase I, clinical effect in phase II and then a phase III randomized controlled trial (RCT) to confirm whether the experimental treatment provides a statistically meaningful improvement over the current standard of care (Eisenstein, M. 2014). The problem of attrition is particularly acute in Phase II trials, owing to factors such as the lack of proof of relevance for the biological target in a given disease intervention and insufficient understanding of the dose–response relationship of the new molecular entity.

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hypothesized and demonstrated that 'Predictive' biomarkers can provide early evidence of safety and efficacy – while a molecule is still in preclinical development – and can provide assurance that lead candidates will have a high probability of success in subsequent milestones potentially reducing the time and cost of drug development (Crivellente, 2011). Leveraging 'intelligent biomarker selection' of patients to participate in early phase clinical trials has potential to make more efficient go/no-go decisions on product candidates at the earliest possible stage (Quintiles, White paper 2013).

Analyzing the data from the Tufts Center for the Study of Drug Development (Tufts, 2010), Davies (Ch. 1 in IOM 2012) reported that 100 percent of the surveyed companies were using a discovery strategy that involved a genetic or genomic approach. Thirty percent required that all their compounds had an associated biomarker before going into clinical development. Pharmacogenomics, the optimization of drug therapy based on genetic information, has been applied to improve clinical outcomes or reduce side effects and adverse events. Incorporation of technological and scientific advances holds a tremendous promise in improving efficiency through reducing high attrition rates. FDA's "Critical Path Report and List" in 2006 enumerated the following leading areas for scientific improvement in the development process: development and utilization of biomarkers; modernization of clinical trial methodologies and processes; the aggressive use of bioinformatics, including disease modeling and trial simulation; and improvement in manufacturing technologies.

The FDA estimates that just a 10% improvement in the ability to predict drug failures before clinical trials could save US\$100 million in development costs per drug (FDA 2004). A recent study spanning 908 oncology drug candidates showed that Phases I, II, and III transition probabilities were 90%, 69%, and 85%, respectively, for agents developed with stratification markers (n=121), compared to 76%, 51%, and 59% for all agents (Frankel Group, 2013).

Additionally, advanced imaging technologies, through earlier selection of candidates for new drugs, can reduce the large attrition rate in the pharmaceutical development process. Molecular imaging may one day be integrated with other diagnostic techniques to dramatically increase the efficiency and effectiveness of cancer care (Kircher et al., 2012).

Modernization of the drug development process also calls for new models of research collaboration that can improve the probability of effective target selection and target validation.

The 2012 PCAST report identifies target validation as a major problem caused by the knowledge gaps in translational medicine. Precompetitive research collaboration on target validation can serve an effective strategy for reducing high failure rates. The following subsection deals with this strategic issue

(ii) New Models of Collaborative and Multidisciplinary Research

New models of research partnership among universities and research institutes, clinical research in hospitals, and drug discovery and development in the biopharmaceutical industry are emerging to address the decline in R&D productivity and high attrition rates. There is a general agreement regarding the need of a new drug development pathway that is compatible with research aimed at understanding the biology of a cancer and simultaneously developing the ability to support the design and conduct of subsequent confirmatory trial (European Organisation for Research and Treatment of Cancer 2014). However, building and maintaining such a drug development pathway is beyond the ability of individual organizations or companies. Moreover, pharmaceutical companies tend to under-invest in the translation of biological insights into new medicines because it is at least partially a 'public good'. This means that a single company financing the development of new foundational approaches to drug discovery cannot entirely appropriate the fruits of its work, because much of it is disseminated to benefit all participants (PCAST report 2012). It has been argued that new forms of partnership as well as an integrated model of cancer research are needed. A collaborative model, based on partnerships in which the rigor and process of industrial drug discovery is combined with the deep understanding of disease biology from academic research centers and teaching hospitals, is emerging as a potential long term solution to the problem of failure of drug candidates in late clinical phases (Grundy, James, Bountra and Harrison, 2014). Innovative collaborations, drawing on the core strengths of pharmaceutical companies and academia, can address one of the key factors thought to underlie high attrition rates, viz., the lack of validation of novel therapeutic targets. (Paul et al., 2010).

Incorporating cutting-edge science into new therapies, which lies at the heart of translational research, is a complex undertaking that requires the collaboration of multiple disciplines. Translational research has the potential to drive the advancement of molecular-based medicine and fulfill the promise of personalized medicine. The success of translational research is not only a function of the quality of the science but also of the collaboration between academia and industry, the organization and management of research and development (R&D), the public

policies that regulate scientific research and the connections among the key people involved (Ibis Sánchez-Serrano 2006.). Public and private research partnership, in addition to bridging the knowledge gap can improve success rate by reducing conflicts of interest, and by actively managing frontier technologies to maximize positive social spillovers (Stiglitz & Jaidev 2010). In view of the various beneficial spill-over effects of public investment, Stiglitz and Jaidev recommend public funding of phase III clinical trials. Particular aspects of this proposal include (a) sharing the costs of this research among all stakeholders (industry, nonprofit research institutions and governments) to spread the risk; (b) placing the research findings in the public domain to disseminate, and (c) conducting the research in partnership between academic and industrial scientists to capitalize on their respective skills and promote collective learning and technology transfer. In a similar vein, Grootendorst et al., (2011), suggest that public funding of phase III clinical trials would relieve drug companies of the single largest cost of research and development (about 21%).

Further, as cancer management becomes increasingly tailored to the individual, there is a need to investigate large populations in order to identify small but significant differences. This often requires national or even international collaborations (Cancer Research UK, 2008).⁹ The European Organization for Research and Treatment of Cancer (EORTC) proposes the use of collaborative molecular screening platforms (CMSPs) as a new approach that aims to offer a high quality integrated infrastructure for efficient screening of patients with cancer for specific molecular alterations. In the US, Translational Research Working Group (TRWG) was established in 2005 to work with the cancer research community to develop recommendations about how the National Cancer Institute could best organize its efforts to further translational research.¹⁰ Structures such as practice-based research networks (PBRNs) have been developed as a mechanism for moving research into clinical practice. In 2011, the NIH proposed the creation of an important new entity, NCATS, to serve as NIH's catalytic hub for translational innovation (Bonter et al 2011).

⁹ Cancer Research UK's Research Strategy 2009/10-2013/2014

http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@fre/@gen/documents/generalcontent/research-strategy-dnld-version.pdf

¹⁰ The TRWG defined a translational continuum and developed a "roadmap" to create a stronger research infrastructure to accelerate the clinical research enterprise. See the steps involved along the translational pathway in How cancer is studied? http://cisncancer.org/research/how_cancer_is_studied/basic/

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Another important recent trend is a move towards open international research partnerships to speed up the drug discovery process, based upon new scientific advances. The 'International Cancer Research Partnership' (ICRP) is an example of international collaboration that includes cancer research funders from USA, Canada, Europe, Japan and Australia. The 'ICRP' is a unique alliance of cancer organizations working together to enhance global collaboration and strategic coordination of research. The group operates through regular teleconferences and annual face-to-face meetings as well as publishing portfolio analyses and evaluation reports. Other examples include 'TRANSCAN' in translational cancer research, 'International Rare Cancers Initiative' (with partners including the European Organization for Research and Treatment of Cancer (EORTC), the US National Cancer Institute (NCI), and International Cancer Genome Consortium (ICGC).

(b) Reforming Clinical trials designs

Despite our improved knowledge of genetics and cell biology, the clinical-study design has not kept pace with the scientific advances. Currently, clinical trials in oncology are designed to test just one drug at a time, and generally are focused on treating patients with advanced, metastatic disease, with success in metastatic disease followed by investigations in the adjuvant setting. This current process of drug development is considered to be appallingly slow, increasingly risky, costly, and inefficient procedure. It involves more than a decade to gather the evidence necessary to approve a new cancer drug, and results in low success rate in which 60% to 70% of late-stage cancer studies fail. (de Lartigue 2014, Menis, Hasan & Besse, 2014). Critics also assert that conventional randomized trials mask the benefits of good drugs that work in only a subset of patients. (Eisenstein 2014). In addition to the staggering cost and poor success rate in new drugs development, the slow and time consuming process takes a 'heavy toll' in terms of traumatic stress and emotional distress caused to the patient and caregivers.

Moreover, this conventional process of drug approval often fails to take into account the complex realities of cancer biology. Historically, clinical trials have been designed to treat cancers classified by their anatomic location, without consideration of molecular alterations that may be present in subsets of such tumors. The failure to account for individual genetics means that they can give rise to misleading results. (See details in Eisenstein 2014).

The new knowledge gained from genomic research is now beginning to be used to reform how clinical trials are designed and conducted. Scientific innovation in the fields of genomics,

proteomics, bioinformatics, and imaging technologies is revealing the molecular basis of disease while rapidly transforming the drug development process – and even starting to change the way we diagnose and treat patients (AACR Cancer Progress Report 2014). As recognized by the US Food and Drug Administration (FDA) Critical Path Initiative (2006), novel approaches to clinical trial and program design could have a crucial role in incorporating new advancements. It is suggested that clinical trials methodologies need to target 3-fold goals¹¹: (a) more effectively matching of drugs to the populations most likely to benefit based on an individual patient's molecular profile; (b) decrease trial costs, and (C) decrease the time from trials to drug approval. Some notable ongoing innovative efforts towards achieving these goals may consist of using the following: (i) 'Basket and Umbrella' trials; (b) alternative surrogate and endpoints; and (iii) expedited review strategies (AACR Cancer Progress Report 2014).

Basket and Umbrella Trials:

In 2006, the FDA's Critical Path Initiative stated that the two most important areas for improving medical product development were biomarker development and streamlining of clinical trials. Multi-arm Bayesian-based adaptive clinical trials offer the possibility of both. Adaptive designs (that "adapt" in response to information generated during the trial) offer the potential to make oncology drug development more efficient and address many questions (including biomarker and surrogate endpoints) at once, thereby potentially reducing trial subjects' exposure to ineffective treatments and allowing for more flexible, less costly incorporation of other promising therapies (Alexander et al 2014).. Unlike traditional approaches, the Bayesian approach uses both the evidence that accumulates over time (eg, interim clinical trial data) and prior information (literature or previous relevant studies). Prior information is combined with the current data to obtain a "posterior distribution" (a term for the probability of an event that is conditional on the prior information and current data) which is analyzed and used to draw conclusions (National Pharmaceutical Council, 2012).

Two examples of the complex adaptive randomized trials design based on Bayesian predictive probabilities include, the I-SPY 2 study in breast cancer and the 'Biomarker Approaches of Targeted Therapy' for Lung Cancer Elimination (BATTLE) study for non–small-cell lung cancer (Alexander et al 2014). Such trials can take the form of basket or umbrella trials. Basket trials

¹¹ This is adapted from Carter. J.L.(2014): New Clinical Trials Designed to Better Leverage Precision Medicine, March 2014 Edition | Vol. 8, Issue 3, http://www.n-of-one.com/obrgreen/obr_vol8_issue3.php

aim to test one drug or one particular genetic mutation across multiple organs. Umbrella trials seek to test a drug or drugs across multiple genetic mutations within a particular type of cancer. For example, both I SPY-2 and BATTLE-2 are umbrella trials in breast and lung cancer,⁵ respectively (AACR Cancer Progress Report 2014). BATTLE-2 and the I SPY-2 are two examples of clinical trials aimed at matching the correct therapy with the correct patient subset (See AACR Cancer Progress Report, 2014). In each of these unique clinical trials, a patient's tumor is examined for unique signatures called biomarkers. The biomarker signatures are used to simultaneously test and match multiple investigational therapies to individual patients, thus maximizing the number of patients likely to benefit. Experimental arms are dropped early in phase II if they fail to be effective in any subset of disease. Biomarker based trials have numerous efficiencies, but the major efficiency is enabling a phase III trial that is smaller than is traditionally needed, because in an adaptive trial only patients most likely to respond are included in the study(See details in American Association for Cancer Research, 2011, 2014). In the near future the trend towards combining clinical practice and clinical trials will also mean a completely different regulatory perspective and an entirely different business model for companies.

Expedited Review Programs for Oncology Drugs

In order to reduce the time needed for the trial to continue before a clear result can be achieved, the two efforts need to be made. They include using alternative or surrogate endpoints¹² and FDAs expedited review strategies (AACR Cancer Progress Report, 2014). There are four evidence based strategies to expedite assessment of therapeutics for life threatening cancer. These strategies are: (i) Accelerated Approval, (ii) Fast Track, (iii) Breakthrough Therapy, and (iv) Priority Review(See page 40 for details on these, in AACR Cancer Progress Report , 2014, see also section 5 below on regulatory reforms). These programs complement one another and serve the common goal: to speed up the approval of effective treatments for serious conditions. Expediting the development of promising agents through use of these programs often entail smaller trials,⁶ which pose both efficacy and safety risks (Klutz & Donoghue, 2014).

¹² A surrogate endpoint as is defined as a biomarker intended to substitute for a clinical endpoint. See Cohn JN (2004). "Introduction to Surrogate Markers". *Circulation* (American Heart Association) **109** (25 Suppl 1): IV20–1.

Through advances in Next Generation Sequencing technologies, it is becoming increasingly feasible to quickly and efficiently generate a molecular profile of each patient's tumor. Under this paradigm, data from clinical trials can be used more expeditiously to adjust participation and improve clinical trial metrics (Carter 2014). Various technological advances in DNA sequencing have dramatically increased the number of known cancer-associated genomic alterations. Enormous research efforts will be needed in the fields of computational biology and bioinformatics in order to efficiently mine the enormous amounts of information generated by the genomic analyses of tumors and to identify the genomic alterations most likely to yield therapeutic targets with the potential to benefit patients.

(c) Promoting Prize-scheme as an alternative to the Current Patent system

An increasingly complex patent landscape that blocks innovation results in poor incentives to share research and provide access to knowledge and few capital market incentives to invest in translational products that have low commercial prospects. However, it may yield useful scientific information for follow-up research efforts. (Love & Hubbard 2009). Most studies have noted that the prevailing patent rights environment presents an inherent trade-off between static inefficiency (which relates to the pricing of a product about to enter) and dynamic efficiency (which relates to product innovation as applied to future market conditions).

According to Love and Hubbard (2007), the prize mechanisms should be thought of as part of a larger ecosystem of financing medical R&D and should be implemented in combination with other instruments, such as direct or indirect government funding of basic research, non-profit product development partnerships (PDPs), clinical trials, and other traditional and non-traditional types of funding R&D. What the prizes offer uniquely is an alternative to the marketing monopoly as an incentive for private investment. The elimination of marketing monopolies, the de-coupling of R&D incentives from product prices to the consumers¹³, and the creation of an evidence-based reward system linked to changes in health outcomes will lead to significant reductions in expenditures to market products, the area of the largest waste in the current system. (See Love & Hubbard 2007).

¹³ If you can divorce the incentive for innovation from the product's price to consumers, knowledge goods, including the R&D for a new medicine, can be placed in the public domain immediately. (Love and Hubbard, 2007)

To improve effectiveness of R&D (and hence productivity), Love & Hubbard (2009) have recommended that rewards can be directly linked to the improvements in health outcomes when benchmarked against existing treatments rather than rewarding the replication of benefits already available from existing products. This has the benefit of driving investment toward treatments that address unmet needs. The elimination of the product monopolies and the enabling of generic competition will also lower prices, reducing treatment costs and personal hardships, while expanding access. It is also possible to design prizes to reward and encourage collaboration and the sharing of knowledge, materials and technologies. Under Prize funds scheme, rewards for innovation are geared to the proven therapeutic value of a drug (Faunce & Nasu 2008; Stiglitz 2006; Love & Hubbard 2007). Although controversial, the prize fund mechanism *inter alia* is now acknowledged in the WHO Global Strategy Plan of Action as a viable mechanism for development.

The study by Gagnon (2010) has advocated the implementation of a prize-system for innovation in Canada. In Gagnon's view, Canada deliberately sets its drug prices high to encourage research and development on Canadian soil. The total R&D spending by the industry is \$1.31 billion, 59% of which consists of tax subsidies. Canada would benefit greatly from using this money instead of encouraging pharmaceutical R&D by funding new types of incentives, for example, through public innovation (Gagnon 2010).

Controlling rising drug cost requires the countries to capture and appraise the totality of reliable evidence that addresses the efficacy and safety of medical intervention (Lyman 2012). Shared decision making, in which patients and health professionals collaborate, is considered to increase the effectiveness of the treatment (See details in Coulter et al., 1999). Evidence-based information is a precondition for informed decision-making and participation in health. Informed decision making becomes quintessential for effective treatment. The following subsection deals with this aspect.

2.2: Improving R&D Effectiveness

Analysts have expressed concerns about the quality of new medicines. The real innovation crisis, Light and Lexchin (2012) state, stems mostly from current incentives that reward companies for developing large numbers of new drugs with few clinical advantages over existing ones. A greater need is now being felt for channeling R&D resources towards

innovative medicines. The accelerated pace of scientific discovery and rapid advances in cancer care, have underscored the need for evidence to assist patients and physicians, among others, in making decisions about clinical effectiveness and risks of a health intervention. These stakeholders also want to know whether the intervention's health benefits are commensurate with its costs—that is, whether it delivers value.

Effectiveness may refer both to the cost effectiveness (the incremental therapeutical value of a new drug in relation to incremental cost), and to higher quality of medicine for individual patients developed by utilizing pharmacogenomics knowledgebase. There are therapies that are much more effective in particular patients because they're based on a better understanding of the mechanisms of cancer in particular patients. In areas especially like cancer therapy, there is both promise for more effective and personalized therapies, as well as growing pressures to reduce costs. Effectiveness of Pharmaceutical R&D can thus be improved through measures like (i) using evidence from Comparative Effectiveness Research, including cost effectiveness criteria, and (ii) developing personalized medicines. The Comparative Effectiveness Research can be used by a range of decision makers, including government regulators determining whether to license a new medical product, policy makers and payers deciding what interventions health plans should cover, and individual providers and patients choosing treatments (Garrison et al 2010b). The following subsection deals with the need for developing evidence based information for pricing and for adopting 'patient-centered outcomes' approach.

2.2.1 Using Evidence-based Decision Making: Incorporating Cost and Clinical Effectiveness

One of the significant obstacles to improved patient care, at a reasonable cost, is the relative lack of real-time access to current, comprehensive patient medical information that is easily retrievable for patients, healthcare providers, and healthcare payers. Physicians and payers alike are demonstrating increased interest in the use of evidence-based medicine (EBM), or implementing of treatments that have proven track records of delivering desired results in specific patient populations. With the variety of oncologic treatments, diseases, and presentations, oncology has been described as depending on evidence-based decision making, possibly more than any other medical specialty (American Society of Clinical Oncology, 2007). With a trend toward health care absorbing an ever-larger fraction of government and private budgets, countries are facing mounting pressure to consider effectiveness of a treatment relative to its costs or to the costs of alternative treatments. With CE (comparative

Effectiveness) as a tool to evaluate not only bottom-line effectiveness for patient outcomes, but cost effectiveness as well, it is likely that this pressure will continue to grow (American Society of Clinical Oncology 2009). American College of Physicians(2008) has called for cost-effectiveness analysis — assessment of the added improvement in health outcomes relative to cost — to be on the agenda for Comparative Effectiveness Research (See also Garber 2008). Adopting any treatment that improves health outcomes, no matter what the cost, can worsen *allocative* inefficiency by paying dearly for small health gains (Chandra et al 2012).¹⁴ CER can be viewed as combining elements of clinical effectiveness (CE), cost effectiveness analysis (CEA), and pragmatic trials in which benefits of treatments in routine clinical practice are assessed.

Cost Effectiveness and CER

In order to reduce medicine costs to consumers as well as to provide reasonable and directed incentives for research-based pharma, economists have advocated for the role of value based prices in rewarding genuine innovation (Husereau & Cameron, 2011b). A value-based system determines initial drug price that considers cost-effectiveness data. Value-based pricing has been advocated as a method of improving the affordability of cancer therapy (See details in Sullivan et al., 2011). Value-based pricing system intends to improve the cost-effectiveness of a medicine, and therefore allows HTA bodies to recommend treatments which they would otherwise have deemed not cost-effective. The primary measurement tool in cost effectiveness is the “incremental cost-effectiveness ratio” (ICER) - the ratio of incremental cost of a new intervention versus the standard of care (the numerator) over the incremental health benefits (the denominator). (Garrison, 2010, Sullivan et al., 2011, among others). The denominator is measured by the “quality-adjusted” life-year (QALY) or “utility. The metric, cost per QALY gained, and a threshold (expressed per QALY) can be considered a basis for “value-based pricing” and reimbursement. Prices could be set at launch based on this standard and the projected incremental QALYs per treated patient and then be revised over time as better data became available on the actual QALYs delivered. It is recommended that VBP regulation would

¹⁴ Allocative Efficiency determines whether health care spending is at the correct level. Should we increase health care spending or instead spend those resources on education, roads or R&D? Allocative inefficiency would arise when the forgone (non-health) consumption involved exceeds the value of improved health. See diagrammatic description in Chandra et al 2012.

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establish a maximum price for a pharmaceutical based on an *ex ante* evaluation for new products and a rolling *ex post* evaluation of existing products. Garrison Jr, (2010) stresses the need to develop new approaches and tools that take in to consideration the entire product life cycle on a global basis.

Value-based pricing systems reward and incentivize development of drugs that substantially improve outcomes, but not subsidize development of me-too or marginally effective new treatments (Sullivan et al., 2011). More effective drugs may lower medical costs through downstream effects, such as decreasing demand for other medical services, inpatient care, and might also lead to a decrease in relapse episodes. Secondly, cancer-related indirect costs may decrease due to increased survival, decreased morbidity and less informal care time (Hofmarcher, Jonson & Wilking 2014). In order to enable access to new medicines that have a higher cost/QALY than the prescribed threshold, the UK and other European nations have introduced PAS(risk sharing) schemes in which drug companies agree to reduce the transaction price of a drug to the NHS while maintaining the list price of the drug.

To improve evidence about the comparative effectiveness of alternative treatment, the US Congress appropriated \$1.1 billion toward accelerating comparative effectiveness research (CER) as part of the American Recovery and Reinvestment Act (ARRA) of 2009. The American Recovery and Reinvestment Act (ARRA) of 2009 allocated a \$1.1 billion “down payment” to support comparative effectiveness research (CER). ARRA aims to provide support for comparative-effectiveness research (CER) which has recently been referred to as “patient-centered outcomes research.” The National Cancer Institute (NCI) has funded seven research teams to perform projects on CER in genomic and precision medicine to begin filling in this gap in knowledge, develop novel methodological approaches, and address necessary data infrastructure needs (Simonds et al., 2013). To empower European citizens, the ECC has created a European Cancer Patient’s Bill of Rights, which defines fundamental pan-European quality standards for provision of information, access and delivery of cancer care and research to European citizens (Lawler, et al., 2014).

In the CER approach, the quality of the intervention is judged solely on the basis of outcome parameters such as survival, quality of life, and so forth. Cost can be considered as an outcome parameter but is not necessarily a component for comparison. In the medium to long term future, increasing health care costs would create a need for considering cost effectiveness when

deciding which health care services insurance should cover or how much to pay for them. Emphasizing the need for considering the cost aspect along with comparative effectiveness research, Chandra et al. (2011), remark that, “Comparative effectiveness research and its half-sibling cost-effectiveness research will provide a solid foundation for reform, once politicians and voters understand how dismal the alternative is.”(P43)

2.2.2. Personalized medicines.

Studies have described the ‘blockbuster model’ of drug development as inefficacious (benefitting only slim majority of the prescribed population), and highly expensive requiring large trials (Ferrara. J. (2007). Medical research has demonstrated that each tumour has a unique set of genetic aberrations and molecular changes. Some of these genetic and molecular characteristics have been termed biomarkers since they can mark how well a tumour will respond to certain treatments or how quickly the disease will progress. The goal of biomarker research in oncology is to personalize cancer treatment based on individual tumour characteristics (Carter & Lokere, 2010, Mak. T. Report Card of cancer in Canada, 2013). In an ideal scenario, each tumour is tested to identify its unique biomarker profile and that information helps to inform decisions about prognosis and treatment. Today subgroups of patients may be optimally selected based on prognostic and/or predictive biomarkers (Burock et al 2013).¹⁵ The strategic use of tumour biomarker profiling can help spare patients from the lost time and potential side effects that come from trying a medication that is unlikely to be effective. Further, tumour biomarker profiling can produce significant savings on a national scale (Carter & Lokere, 2010).

Personalized medicine offers apparently clear clinical advantages -- a biomarker points directly to the most appropriate therapeutic intervention. Pharmacogenomics, -- the ability to test for variations in genes and their expression through molecular diagnostics and then to treat with targeted drugs - is now considered as an essential tool for optimizing both the development and clinical utility of drugs. In 2005, the FDA created guidance for drug developers to link biomarkers to therapeutics in the clinical development process (Ferrara, 2007).

¹⁵ Biomarkers can be broadly of three types: *Predictive* – a factor that can be used to predict response to a drug; *Prognostic* – a factor predictive of disease outcomes, irrespective of treatment; *Pharmacologic* – a factor that can be used to demonstrate drug activity/MOA(drug mechanism of action). See Quintiles(2010).

The targeted interventions have the potential for increasing the effectiveness of cancer therapies while reducing the frequency of treatment-related complications (Lyman 2012). The promise of personalized approaches includes more effective therapies and improved treatment outcomes, and spares patients the toxicity and cost associated with ineffective treatment. In some cases, although diagnostic tests themselves might be expensive, their use may be cost-saving from a societal perspective (Sullivan et al 2011). Genomics technologies, notwithstanding the rising complexity and low productivity to date, once translated to clinical care, promise significantly improved outcomes through cost-effective interventions and prevention (Carlson 2009). According to its National Cancer Institute, France has saved hundreds of millions of euros since it set up a network of 28 hospital-linked centers across the country to analyze the molecular diagnostics of cancer patients' particular tumors. The free testing, operated by the institute and the Ministry of Health, aims to ensure that new targeted therapies are prescribed only to individuals who will actually benefit (Keogh 2012). In the UK, the Stratified Medicine Program's aim is to help establish a national service to "ensure standardized, high-quality, cost-effective genetic testing of tumors available to people with cancer. The UK's Technology Strategy Board is also investing as much as £75 million in research and development grants to help develop "stratified" cancer treatment over five years (Keogh 2012).

Garber and Tunis (2009) believe that CER offers a way to hasten the discovery of the best approaches to personalization and will provide better information which will help to craft a management strategy for individual patients. Sox and Goodman (2012) believe that CER must identify clinical characteristics to predict which intervention would be most successful in an individual patient as well as subpopulations of patients that are more likely to benefit from one intervention than the other.

Some Economic Aspects of Personalized Drug Market

Trusheim and Berndt (2012) have analyzed the economic/financial viability of stratified medicine versus the empiric medicine (a medicine prescribed to all patients with a particular condition) using Net Present Value Analysis. The authors have demonstrated (with simulation exercise) that with current incentive structures, the segmenting and sub-segmenting of a disease, as under a stratified medicine system, runs the risk of making therapeutic markets too small to be economically viable. Their analysis shows that in the absence of significant pricing and total

oncology outlay flexibility by payers, private sector investment in small oncology segments, and in stratified medicine generally, may not prove to be economically sustainable, thus endangering the translation of scientific advances into bedside medicines. Trusheim and Berndt (2012b) suggest that, beyond increasing reimbursement, decreasing development cycle time and costs, or both, would most directly improve the economic incentives facing drug developers. Their analysis suggests that policy tools such as accelerated approvals, adaptive licensing, and novel clinical trial designs appear most promising to effect these changes.

3. Regulatory Reforms: Adaptive Licensing

To achieve the goal of speeding patient access to needed therapies, regulators and HTA bodies/payers around the world have been actively pursuing various approaches to ensure the timely availability of important medicines to the needy patients. The UK has set up a special program called the Early Access to Medicines Scheme (EAMS) to speed up development of new treatments in areas of high unmet medical need. In parallel, the European Medicines Agency (EMA) launched a pilot project in adaptive licensing. The Massachusetts Institute of Technology's (MIT) NEWDIGS (New Drug Development Paradigms) programme is working to build a shared view of what evidence is needed to support the development of new pathways bringing all stakeholders together under safe harbour agreements to build relationships between multiple parties to push adaptive pathways forward (See Vital Transformation, 2014). The broader concept of Medicines Adaptive Pathways to Patients (MAPPs) has been adopted as it embraces all elements of the switch from basing marketing approvals on retrospective trials. It takes a prospective approach in which a drug is approved in a niche indication and then brought into wider use on the basis of iterative phases of real world evidence gathering (Vital Transformation, 2014).

The basic tenet of adaptive licensing is premised on the assumption that knowledge of a particular technology is not binary and evolves over time. As such, these proposals for reform move away from a 'one time' licensing approach with a 'magic moment' of approval to a licensing process involving several smaller steps. Precursors to adaptive licensing already exist in a number of forms including Food and Drug Administration's (FDA) Accelerated Approval and European Medicines Agency's (EMA) Conditional Marketing Authorization; FDA's Risk Evaluation and Mitigation Strategy and EMA's Risk Management Plan; FDA's Sentinel Initiative and EMA's Periodic Safety Update Reports; and EMA requirements for Five Year Reviews of

new products (See Workshop-Summary 2012). EMA recently changed the name of its pilot project from adaptive licensing to adaptive pathways.

It is conjectured that adaptive licensing (AL) could bring the data requirements of regulators and Health Technology Assessment (HTA used for reimbursement decisions) bodies closer than ever before. It means that pharmaceutical countries may have greater certainty that their drugs will be reimbursed (Finn. K. 2013). The concept is built upon the conditional market authorization (EU) and accelerated market approval (USA)¹⁶ regulatory routes in which products are licensed earlier than they would normally be on the condition that the manufacturer would carry out additional post approval studies.

AL (Adaptive licensing) should reduce expensive late-stage attrition and post-market withdrawals. Earlier and better-informed product viability decisions added together should address many of the root causes of the overall high costs of product development and sustained return. AL should not be expected to reduce overall attrition rates during drug development (e.g., due to target failure), but it may reduce the overall cost of development by allowing better-informed decisions on product viability to be made earlier in the development process. (Eichler et al . 2012). Elements and technologies that support a new adaptive drug licensing paradigm include: biomarkers and surrogate end points; infrastructure for proactive drug safety monitoring; electronic medical records; new clinical trial designs in which safety and efficacy are decoupled to optimize study designs for optimal knowledge generation; and tools to enable appropriate utilization of new drugs.

For adaptive approval to be a viable approach, it would be necessary to have mechanisms to ensure that (1) drugs are prescribed largely to patients for which they have been approved at the time; (2) evidence whether drugs' risks and benefits is generated on an ongoing basis, including through randomized controlled studies, pharmaco-epidemiological data, and robust monitoring after initial approval; and (3) drugs with incomplete follow-up studies and monitoring or drugs demonstrating an unfavorable risk-benefit balance can be readily removed from the market.

¹⁶ In the USA, the current fast track approval process, known as, 'Accelerated Approval and SMU'(drugs intended to address unmet medical need, also referred to as a Special Medical Use (SMU) can be viewed as specific instances of the concept of adaptive approval. (PCAST 2012)

There is also currently a gap between the evidentiary standards required by regulatory agencies and payers for assessing the benefits and risks of a therapeutic. This gap often delays access for patients to new, high-value treatments; compromises the quality of our knowledge about new products; and increases risks and uncertainties associated with the innovation process. Innovative approaches such as AL and Coverage with Evidence Development (CED) respectively, if designed and implemented jointly, have the potential to bridge this gap (Workshop-Summary 2011). While AL and CED have been two traditionally distinct areas of pharmaceutical policy, the Center for Medical Technology Policy (CMTP) and the NEWDIGS (New Drug Development Paradigm) program led by the MIT Center for Biomedical Innovation (CBI) have expressed the need to explore potential approaches to integrate AL and CED (Workshop Summary 2011).

4. Summary and Conclusions:

Rising cancer drugs prices have become a matter of grave concern both for public payers and patients in particular. From their studies, many professionals have expressed the view that the huge expenses involved in research and development (R&D) are mostly responsible for the high costs of cancer drugs.

A recent analysis has shown that the number of new drugs approved per billion US dollars spent on research and development has halved every nine years since 1950, falling around 80-fold in inflation-adjusted terms (Scannell et al 2012). The available evidence indicates that approved oncology drugs were more often the first-in-class than was the case for drugs in other classes. However, compared to other drugs, a higher percentage of oncology drugs failed after entering phase III testing (DiMasi and Grabowski 2007).

Issues like cost escalations, productivity slow down, proliferation of 'me too' drugs, increasing 'translational gap' have raised serious concerns about the efficiency, effectiveness and sustainability of the entire drugs development process - from clinical trials stages to regulatory approval phase. Under the present scenario, stakeholders have expressed a strong and inevitable need for developing new therapies that are safe, effective, and affordable. In recent attempts to improve the drugs' development performance, policy initiatives in Europe and USA are aiming to improve at least three performance metrics, viz., safety, efficacy (including shorter development times), and effectiveness.

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Utilizing the R&D productivity model of Paul et al (2010), this paper analyzes both the efficiency and effectiveness aspects of the drug discovery and development process. Improving efficiency calls for adopting strategic measures that modernize the drugs development process, including the introduction of novel clinical trials designs. Among the most commonly agreed strategic initiatives mention may be made of open model of research partnerships between academia and pharmaceutical companies, stronger reliance on precompetitive research at early stages of drug discovery, and the use of novel 'Adaptive Design' of clinical trials. New models of research collaboration are needed to bridge the knowledge gap and to improve better understanding of how best to apply biomarkers and genomic medicine in the future for Phase I studies. The challenge before us is to develop streamlined and directed approaches that can rapidly generate the biological insights and that will allow cancer genome discoveries to be translated to the clinic (Chin et al., 2011). In addition to improving R&D efficiency, policies in most countries have emphasized the rationale to link prices of the new medicines to their therapeutical value. The application of this value-based pricing approach (VBP) is expected to incentivize the development of more cost effective drugs. Additionally, the emergence of "Personalized medicine," being made possible on account of the advances in a wide range of fields from genomics to medical imaging and to regenerative medicine, is holding a great promise of allowing patients to be treated and monitored more precisely and effectively in the ways that will better meet their individual needs.

Increasing public investment in biomedical research is needed so that frontier technologies are as much in the public domain as possible at the outset. Further, the complex advances in biomedical research have created immense uncertainty about the clinical utility and safety of new applications, eg. genomic applications for cancer treatment. Comparative Effectiveness Research (CER) can provide evidence to clarify this uncertainty, and to help evidence-based decisions by describing potential challenges and opportunities. Furthermore, it is widely held that accelerating innovations in the creation of safe, effective, and affordable medicines will also require improvements in the nation's regulatory processes for drug evaluation. Regulatory systems need to play a critical role in promoting efficiency and directing innovations toward socially beneficial output. More informed regulatory decisions will be needed in the near futures based on CER evidence. Another challenge is to develop innovative approaches that facilitate faster approval of drugs without compromising with the safety standards. It is also expected that the 'adapting licensing' approach will replace the traditional, long drawn out regulatory process.

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As a final note, it is important to recognize that a complete understanding of human (disease) biology will still be required before many real breakthrough medicines emerge. Finding molecules with high efficacy and low toxicity for effective treatment is extremely a difficult task that calls for addressing the gap between basic research and commercial projects with 'translational research'. (PCAST report 2012, and Scannell, et al., 2012). The vast majority of currently approved drugs act against only a few classes of proteins (such as proteases and kinases). Scientific advances are, however, paving the way for developing safer and highly effective oncology drugs in the near future.

The necessity of expediting the clinical applications of new advances is now being felt more than ever before for the sake of large scale public sector investment in basic research, developments in translational medicines, and regulatory reforms for advancement of drug development science (DiMasi and Grabowaski 2007). What is needed at this time are open and integrated partnerships at global scale as well as research collaborations between academia and the Pharma industry (large and/or biotech).

References

Alexander BM, Wen PY, Trippa L, Reardon DA, Yung WK, Parmigiani G, Berry DA.(2013): Biomarker-based adaptive trials for patients with glioblastoma--lessons from I-SPY 2. *Neuro Oncol.* 2013 Aug; 15(8):972-8.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3714161/>

American Association for Cancer Research (2011): AACR Cancer Progress Report 2011, <https://www.roswellpark.org/sites/default/files/node-files/asset/nid91575-2011-aacr-cpr-text-web.pdf>

American Association for Cancer Research (2014): AACR Cancer Progress Report 2014 http://cancer.uchicago.edu/docs/2014_AACRReport.pdf

American College of Physicians Information on cost-effectiveness: an essential product of a national comparative effectiveness program. *Ann Intern Med.* 2008;148:956–61

American Society of Clinical Oncology (2006): Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications Revised February 27, 2006, by the, *Journal of Clinical Oncology* Vol 24 No 19, July 1, 2006, <http://jco.ascopubs.org/content/24/19/3206.full>

American Society of Clinical Oncology (2007): Medicare's Coverage With Evidence Development: A Policy-Making Tool in Evolution, <http://jop.ascopubs.org/content/3/6/296.full>

American Society of Clinical Oncology (2009): Comparative Effectiveness: Its Origin, Evolution, and Influence on Health Care, <http://jop.ascopubs.org/content/5/2/80.full>

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Armstrong.K.(2012): Methods in Comparative Effectiveness Research, American Society of Clinical Oncology, VOLUME 30 _ NUMBER 34 _ DECEMBER 1 2012,
<https://register.mssm.edu/summer/clr/2014/methods-in-cer.pdf>

Arozullah AM, Calhoun EA, & Wolf M, Finley, D.K., Fitzner, K.A., Heckinger, E.A., Gorby, N.S., Schumock, G.T. & Bennett, C.L.(2004) The financial burden of cancer: Estimates from a study of insured women with breast cancer. *J Support Oncol*, 2(3), 271–278.

Baird LG & Hirsch G(2014): Be bold and creative: food for thought for drug sponsors pursuing adaptive licensing, *Scrip Regulatory Affairs*, August 2014

Bach, P.B.(2009):Limits on Medicare's Ability to Control Rising Spending on Cancer Drugs, *N Engl J Med* 2009; 360:626-633February 5, 2009,
<http://www.nejm.org/doi/full/10.1056/NEJMhpr0807774>

Berry SR, Evans WK, Strevel EL, Bell CM(2012): Variation and consternation: access to unfunded cancer drugs in Canada.*J Oncol Pract.* 2012 Jan;8(1):35-9. doi: 10.1200/JOP.2011.00

BONNETT. C., (2010): Does Private Insurance Protect Canadians from the Cost of Cancer Drugs? REPORT CARD ON CANCER IN CANADA, 2009–10, P 14-18,
<http://www.canceradvocacy.ca/reportcard/2009/pdf/Does%20Private%20Insurance%20Protect%20Canadians%20from%20the%20Cost%20of%20Cancer%20Drugs%20-%20Chris%20Bonnett.pdf>

Bonter K, Desjardins C, Currier N, Pun J, and Ashbury F D, (2011): Personalised medicine in Canada: a survey of adoption and practice in oncology, cardiology and family medicine. *BMJ Open* 2011;1:e000110. <http://bmjopen.bmj.com/content/1/1/e000110.full?rss=1>

Branzén. Karl. (2013): Personalized Medicine , A new era for healthcare and industry, Life Science Foresight Institute, Retrieved from [http://ec.europa.eu/digital-agenda/futurium/sites/futurium/files/futurium/library/Branz%C3%A9n%20-%202013%20-%20Personalized%20Medicine\(2\).pdf](http://ec.europa.eu/digital-agenda/futurium/sites/futurium/files/futurium/library/Branz%C3%A9n%20-%202013%20-%20Personalized%20Medicine(2).pdf)

Burock S, Meunier F, and Lacombe D(2013): How can innovative forms of clinical research contribute to deliver affordable cancer care in an evolving health care environment? *Eur J Cancer* 2013;49:2777-83

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Butts, C., Kamel–Reid, S., Batist, G., Chia, S., Blanke, C., Moore, M., Sawyer, M., Desjardins, C., Dubois, A., Pun, J., Bonter, K., & Ashbury, F. (2013). Benefits, issues, and recommendations for personalized medicine in oncology in Canada. *Current Oncology*, *20*(5), e475-e483. doi:10.3747/co.20.1253

Cancer Advocacy Coalition of Canada (2011): Report Card On Cancer in Canada, VOLUME 13, WINTER 2010–11, Retrieved from, <http://www.canceradvocacy.ca/reportcard/2010/2010-2011%20REPORT%20CARD%20ON%20CANCER%20IN%20CANADA.pdf>

Cancer Advocacy Coalition of Canada (2014) Annual report Card on cancer in Canada 2012-2013, Vol 14, Available at <http://www.canceradvocacy.ca/reportcard/2013/Report%20Card%20on%20Cancer%20in%20Canada%202012-2013.pdf>

Canadian Cancer Action Network, (2008): *Issues of Access to Cancer Drugs in Canada*, A Report for the Canadian Cancer Action Network Updated April 2008, <http://www.ccanceraction.ca/wp-content/uploads/2010/11/3-CCAN-Pharma-Report-Final-PDF.pdf>

Cancer Care Ontario (2011): Mapping a Way through the Double Helix: Making sense of personalized medicine for Ontario's cancer system, May 2011, Cancer Quality Council of Ontario Members, <http://www.cqco.ca/common/pages/UserFile.aspx?fileId=98415>

Canadian Centre for Policy Alternatives (2010) The economic case for universal pharmacare costs and benefits of publicly funded drug coverage for all Canada.

Canadian Cancer Society (2009): Cancer Drug Access for Canadians, http://www.colorectal-cancer.ca/IMG/pdf/cancer_drug_access_report_en.pdf

Canadian Cancer Society (2012). Financial hardship of cancer in Canada A CALL FOR ACTION, Canadian Cancer Action Network , Manitoba Division. Retrieved from <http://www.ccanceraction.ca/wp-content/uploads/2012/10/ENGLISH-FINAL-FINANCIAL-HARDSHIP-OF-CANCER.pdf>

Canada Institute for Health Information (2013): National Health Expenditure Trends, 1975 to 2013 https://secure.cihi.ca/free_products/NHEXTrendsReport_EN.pdf

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Carlson, J. J., Sullivan, S., Garrison, L.P., Neumann, P.J., & Veenstra, D.L..(2010). Linking payment to health outcomes: A taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *Health Policy*, 3, 179-190. <http://htaiced.files.wordpress.com/2010/11/linking-payment-to-performance1.pdf>

Carpenter WR, Meyer AM, Abernethy AP, Sturmer T, Kosorok MR(2012):. A framework for understanding cancer comparative effectiveness research data needs. *Cancer Epidemiology, Biomarkers & Prevention J Clin Epidemiol*. 2012 November ; 65(11): 1150–1158. doi:10.1016/j.jclinepi.2012.06.005

Carter, J.L., and Lokere, J. (2010): Personalized Medicine, What is missing? REPORT CARD ON CANCER IN CANADA, 2010–11P1-3, <http://www.canceradvocacy.ca/reportcard/2010/Personalized%20Medicine%20What%20is%20Missing.pdf>

Carter. J.L.(2014): New Clinical Trials Designed to Better Leverage Precision Medicine, March 2014 Edition | Vol. 8, Issue 3, http://www.n-of-one.com/obrgreen/obr_vol8_issue3.php

Chafe,R., Culyer, A., Dobrow,M., Coyte, P.C., Sawka, C., O'Reilly, S., Laing, K., Trudeau, M., Smith, S., Hoch, J.S., Morgan, S., Peacock, S., Abbott, R., Sullivan, T., (2011): Access to cancer drugs in Canada:Looking beyond coverage decisions. *Healthc Policy* 6:27-35, 2011

Chan, K. K., B. Wong, L. L. Siu, S. E. Straus, J. Chang, and S. R. Berry (2012). Less Than Ideal: How Oncologists Practice With Limited Drug Access. *Journal of Oncology Practice* 8: 190–5., <http://jop.ascopubs.org/content/8/3/190.full>

Chandra, Amitabh, Anupam B. Jena, and Jonathan S. Skinner. 2011. "The Pragmatist's Guide to Comparative Effectiveness Research." *Journal of Economic Perspectives*, 25(2): 27-46.

Cheema, P.K, Gavura , S., Migus, M., Godman, B., Yeung, L., & Trudeau, M.E. (2012). International variability in the reimbursement of cancer drugs by publically funded drug programs. *Current Oncology*, 19(3), 165-176. Retrieved from: <http://www.current-oncology.com/index.php/oncology/article/view/946/924>.

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Chin L, Andersen JN and Futreal PA (2011): Cancer genomics: from discovery science to personalized medicine. *Nat Med.* 2011 Mar;17(3):297-303. doi: 10.1038/nm.2323

Claxton K. OFT, VBP: QED? *Health Econ* 2007;16:545-58.

Claxton, K.; Briggs, A.; Buxton, M.J.; Culyer, A.J.; McCabe, C.; Walker, S.; Sculpher, M.J. Value based pricing for NHS drugs(2008a): an opportunity not to be missed? *BMJ* 2008, 336, 251–254.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2223028/>

Claxton K, A Briggs, MJ Buxton, AJ Culyer, C McCabe, S Walker and MJ Sculpher. (2008b). Value based pricing for NHS drugs: an opportunity not to be missed ? *BMJ* 336:251 – 254 Retrieved from

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2223028/>

Claxton, K., Sculpher, M., and Carroll, S. Value-based pricing for pharmaceuticals: Its role, specification and prospects in a newly devolved NHS. *CHE Research Papers.* ; 2011 (Available at: <http://www.york.ac.uk/che/publications/in-house/#tab-3>)

Cohn JN (2004). Introduction to Surrogate Markers. *Circulation* (American Heart Association) 109 (25 Suppl 1): IV20–1

Congressional Budget Office.(2009) : Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role. Accessed at www.cbo.gov/ftpdocs/88xx/doc8891/12-18-ComparativeEffectiveness.pdf on 19 June 2009;

Coulter A, Entwistle V, Gilbert D (1999): Sharing decisions with patients: is the information good enough? *BMJ* 1999, 318:318–322.

Crivellente.F(2011): The Sooner the Better: Utilizing biomarkers to eliminate drug candidates with cardiotoxicity in preclinical development. Summer 11, DDW

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

<http://www.ddw-online.com/personalised-medicine/p149290>

Daemmrich, A. (2011). U.S. Healthcare reform and the pharmaceutical industry. Harvard Business School, Working Paper 12-015. Retrieved from:
<http://www.hbs.edu/faculty/Publication%20Files/12-015.pdf>

Daw, J. R. & Organ, S.G. (2012). "Stitching the gaps in the Canadian public drug coverage patchwork? A review of provincial pharmacare policy changes from 2000 to 2010." *Health Policy* 104(1): 19-26.

Danzon PM & Taylor E. (2010): Drug Pricing and Value in Oncology, *Oncologist*. 2010;15 Suppl 1:24-31. doi: 10.1634/theoncologist.2010-S1-24.

DiMasi JA, Hansen RW, and Grabowski HG (2003), The price of innovation: new estimates of drug development costs. *J Health Econ* 2003;22:151–85.

DiMasi JA and Grabowski HG (2007) Economics of new oncology drug development. *J Clin Oncol* 25: 209–216.

DiMasi. J.A., (2013): Metrics on Technical Risks, Clinical Development Times, and Approval Times for Cancer Drugs, ASCO/IOM Workshop Washington, DC February 11, 2013, Retrieved from

<http://www.iom.edu/~media/Files/Activity%20Files/Disease/NCPF/2013-FEB-11/DiMasi.pdf>

Duestzina, S. B., Muluneh, B., Khan, T., Richards, K, L., Keating NL (2014):. Obstacles to affordable cancer treatments, *N C Med J*. 2014 Jul-Aug;75(4):257-60.

Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J (2007): Assessing the economic challenges posed by orphan drugs. *Int J Technol Assess Health Care* 2007, 23:36–42.
http://cameroninstitute.com/attachments/020_Evidence%20and%20Values.pdf

Docteur, E., & Paris, V. (2009). Ensuring efficiency in pharmaceutical expenditures. in OECD, *Achieving Better Value for Money in Health Care*, OECD Publishing. Retrieved from:
<http://dx.doi.org/10.1787/9789264074231-5-en>

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Eichler HG, Oye K, Baird LG, Brown J, Drum CL, Ferguson J, Garner S, Honig P, Hukkelhoven M, Lim JCW, Lim R, Lumpkin M, Neil G, O'Rourke B, Pezalla E, Shoda D, Seyfert-Margolis V, Sigal EV, Sobotka J, Tan D, Unger TF and Hirsch G.(2012): Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval, *Nature*, 91(3):426-437, Mar 2012.

<http://www.nature.com/clpt/journal/v91/n3/full/clpt2011345a.html>

Eisenstein, M. (2014): Clinical Trials. More trials, fewer tribulations: Clinical studies that group patients according to their molecular profile can make for better and faster drug approval decisions. *Cancer Outlook*, 29 MAY 2014 | VOL 509 | NATURE | S55-S57, May

European Commission (2013): Use of '-omics' technologies in the development of personalised medicine. Commission Staff working paper, Retrieved from

http://ec.europa.eu/health/files/latest_news/2013-10_personalised_medicine_en.pdf

European Organisation for Research and Treatment of Cancer(2014): European solution for effective cancer drug development presented,

<http://www.sciencedaily.com/releases/2014/07/140701101457.htm>

European Science Foundation(2012): Personalised Medicine for the European Citizen – Towards more precise medicine for the diagnosis, treatment and prevention of disease (iPM), An ESF Forward Look,

http://www.esf.org/fileadmin/Public_documents/Publications/Personalised_Medicine.pdf

Evans, Robert G. (2007). Economic myths and political realities. Vancouver Centre for Health Services and Policy Research. Retrieved from: <http://medicare.ca/wp-content/uploads/2010/06/evansstudy.pdf>

FDA (2013): Paving the Way for Personalized Medicine, FDA's Role in a New Era of Medical Product Development, Section v: Advancing Regulatory Science in Support of Personalized Medicine

<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf>

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Faunce, T. A. and H. Nasu (2008). 'Three proposals for rewarding novel health technologies benefiting people living in poverty: a comparative analysis of prize funds, health impact funds and a cost-effectiveness/competitive tender treaty'. *Public Health Ethics*, 1(2): 146–53.

Ferrara. J. (2007): *Personalized Medicine: Challenging Pharmaceutical and Diagnostic Company Business Models*, *McGill Journal of Medicine*, MJM 2007 10(1):59-61

Finn, Karen. (2013). *Adaptive licensing: A new approach for authorizing medicines*. MedNous. Retrieved from: <http://www.sayitbetter.co.uk/wp-content/uploads/2011/11/AdaptivelicensingKFinn.Jan-20131.pdf>

Frankel Group LLC Advisory Board (2013): *The Current State of Pharmaceutical Industry Research and Development: Increasing Translational Research to Improve R&D Productivity Fourth in a Series*,
<http://www.frankelgroup.com/docs/default-source/default-document-library/fg-advisory-board-whitepaper-4may2013.pdf?sfvrsn=2>

Friends of Cancer Friends of Cancer Research (2009): *Improving Medical Decisions Through Comparative Effectiveness Research: Cancer as a Case Study*. Published May 13,2009. Available at: http://focr.org/files/CER_REPORT_FINAL.pdf. Accessed January 12, 2010)

Friends of Cancer Friends of Cancer Research (2009): *Improving Medical Decisions Through Comparative Effectiveness Research: Cancer as a Case Study*. Published May 13,2009. Available at: <http://www.focr.org/sites/default/files/CER%20REPORT%20FINAL.pdf>

Gagnon, Marc-André et al (2010): *The economic case for universal pharmacare*. Ottawa: Canadian Centre for Policy Alternatives. Retrieved from: <http://pharmacarenow.ca/wp-content/uploads/2010/09/Universal-Pharmacare-Report-e.pdf>

Garber, Alan M.; Sox, Harold C.(2010) *The Role of Costs in Comparative Effectiveness Research*. *Health Affairs*. 2010; 29(10):1806–07.

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Garber, A and Tunis, S (2009): Does Comparative-Effectiveness Research Threaten Personalized Medicine? *N Engl J Med* 2009; 360:1925-1927 May 7, 2009

Garber AM(2008): A menu without prices. *Ann Intern Med.* ;148:964–6.

Garrison Jr., L.P(2010a):Rewarding value creation to promote innovation in oncology: The importance of considering the global product life cycle. *The oncologist.* 2010;15 Suppl 1:49-57.

Garrison, Louis P. and Neumann, Peter J. and Radensky, Paul and Walcoff, Sheila D.(2010b): A Flexible Approach To Evidentiary Standards For Comparative Effectiveness Research,29,10,1812-17, <http://content.healthaffairs.org/content/29/10/1812.full>

Garassino.M., (2013): “What is personalized medicine” Let us understand. 2013. ESMO Patients Guide Series <http://www.esmo.org/content/download/20122/337223/file/ESMO-Patient-Guide-Personalised-Cancer-Medicine.pdf>

Giedion U, Alfonso E, & Diaz Y. (2013): The impact of universal coverage UHC schemes in the developing world: A review of the existing evidence. Washington, DC: The World Bank.

Godman, B.,Finlayson,A.E.,Cheema,P.K.,Zebedin-Brandl,E.,Gutiérrez-Ibarluzea,I.,Jones,J.,etal.(2013).Personalizinghealthcare:feasibilityand future implications. *BMC Med.* 11:179. doi:10.1186/1741-7015-11-179, Retrieved from

<http://www.biomedcentral.com/1741-7015/11/179>

Grootendorst P. (2002). Beneficiary cost sharing under Canadian provincial prescription drug benefit programs: history and assessment. *Canadian Journal of Clinical Pharmacology* 9(2): 79–99.

Grundy,R, Iain James, Chas Bountra and Timothy Harrison: (2014): Reconfiguring drug discovery through innovative partnerships, Fall 2014, *Drug Discovery World*, <http://www.ddw-online.com/fall-14-full-articles/p218116-reconfiguring-drug-discovery-through-innovative-partnerships.html>

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Gruber J. (2008). Incremental Universalism for the United States: The States Move First? *Journal of Economic Perspectives*, 22(4), 51-68. Fall 2008, Retrieved from <http://economics.mit.edu/files/6417>

Gruber J. (2010). Health care reform is a “three-legged stool”: the costs of partially repealing the Affordable Care Act. Center for American Progress. Retrieved from: http://www.americanprogress.org/issues/2010/08/pdf/repealing_reform.pdf .

Gruber J. (2011a). The impact of the Affordable Care Act: How reasonable are the projections? National Bureau of Economic Research Working Paper #17168.

Gruber J. (2011b). Massachusetts points the way to successful health care reform. *Journal of Policy Analysis and Management*, 30(1), 184-192.

Hanley G.E., & Morgan S. (2009). Chronic catastrophes: Exploring the concentration and sustained nature of ambulatory prescription drug expenditures in the population of British Columbia, Canada. *Social Science and Medicine* 68(5), 919–24

Hay, M., Thomas, D.W., Craighead, L., Economides, C., and Rosenthal, J. (2014). Clinical development success rates for investigational drugs. *Nat. Biotechnol.* 32, 40–51. doi:10.1038/nbt.2786

Health Council of Canada (2009, January). A status report on the national pharmaceuticals strategy: a prescription unfulfilled. *Health Council of Canada*, Retrieved from <http://www.parl.gc.ca/Content/LOP/ResearchPublications/prb0906-e.pdf>

Henry J Kaiser Family Foundation (2006). Toplines: National survey of households affected by cancer. <http://www.kff.org/kaiserpolls/7590.cfm>.

Hillner, B. E. & Smith, T.J. : (2009) *Efficacy does not necessarily translate to cost effectiveness: A case study in the challenges associated with 21st-century cancer drug pricing. J Clin Oncol* 27:2111–2113.

Heymann S.J., Gerecke M, & Chaussard M (2010a): Paid health and family leave: the Canadian experience in the global context. *Can J Public Health. Suppl* 1, 9-15.

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Heymann J, Rho H. J., Schmitt J, & Earle A (2010b): Ensuring a healthy and productive workforce: Comparing the generosity of paid sick day and sick leave policies in 22 countries. *Int J Health Serv.* 40(1), 1-22.

Hofmarcher T, Jonsson B, Wilking N. (2014): Access to high-quality oncology care across Europe. Lund: Swedish Institute for Health Economics, 2014. Available at: <http://www.ihe.se/access-to-high-quality-oncology.aspx>

Hopkins, R.B., Goeree, R. & Longo, C.J. (2010). "Estimating the national wage loss from cancer in Canada." *Current Oncology* 17(2): 40-49.

Husereau, D. & C. G. Cameron. (2011b). Value-based pricing of pharmaceuticals in Canada: Opportunities to expand the role of health technology assessment? Canadian Health Services Research Foundation. Ottawa: Canada. Retrieved from: http://www.chsrf.ca/Libraries/Commissioned_Research_Reports/Husereau-Dec2011-EN.sflb.ashx

Hutchinson, L. & Kirk, R.(2011): High drug attrition rates—where are we going wrong? *Nature Rev. Clin Oncol.* Vol 8, Pages 189-90, <http://www.nature.com/nrclinonc/journal/v8/n4/pdf/nrclinonc.2011.34.pdf>

Ibis Sánchez-Serrano (2006): Success in translational research: lessons from the development of bortezomib, *NATURE REVIEWS | DRUG DISCOVERY VOLUME 5 | FEBRUARY 2006*, <http://www.ibissanchezserrano.com/Sanchez-Serrano-NRDD-article.pdf>

ILO (2007): Social health protection. An ILO strategy towards universal access to health care. A consultation, *Issues in social protection. Discussion paper 19, working paper*, January 20079789221200970,9789221200987[ISBN], http://www.ilo.org/secsoc/information-resources/publications-and-tools/Discussionpapers/WCMS_SECSOC_14083/lang-en/index.htm

ILO (2009): A joint Crisis Initiative of the UN Chief Executives Board for Co-ordination on the social protection floor. Geneva International Labour Organization.

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

ILO (2010): World Social Security Report 2010/11: providing coverage in times of crisis and beyond. Geneva: ILO

ILO. (2013): Social protection. Retrieved from:
<http://www.ilo.org/gimi/gess/ShowTheme.do?tid=3285>

ILO (2014): World Social Protection Report 2014/15, Building economic recovery, inclusive development and social justiceCh 5, coverage in health.
http://www.ilo.org/wcmsp5/groups/public/---dgreports/---dcomm/documents/publication/wcms_245201.pdf

¹ Institute of Medicine(2013). *Implementing a National Cancer Clinical Trials System for the 21st Century: Second Workshop Summary*. Washington, DC: The National Academies Press, 2013. Summary report, <http://www.ncbi.nlm.nih.gov/books/NBK202108/pdf/TOC.pdf>

IMS (2014): Innovation in cancer care and implications for health systems. Global oncology trend report May 2014, http://340breform.org/userfiles/IMSH_Oncology_Trend_Report.pdf

Issues of Access to Cancer Drugs in Canada. (2008): A Report for the Canadian Cancer Action Network. Turner and Associates, <http://www.ccanceraction.ca/wp-content/uploads/2010/11/3-CCAN-Pharma-Report-Final-PDF>

Jakka, S., and Rossbach, M. (2013): An economic perspective on personalized medicine, Review. The HUGO Journal Official Journal of the Human Genome Organisation, Retrieved from <http://link.springer.com/article/10.1186/1877-6566-7-1/fulltext.html>

Jayadev A and J Stiglitz(2009): Two Ideas To Increase Innovation And Reduce Pharmaceutical Costs And Prices. *Health Affairs*, 28, no.1 (2009):w165-w168. Retrieved from <http://content.healthaffairs.org/content/28/1/w165.full>

Kaitin KI, DiMasi JA.(2011): Pharmaceutical innovation in the 21st century: new drug approvals in the first decade, 2000–2009. *Clin Pharmacol Ther* 2011;89:183–8.

Kantarjian HM, Fojo T, Mathisen M, Zwelling LA.(2013): Cancer drugs in the United States: Justum Pretium--the just price. *J Clin Oncol*. 2013 Oct 1;31(28):3600-4.

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Kelly RJ, Hillner BE, Smith TJ.: (2014): Cost effectiveness of crizotinib for anaplastic lymphoma kinase-positive, non-small-cell lung cancer: who is going to blink at the cost? *J Clin Oncol.* 2014 Apr 1;32(10):983-5. doi: 10.1200/JCO.2013.54.6002. Epub 2014 Feb 24

Keogh. B(2012): Era of Personalized Medicine May Herald End of Soaring Cancer Costs, *JNCI J Natl Cancer Inst* (2012) 104 (1): 12-17. <http://jnci.oxfordjournals.org/content/104/1/12.long>

Khanna, I., (2012): Drug discovery in pharmaceutical industry: productivity challenges and trends, *Drug Discovery Today* _ Volume 17, Numbers 19/20 _ October 2012, Retrieved from [http://csmres.co.uk/cs.public.upd/article-downloads/Khanna\[1\].pdf](http://csmres.co.uk/cs.public.upd/article-downloads/Khanna[1].pdf)

Kircher MF, Hricak H, and Larson SM (2012). Molecular imaging for personalized cancer care. *Mol Oncol* 6, 182–195. <http://www.sciencedirect.com/science/article/pii/S1574789112000178>

Kluetz.P., and Donoghue, M., (2014): FDA Programs to Expedite Drug and Biologic Product Development A Conversation With FDA's Office of Hematology and Oncology Products, *The ASCO Post*, February 15, 2014, Volume 5, Issue 3. <http://www.ascopost.com/issues/february-15,-2014/fda-programs-to-expedite-drug-and-biologic-product-development.aspx>

Knaul FM, González-Pier E, Gómez-Dantés O, García-Junco D, Arreola-Ornelas H, Barraza-Lloréns M,

Sandoval R, Caballero F, Hernández-Avila M, Juan M, Kershenobich D, Nigenda G, Ruelas E, Sepúlveda J,

Tapia R, Soberón G, Chertorivski S, Frenk J: The quest for universal health coverage: achieving social

protection for all in Mexico. *Lancet* 2012, 380:1259–1279. Retrieved from :

<http://download.thelancet.com/flatcontentassets/pdfs/S014067361261068X.pdf>

Kola, I. & Landis, J. Can the pharmaceutical industry reduce attrition rates? *Nature Rev. Drug Discov.* **3**, 711–715 (2004).

Kutzin.J., (2012): Anything goes on the path to universal health coverage? No. *Bulletin of the World Health Organization* 2012;90:867-868. doi: 10.2471/BLT.12.113654, <http://www.who.int/bulletin/volumes/90/11/12-113654/en/>

Lawler M, Le Chevalier T, Murphy MJ Jr, Banks I, Conte P, De Lorenzo F, Meunier F, Pinedo HM, Selby P, Armand JP, Barbacid M, Barzach M, Bergh J, Bode G, Cameron DA, de Braud F,

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

de Gramont A, Diehl V, Diler S, Erdem S, Fitzpatrick JM, Geissler J, Hollywood D, Højgaard L, Horgan D, Jassem J, Johnson PW, Kapitein P, Kelly J, Kloezen S, La Vecchia C, Löwenberg B, Oliver K, Sullivan R, Tabernero J, Van de Velde CJ, Wilking N, Wilson R, Zielinski C, Zur Hausen H, Johnston PG. (2014) : A catalyst for change: The European cancer patient's bill of rights. *The Oncologist* 2014;19: 217–224

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3958470/pdf/theoncologist_13452.pdf

de Lartigue. J. (2014): A Look at I-SPY 2: Novel Trial Design May Expand the Scope of Oncology Drug Development , Published Online: Wednesday, April 2, 2014. *OncLive*
<http://www.onclive.com/publications/oncology-live/2014/march-2014/a-look-at-i-spy-2-novel-trial-design-may-expand-the-scope-of-oncology-drug-development/1>,

Liu Y, Lacombe D, Stupp R.(2014):The changing world of drug development: an academic research organization's perspective on the "Seven Wonders" of the future world of anticancer drug development. *Chin Clin Oncol* 2014;3(2):19. doi: 10.3978/j.issn.2304-3865.2014.05.06
Retrieved From

<http://www.thecco.net/article/view/3861/4826>

Longo CJ, Fitch M, Deber RB, Williams AP (2006): Financial and family burden associated with cancer treatment in Ontario, Canada. *Support Care Cancer* 2006, 14:1077–1085.

Longo, C. J. (2010a). Financial hardship of cancer in Canada: A call for action. *Canadian Cancer Action Network*. Retrieved from: https://archive.org/stream/496264-financial-hardship-of-cancer-english/496264-financial-hardship-of-cancer-english_djvu.txt

Longo, C.J. (2010b). Equitable access to healthcare services and income replacement for cancer: Is critical illness insurance a help or a hindrance? *Healthcare Policy*, 5(4), 132-138.

Love.J., and Hubbard,T., (2007): The Big Idea: Prizes to Stimulate R&D for New Medicines. *Chicago-Kent Law Review*, Volume 82, Number 3

Love.J., and Hubbard,T., (2009): "Prizes for Innovation of New Medicines and Vaccines," *Annals of Health Law*, Vol. 18, No 2, pages 155-186, *Summer*

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Luce BR, Kramer JM, Goodman SN, Connor JT, Tunis S, Whicher D, Schwartz JS.(2009) Rethinking randomized clinical trials for comparative effectiveness research: The need for transformational change. *Annals of Internal Medicine*. 2009;151:206-209

Lyman GH, Levine M., (2012): Comparative effectiveness research in oncology: An overview. *J Clin Oncol* 30:4181-4184, 2012

Mak. T. (2013): Cancer Advocacy Coalition of Canada, Report Card on Cancer, 2012-13, VOLUME 14, WINTER 2012–13

Mellace.J., (2010) , The Financial Burden of Cancer Care, *Social Work Today* Vol. 10 No. 2 P. 14 Association of Oncology Social Work (AOSW), March/April 2010 Issue, <http://www.socialworktoday.com/archive/032210p14.shtml>

Menis J, Hasan B, and Besse B(2014): New clinical research strategies in thoracic oncology: clinical trial design, adaptive, basket and umbrella trials, new end-points and new evaluations of response, *Eur Respir Rev*. 2014 Sep;23(133):367-78. doi: 10.1183/09059180.00004214.

Meyer, A.-M., Carpenter, W. R., Abernethy, A. P., Stürmer, T. and Kosorok, M. R. (2012), Data for cancer comparative effectiveness research. *Cancer*, 118: 5186–5197. doi: 10.1002/cncr.27552

Moreno-Serra R, Millett C, Smith PC, 2011, Towards Improved Measurement of Financial Protection in Health, *PLOS Medicine*, Vol:8, ISSN:1549-1277, Retrieved from: <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001087>

Morgan S, Kennedy J. (2010). Prescription drug accessibility and affordability in the United States and abroad. *Issue Brief (Commonwealth Fund)* 8, 1–12.

Morgan, S. G.& Draw, J. R.(2012). “Canadian pharmacare: Looking back, looking forward. *Healthcare Policy* 8(1): 14-23.

Morgan, S.G., Daw, J.R., and Law.M.R.,(2013): Rethinking Pharmacare in Canada, Commentary No. 384, June, *Health Policy*, http://www.cdhowe.org/pdf/Commentary_384.pdf

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

National Pharmaceutical Council(2012): Making Informed Decisions: Assessing the Strengths and Weaknesses of Study Designs and Analytic Methods for Comparative Effectiveness Research A Briefing Document for Stakeholders,
http://www.npcnow.org/system/files/research/download/experimental_nonexperimental_study_final.pdf

Nelson, C.(2010). The financial hardship of cancer in Canada: A literature review. Winnipeg, Man.: Canadian Cancer Society Manitoba Division. <http://www.ccanceraction.ca/wp-content/uploads/2010/11/FinancialHardshipofCancerInCanada-Literature-Manitoba.pdf>

Neumann, P.J., Chambers, J.D., Simon.F., and Meckley. L.M (2011): "Risk-Sharing Arrangements That Link Payment For Medications To Health Outcomes Are Proving Hard To Implement." *Health Affairs*. 2011;30(12):2329–2337.
Retrieved from
<http://content.healthaffairs.org/content/30/12/2329.full>

OECD (2009),*Achieving Better Value for Money in Health Care*, OECD Health Policy Studies, OECD, Ch 4, Ensuring Efficiency in Pharmaceutical Expenditures,
http://www.keepeek.com/Digital-Asset-Management/oecd/social-issues-migration-health/achieving-better-value-for-money-in-health-care_9789264074231-en#page1 ISBN: 978-92-6407423-1 (PDF)

OECD(2013): Health at a Glance 2013, OECD Indicators, Health systems,
<http://www.oecd.org/els/health-systems/Health-at-a-Glance-2013.pdf>

Orszag P. (2007): Research on the Comparative Effectiveness of Medical Treatments: Options for an Expanded Federal Role. Testimony before the Subcommittee on Health, Committee on Ways and Means, U.S. House of Representatives, June 12, 2007

Ozdemir, V., Williams-Jones, B., Cooper, D.M., Someya, T., Godard, B. (2007) "Mapping Translational Research in Personalized Therapeutics: From Molecular Markers to Health Policy" *Pharmacogenomics* 8(2): 177-85., Retrieved from
<http://genethics.ca/personal/papers/PGxMapping.pdf>

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Padzur (2013)??Institute of Medicine. *Implementing a National Cancer Clinical Trials System for the 21st Century: Second Workshop Summary*. Washington, DC: The National Academies Press, 2013. Summary report, <http://www.ncbi.nlm.nih.gov/books/NBK202108/pdf/TOC.pdf>

Palmer, W. N., (2010): Pricing & Reimbursement Trends in Canada, SMI's 16th annual European Pharmaceutical Pricing and Reimbursement Conference, Munich
[http://pdci.ca/pdf/events/Palmer-Presentation-EyeforPharma-\(October%2028,2013\).pdf](http://pdci.ca/pdf/events/Palmer-Presentation-EyeforPharma-(October%2028,2013).pdf)

Pammolli F, Magazzini L, Riccaboni (2011): M. The productivity crisis in pharmaceutical R&D. *Nat Rev Drug Discov.* 2011;10(6):428–38. Retrieved from
http://emoglen.law.columbia.edu/twiki/pub/LawNetSoc/BahradSokhansanjFirstPaper/10NatRevDrugDisc428_pharma_productivity_crisis_2011.pdf

Paris, V. and E. Docteur (2006), “Pharmaceutical Pricing and Reimbursement Policies in Canada”, OECD Health Working Paper, No. 24, OECD Publishing, Paris

Patel, J.D., Krilov, L., Adams, S., Aghajanian, C., Basch, E., Brose, M.S., Carroll, W.L., deLima, M., Gilbert, M.R., Kris, M.G., Marshall, J.L., Masters, G.E., O’Day, S.J., Polite, B., Schwartz, G.K., Sharma, S., Thompson, I., Vogelzang, N.J., and Roth, B.J., (2013): *Clinical Cancer Advances 2013: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology*, *JCO Jan 10, 2014:129-160; published online on December 10, 2013;*
<http://jco.ascopubs.org/content/32/2/129.full.pdf+html>

Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. (2010): How to improve R&D productivity: the pharmaceutical industry’s grand challenge. *Nat. Rev. Drug Discov.* 9, 203–214. Retrieved from
<http://www.nature.com/nrd/journal/v9/n3/full/nrd3078.html>

Phillips, K., (2009): *Catastrophic Drug Coverage in Canada*, Social Affairs Division, Library of Parliament

<http://www.parl.gc.ca/Content/LOP/ResearchPublications/prb0906-e.pdf>

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Porter ME. A strategy for health care reform—toward a value-based system. *N Engl J Med* 2009; 361: 109–12

President's Council of Advisors on Science and Technology (PCAST 2012): Propelling innovation in drug discovery, development and evaluation, Executive Office of the President, <http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf>

Public Policy Forum (2010): REPORT ON Second Annual Symposium on Cancer Drugs Access. Dec 2010. http://ppforum.com/sites/default/files/Cancer%20-%20Report%20Final%20-%20low%20res%20for%20web_0.pdf

Quintiles(2013): Tomorrow's Path to Improved Early-Phase Oncology Drug Development: Maximizing Quality and Efficiency of Go/No-Go Decisions in Early-phase Studies, White paper April 2013, <http://www.quintiles.com/library/white-papers/tomorrows-path-to-improved-earlyphase-oncology-drug-development>

RAGAZ,J.,(2011): The 21-Gene Assay, Canada's Uneven Response, REPORT CARD ON CANCER IN CANADA, 2010–11, <http://www.canceradvocacy.ca/reportcard/2011/The%2021-Gene%20Assay%20Canadas%20Uneven%20Response.pdf>

Ramsey SD & Sullivan SD.(2014): A new model for reimbursing genome-based cancer care. *Oncologist*. 2014 Jan;19(1):1-4. <http://theoncologist.alphamedpress.org/content/19/1/1.long>.

Rawson.N., (2012): Access to New Oncology Drugs in Canada Compared with the United States and Europe, Fraser Institute, <http://www.fraserinstitute.org/uploadedFiles/fraser-ca/Content/research-news/research/publications/access-to-new-oncology-drugs-in-canada.pdf>

Rawson.N., (2013): Potential Impact of Delayed Access to Five Oncology Drugs in Canada, Fraser Research Bulletin, <http://www.fraserinstitute.org/uploadedFiles/fraser-ca/Content/research-news/research/publications/potential-impact-of-delayed-access-to-five-oncology-drugs-in-canada.pdf>

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Rawson. N.(2014): Has pCODR improved access to oncology drugs? Timeliness and provincial acceptance of pan-Canadian Oncology Drug Review recommendations,

Report on Second Annual Symposium on Cancer Drugs Access (2010). Public Policy Forum. Retrieved from: <http://www.ppforum.ca/publications/second-annual-symposium-cancer-drug-access>

Rocchi A, Menon D, Verma S, Miller E. (2008). The role of economic evidence in Canadian oncology reimbursement decision-making: to lambda and beyond. *Value in Health*, 11(4), 771–783.

Rx&D (2013): The Rx&D International Report on Access to Medicines, 2011-2012, Canada's Research-Based Pharmaceutical Companies (Rx&D), http://www.canadapharma.org/CMFiles/Our%20Industry/Industry%20Facts/20130613_IRAM_2012_en_web.pdf

Scannell, J.W., Blanckley, A., Boldon, H., and Warrington, B. (2012). Diagnosing the decline in pharmaceutical R&D efficiency. *Nat. Rev. Drug Discov.* 11, 191–200. doi:10.1038/nrd3681

Scheil-Adlung, X., B. Florence, T. Wiechers, and T. Ayangbayi. (2010): . *New approaches to measuring deficits in social health protection coverage in vulnerable countries*. World Health Report Background Paper 56, WHO. <http://www.who.int/healthsystems/topics/financing/healthreport/BP56MeasurementILO.pdf>

Scheil-Adlung, X. & Sandner, L. (2010). Paid sick leave: Incidence, patterns and expenditure in times of crisis *Extension of Social Security Series, ESS Paper 27*.

Scheil-Adlung, X. and B. Florence. 2011. Beyond legal coverage: Assessing the performance of social health protection. *International Social Security Review* 64.

Schoen C, Osborn R, Squires D, Doty M, & Pierson R, et al. (2010). How health insurance design affects access to care and costs, by income, in eleven countries. *Health Affairs* 29, 2323–2334.

Schwartz D, and Lellouch J.(2009): Explanatory and pragmatic attitudes in therapeutical trials. *J Clin Epidemiol.* 2009;62:499-505. [PMID: 19348976]

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Simonds NI, Khoury MJ, Schully SD, Armstrong K, Cohn WF, Fenstermacher DA, Ginsburg GS, Goddard KA, Knaus WA, Lyman GH, Ramsey SD, Xu J, Freedman AN(2013): Comparative Effectiveness Research in Cancer Genomics and Precision Medicine: Current Landscape and Future Prospects. *J Natl Cancer Inst.* Jul 3; 2013 105(13):929–936

Soliman, H. and Agresta, S.V. (2008). Current Issues in Adolescent and Young Adult Cancer Survivorship. *Cancer Control*, 15(1), 55-62.

Sørensen HT, Lash TL, Rothman KJ. (2006): Beyond randomized controlled trials: A critical comparison of trials with nonrandomized studies. *Hepatology* 2006;44:1075–1082

Sox. H.C. and S. N. Goodman(2012): The Methods of Comparative Effectiveness Research, *Annual Review of Public Health* Vol. 33: 425-445 (Volume publication date April 2012)

Stiglitz, J. E. (2006). 'Scrooge and intellectual property rights'. *British Medical Journal*, 333(7582): 1279–80, 23 December

Stiglitz.J.A., and Taneja,J., (2010): Medicine for Tomorrow: Some Alternative Proposals to Promote Socially Beneficial Research and Development in Pharmaceuticals, *Journal of Generic Medicines: The Business Journal for the Generic Medicines Sector* July 2010 vol. 7 no. 3 217-226

Stranne.S.K.(2013): Protecting Patient Access to Oral Cancer Drugs in the United States. *JOURNAL OF ONCOLOGY PRACTICE • VOL. 9, ISSUE 4, 2013*, Retrieved from <http://jop.ascopubs.org/content/9/4/194.full>

Sullivan R, Peppercorn J, Sikora K, Zalcborg J, Meropol NJ, Amir E, Khayat D, Boyle P, Autier P, Tannock IF, Fojo T, Siderov J, Williamson S, Camporesi S, McVie JG, Purushotham AD, Naredi P, Eggermont A, Brennan MF, Steinberg ML, De Ridder M, McCloskey SA, Verellen D, Roberts T, Storme G, Hicks RJ, Ell PJ, Hirsch BR, Carbone DP, Schulman KA, et al: Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011, 12:933–980.

Taylor. D. W.(2014b): Benefits Outweigh Costs in Universal Healthcare: Business Case for Reimbursement of Take-home Cancer Medicines in Ontario and Atlantic Canada *American Journal of Medicine and Medical Sciences* 2014, 4(4): 126-138, DOI: 10.5923/j.ajmms.20140404.05, http://cameroninstitute.com/attachments/084_10.5923.j.ajmms.20140404.05.pdf

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Taylor, D.W (2014a): The institutionalized discrimination of cancer patients– not what Tommy Douglas intended: A business case for the universal coverage of oral cancer medicines in Ontario and Atlantic Canada. Retrieved from: <http://cillpag.ca/CameronInstitute.pdf>

Thomas D.(2012): Oncology Clinical Trials--Secrets of Success. February 24, 2012. www.biotech-now.org/business-andinvestments/2012/02/oncology-clinical-trials-secrets-ofsuccess#frameId=jim-frame&height=485

Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, Tunis S, Bergel E, Harvey I, Magid DJ, Chalkidou K(2009): A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol* 2009, 62(5):464–475.

Trusheim, Mark R. and Berndt, Ernst R., 2012b, Economic challenges and possible policy actions to advance stratified medicine , *Personalized Medicine* (2012) 9(4), 413–427

Tsimicalis, A.(2010): *Costs Incurred by Families of Children Newly Diagnosed with Cancer in Ontario*. University of Toronto, 2010, Doctoral Thesis

Tunis SR, Stryer DB, and Clancy CM.(2003): Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA*.2003;290:1624-32. [PMID: 14506122]

Xu K, Evans DB, Carrin G, Aguilar-Rivera AM, Musgrove P, Evans T.(2007): Protecting households from catastrophic health spending. *Health Aff (Millwood)* 2007; 26: 972-83

<http://content.healthaffairs.org/content/26/4/972.full.pdf+html>

U.S. Department of Health & Human Services. Key Features of the Affordable Care Act. Retrieved from: <http://www.hhs.gov/healthcare/facts/timeline/index.html>

Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Kinzler KW.(2013): Cancer genome landscapes. *Science* 2013; 339: 1546-1558, Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749880/>

Weinstein, M., and Skinner J. Comparative effectiveness and health care spending implications for reform. *N Engl J Med*. 2010;362:460–465.

RESTRAINING HIGH AND RISING CANCER DRUG PRICES

Woodcock, J. Joseph P. Griffin, J.D., and Behrman, R.E., (2011): Development of Novel Combination Therapies, *N Engl J Med* 2011; 364:985-987 March 17, 2011 DOI: 10.1056/NEJMp1101548, Retrieved from, <http://www.nejm.org/doi/full/10.1056/NEJMp1101548>

World Health Organization. (2010). Health Systems Financing: The Path to Universal Coverage. World Health Report. Retrieved from: <http://www.who.int/whr/2010/en/index.html>.

Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al. (2008): CONSORT Group. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ*. 2008;337:a2390. [PMID: 19001484]

Workshop and Conferences

Workshop (2011): Coverage with Evidence Development and Adaptive Licensing: Two sides of the same coin? Workshop Summary. January 2012. Center for Medical Technology Policy & MIT Center for Biomedical Innovation. Available at: http://cbi.mit.edu/wp-content/uploads/2011/03/Coverage-with-Evidence-Development-Adaptive-Licensing_Workshop-Summary_February-2012.pdf

This workshop hosted by the Center for Medical Technology Policy (CMTP) and Massachusetts Institute of Technology's (MIT) Center for Biomedical Innovation (CBI) NEWDIGS program (New Drug Development Paradigms) on November 8th, 2011 in Baltimore, MD.

Conference: 2014

Vital Transformation, 2014: New Pathways for Development and Better Patient Outcomes, A report of an international conference held at the Royal College of Physicians, London, 21 October 2014.

<http://vitaltransformation.com/2014/10/conference-report-better-science-better-health-new-trial-pathways-and-better-patient-data/>